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A new chiral diol derived from tetralone for the complexation of Lewis acids

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Abstract—A new approach to the rational design of Lewis acids based on face–face π–π interactions is described. The synthesis of two novel diols (−)(1*R*,3*R*)-2,2-dimethyl-1,2,3,4-tetrahydronaphthalene-1,3-diol (−)-**1** and (−)(1*S*,3*R*)-*trans*-2,2-dimethyl-1,2,3,4-tetrahydronaphthalene-1-3-diol (−)-**9** is reported in six and five steps respectively starting from α-tetralone. Complexation of (−)(1*R*,3*R*)-2,2-dimethyl-1,2,3,4-tetrahydronaphthalene-1,3-diol (−)-**1** to phenylboronic acid shows the interplanar distance between the boron atom and the aromatic ring to be 3.05 Å, which is ideal for the proposed interactions.

1. Introduction

Over the past 30 years the chemistry of Lewis acids has been at the forefront of investigative synthetic research.[1] In the case of catalytic asymmetric variants of the numerous reactions that Lewis acids are known to accelerate, significant advances have been made such that methods are now available to construct complex and challenging molecules in a reliable and predictable manner.[2] Amongst these reactions, the asymmetric Diels–Alder reaction has received special attention due to the possibility of controlling up to four contiguous stereogenic centres in one step.[3] Particularly noteworthy amongst the reported systems are the chiral (acyloxy)borane (CAB)[4] and tyrosine[5] catalysts reported by Yamamoto and Corey, respectively, which are effective in catalysing the Diels–Alder reactions of α,β-unsaturated aldehydes, and the naphthalene derived catalysts of Hawkins,[6] which are highly efficient in the reactions of acrylates. Very recently, Corey has shown that it is possible to carry out highly enantioselective reactions with α,β-unsaturated ketones as the dienophile.[7] There is, however, to the best of our knowledge, still no reported effective asymmetric method for the use of the simplest α,β-unsaturated ketone, methyl vinyl ketone, using a Lewis acid to catalyse the reaction.

As part of our ongoing research into the modulation of face–face π–π interactions[8] and the design of novel Lewis acids, we sought to develop a new family of ligands that were capable of discriminating between the diastereotopic faces of α,β-unsaturated ketones providing the opportunity to utilise this fundamental class of molecule in the Diels–Alder reaction.

The diol **1** represents a new class of ligand capable of ligating to a Lewis acidic metal. On complexation with methyl vinyl ketone, the resulting complex can adopt four possible *s-trans* conformations **A**–**D** (Fig. 1). In all the effective ligand systems described above for the Diels–Alder reactions of both α,β-unsaturated aldehydes and acrylates, the diastereofacical discrimination observed within the reactions was rationalised by face–face π–π interactions between the substrate and the aromatic ring incorporated into the structure of the ligand.[9] We believed that conformer **D** may be favoured over the other possibilities due to a face–face π–π interaction. If this were to be the case then the bottom face of the substrate would most certainly be blocked from approach of a reagent by the aromatic ring, allowing the possibility of carrying out stereoselective transformations.

Essential features in the design of this ligand include the geminal dimethyl group, which should block the rear face of the metal from approach of the Lewis base substrate, together with the fact that the proposed discrimination between the diastereotopic faces of the methyl vinyl ketone is electronic rather than steric, therefore, if the catalyst proves to be effective, it should not be substrate specific as is the inherent problem with many of the catalysts previously reported in the literature. Herein we report a simple, scalable

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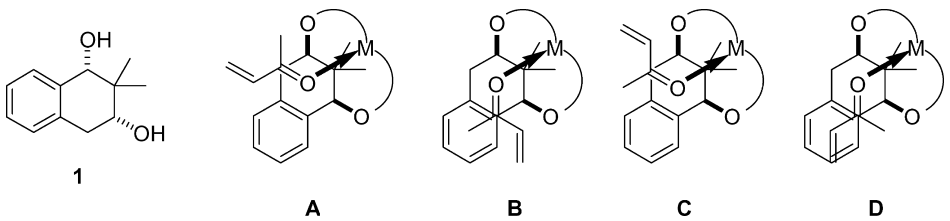


Figure 1.

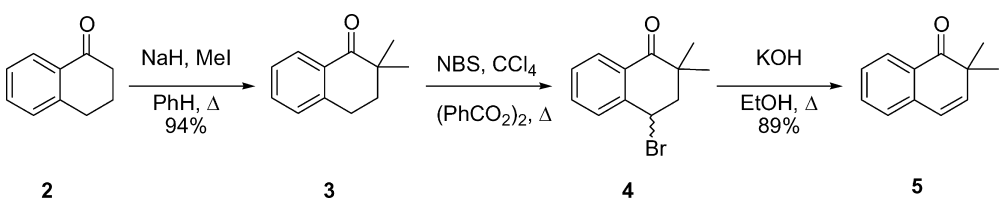
method to access this new class of ligand **1** together with our initial complexation studies that pave the way to future catalytic investigations.

2. Results and discussion

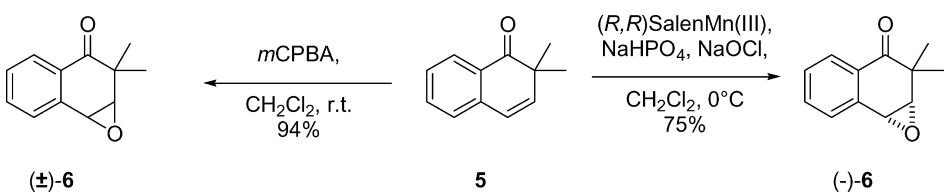
Treatment of commercially available α-tetralone **2** with methyl iodide and sodium hydride in benzene at room temperature followed by heating at reflux for 4 days gave the dimethylated ketone **3** (Scheme 1).[10] Purification by simple distillation gave analytically pure material in 94% yield. This synthesis was amenable to scale-up and the reaction proceeded on a 30 g scale without compromise in yield. Introduction of the double bond in **5** was carried out via a two-step bromination–elimination sequence. Treatment of **3** with one equivalent of *N*-bromosuccinimide in refluxing carbon tetrachloride in the presence of a catalytic amount of benzoyl peroxide followed by filtration, removal of solvent and treatment of the crude residue with a 10% ethanolic potassium hydroxide solution gave the alkene **5** in 89% yield for the two steps after purification by distillation. Once again this procedure was amenable to scale-up allowing access to large quantities of the alkene **5**.

Introduction of asymmetry into the system was achieved using the Jacobsen epoxidation.[11] Treatment of a solution of **5** in dichloromethane at 0°C with (*R*,*R*)-(−)-*N*,*N*′-bis-(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-manganese(III) chloride catalyst under standard conditions for 3 days gave the corresponding epoxide (−)-**6** in 75% yield. This synthesis was also carried out to produce a racemic sample of the epoxide (±)-**6** using *meta*-chloro-peroxybenzoic acid as the oxidant, enabling the determination of the enantiomeric excess of the epoxide (−)-**6** (Scheme 2). This was achieved by GC analysis using a chiral stationary phase with a Chrompack column (CP7532) which separated the authentic racemic sample (see Section 4 for details). Analysis of the epoxide derived from the Jacobsen epoxidation showed only one enantiomer to be present up to the detection limits of the GC showing the ee of the epoxide (−)-**6** was >98%.

Having successfully prepared the epoxide (−)-**6** in significant quantities we then sought to convert this into the desired *cis*-diol (−)-**1**, which was initially achieved by one step by hydrogenation procedure. Treatment of a stirred solution of (−)-**6** in ethyl acetate containing 2 equiv. of methanol with 10% palladium on carbon under an atmosphere of hydrogen for 4 h gave the desired diol (−)-**1** in 59% yield (Scheme 3). Confirmation of the relative stereochemistry of the diol was achieved by X-ray crystallographic analysis, which clearly shows the two hydroxyl functionalities adopting equatorial positions in a *cis*-configuration (Fig. 2). Unfortunately, this methodology did not prove amenable to scale up and yields of the diol (−)-**1** were often capricious, frequently leading to mixtures of the hydroxy ketone (−)-**7** and the alcohol (−)-**8** together with the desired diol (−)-**1**. Interestingly, it proved possible to produce either the hydroxy ketone (−)-**7** or the alcohol (−)-**8** selectively by simple modification of the reaction conditions. Treatment of the epoxide (−)-**6** with 10% palladium on carbon in ethyl acetate, containing 1 equiv. of methanol, under an atmosphere of hydrogen for just 10 min gave the hydroxy ketone (−)-**7** exclusively in 98% yield. Changing the solvent to methanol and stirring the reaction mixture for 24 h resulted in reduction of both the epoxide and the carbonyl functionalities to give the alcohol (−)-**8** in 90% yield after purification by column chromatography.



Scheme 1.



Scheme 2.

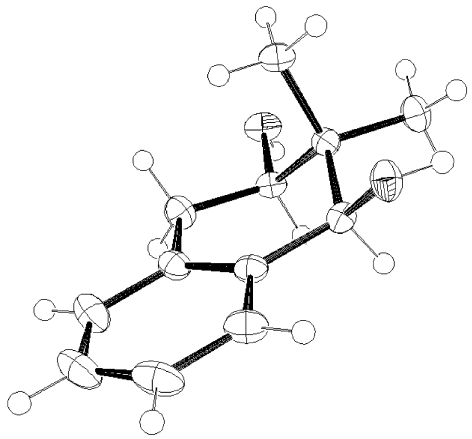
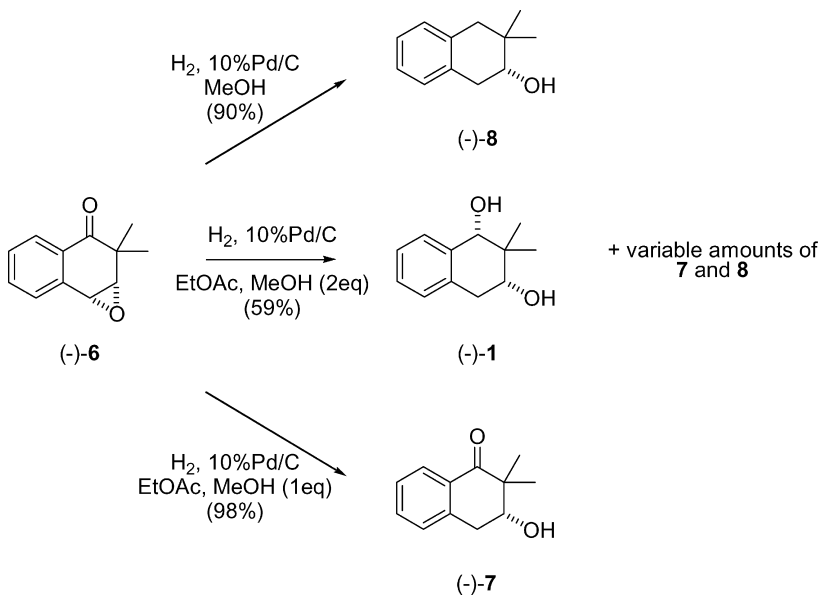


Figure 2. X-Ray crystal structure of the *cis*-diol (−)-**1**.

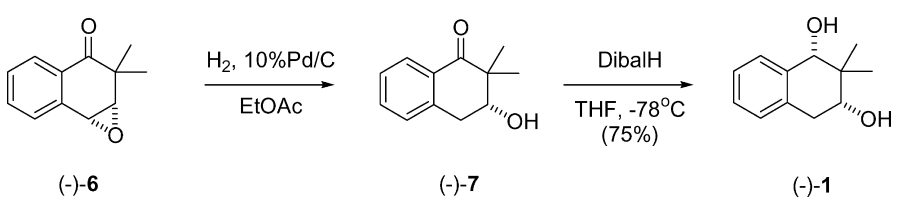
After much experimentation, a reliable route to the desired alcohol (−)-**1** was discovered by adopting a two step procedure (Scheme 4). This involved initial hydrogenation to give the hydroxy ketone (−)-**7**, as described above, followed by reduction with di-*iso*butyl aluminium hydride at −78°C for 30 min, to give the diol (−)-**1** in a gratifying 75% yield for the two steps. Although this represents a more lengthy procedure than the simple one step hydrogenation protocol originally adopted, the reaction was found to be both convenient and reliable allowing access to the target ligand (−)-**1** in acceptable quantity.

Due to the known reactivity of both epoxides and ketones to hydride reducing agents the possibility of using a one-pot protocol as a means of accessing the diol (−)-**1** was also investigated. Treatment of a stirred solution of (−)-**6** in tetrahydrofuran with three equivalents of di-*iso*butyl aluminium hydride led to the *trans*-diol (−)-**9** in 85% yield. By consideration of the result obtained in the reduction of hydroxy ketone (−)-**7**, this suggested that the carbonyl group was being reduced prior to reduction of the epoxide. Indeed, treatment of the epoxide (−)-**6** with just 1 equiv. of di-*iso*butyl aluminium hydride at −78°C selectively gave the epoxy alcohol **10** in 62% isolated yield (Scheme 5). This represents a simple manner with which to manipulate the oxidation levels of both the 1- and 3-positions of **1** and allows access to both diastereoisomers of the diol in either enantiomeric form by judicious choice of the reduction protocol adopted within the synthetic sequence as well as allowing both of the oxygen functionalities to be treated orthogonally without the need for protecting group strategies.

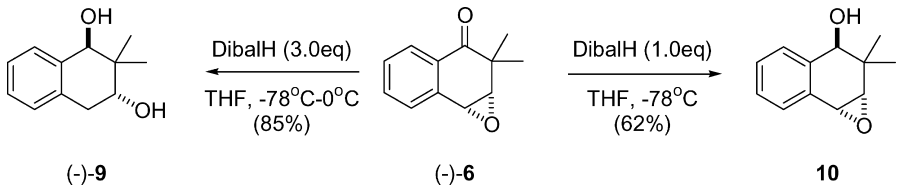
The selectivities observed in the DibalH reduction of epoxy ketone (−)-**6** and hydroxy ketone (−)-**7** may be attributed to the fact that in the case of (−)-**6**, the DibalH co-ordinates to the epoxide oxygen, delivering the hydride from the same face as the epoxide, subsequent stereospecific hydride ring opening of the epoxide then provides the *trans*-diol (−)-**9**. In the hydride reduction of (−)-**7** it was necessary to add 2.5 equiv. of DibalH in order to bring about complete transformation, addition of just 1 equiv. returning only starting material. It is therefore possible that the first equivalent of hydride deprotonates the hydroxyl group,



Scheme 3.



Scheme 4.



Scheme 5.

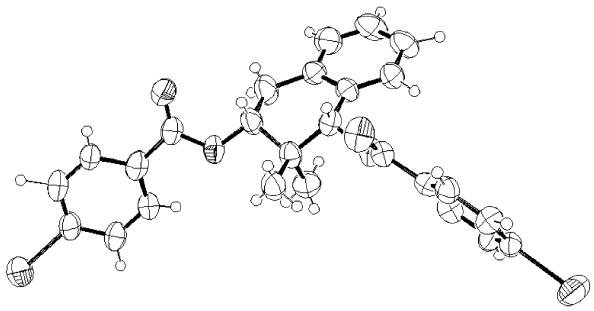


Figure 3. X-Ray crystal structure of (−)-**11**.

forcing the second equivalent of hydride to approach the carbonyl from the opposite face to the alkoxide anion, resulting in the observed *cis*-diol (−)-**1**.

In order to confirm the absolute configuration of the diol (−)-**1**, the ester (−)-**11** was prepared by treatment of the diol with 2 equiv. of 4-iodobenzoyl chloride in the presence in triethylamine which gave the adduct (−)-**11** in 76% yield. X-Ray analysis of a single crystal grown from this product confirmed the absolute stereochemistry of the diol (−)-**1** to be (1*R*,3*R*) as would be expected from the epoxidation model proposed by Jacobsen (Fig. 3).

As the principle aim of this project was to develop a clearer understanding of face–face π–π interactions and to use the diols in Lewis acid catalysed reactions we then sought to investigate the complexation of the ligand (−)-**1** to a series of Lewis acids. In the case of phenyl boronic acid single crystals of the adduct **12** were obtained that were suitable for X-ray crystallographic analysis (Fig. 4). The structure clearly shows that the two-hydroxyl groups adopt axial positions in order to ligate to the metal as desired. Examination of the structure also shows the inter-planar distance between the aromatic ring incorporated into the structure of the ligand and the boron atom to be 3.04 Å. This appears to be ideal for the proposed face–face π–π interaction, which is suggested to be optimal between 3.0–3.5 Å[12] and bodes well for future catalytic investigations using the diol (−)-**1**.

3. Conclusion

In conclusion, we have developed a short (6 step) synthesis of the diol (−)-**1** starting from commercially available α-tetralone in 59% overall yield. We have confirmed both the relative and absolute configuration of (−)-**1** by single crystal X-ray analysis on the parent diol and the derived 4-iodobenzoyl ester (−)-**11**. By simple modification of the reaction conditions it is possible to obtain both enantiomers of the two diastereomeric diols (−)-**1** and (−)-**9** stereo-

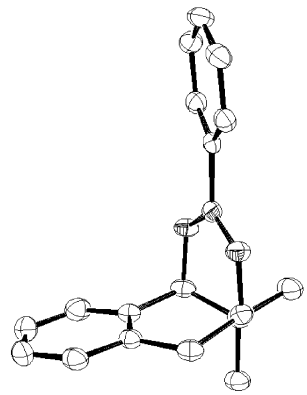


Figure 4. X-Ray crystal structure of **12**.

specifically and in good yield. We have also shown that it is possible to synthesise the hindered secondary alcohol (−)-**8**, in enantiomerically pure form in just five steps starting from α-tetralone. Complexation of the diol (−)-**1** to phenyl boronic acid occurs readily, producing the boronate ester **12** in which the interplanar distance between the boron atom and the aromatic ring is 3.04 Å suggesting that this novel class of ligand may well prove useful in Lewis acid catalysed reactions of α,β-unsaturated ketones. We will report on our findings in these and related areas shortly.

4. Experimental

4.1. General

All ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker DPX-400 spectrometer, with ^{13}C spectra being recorded at 100 MHz. Mass spectra were obtained using a Fisons VG platform II spectrometer. High-resolution mass spectra were obtained by the EPSRC mass spectrometry service, Swansea. Melting points were determined on a Kofler Hot Stage Micro Melting Point Apparatus and are uncorrected. Infrared spectra were recorded in the range 4000–600 cm^{-1} using a Perkin–Elmer 1600 series spectrophotometer as thin films. Optical rotations were measured on an Optical Activity AA-1000 polarimeter at room temperature. Thin layer chromatography (TLC) was performed on Merck 5554 60F silica gel coated aluminium plates and detection was effected with a solution of 10% ceric sulfate in 10% sulfuric acid, followed by heating the plates. Purification of compounds was achieved by medium pressure chromatography using Merck 9385 60 silica gel.

4.1.1. 2,2-Dimethyl-3,4-dihydro-2*H*-naphthalen-1-one (3). Sodium hydride (4.7 g, 119 mmol) was added to a stirred solution of freshly distilled α-tetralone **2** (5 g, 34 mmol) and anhydrous methyl iodide (17 g, 119 mmol)

in benzene (70 mL) at 5°C under an atmosphere of nitrogen. The reaction mixture was stirred at reflux for 4 days and the progress was monitored by TLC (R_f (40% diethyl ether/light petroleum) 0.6). On completion, the reaction mixture was quenched by the dropwise addition of methanol (3 mL) at 0°C. The resulting suspension was separated between ethyl acetate (100 mL) and water (50 mL), washed with saturated sodium hydrogen carbonate solution (2×50 mL), dried over magnesium sulfate and concentrated to give a dark oil. The product was purified by short path distillation under high vacuum to give the title compound **3** (5.64 g, 94%) as a colourless oil, bp 86–89°C (1.0 mm Hg); ν_{max}/cm^{-1} (NaCl plate) 3147–2931, 1672, 1598; δ_H (400 MHz, $CDCl_3$) 8.05 (1H, d, J=7.6 Hz, Ar*H*), 7.45 (1H, dd, J=7.6, 7.6 Hz, Ar*H*), 7.30 (1H, dd, J=7.6, 7.6 Hz, Ar*H*), 7.22 (1H, d, J=7.6 Hz, Ar*H*), 2.98 (2H, t, J=6.3 Hz, ArCH_2), 1.98 (2H, t, J=6.3 Hz, CH_2), 1.14 (6H, s, 2×CH_3); δ_C (100 MHz, $CDCl_3$) 204.0, 142.8, 132.5, 130.7, 128.1, 127.3, 126.0, 41.0, 35.9, 25.1, 23.7; *m/z* (APCI) 175.1 (MH^+); HRMS (ES): MH^+, found 175.1124. $C_{12}H_{15}O$ requires 175.1123.

4.1.2. 2,2-Dimethyl-2*H*-naphthalen-1-one (5). A mixture of **3** (1 g, 5.74 mmol), *N*-bromosuccinimide (1.07 g, 6.03 mmol) and benzoyl peroxide (14.5 mg, 0.06 mmol) in carbon tetrachloride (10 mL) was stirred at reflux for 5 h. The reaction mixture was then filtered through a sinter, washed with dichloromethane and reduced. The crude product was treated with 10% potassium hydroxide in ethanol (10 mL) and the mixture was stirred at 45°C for 6 h, the progress of the reaction being monitored by TLC (R_f (30% dichloromethane/light petroleum) 0.7). The crude reaction mixture was separated between diethyl ether (15 mL) and water (15 mL) and washed with saturated sodium bicarbonate solution (15 mL). After drying over $MgSO_4$, the product was concentrated to give an orange oil. The crude material was purified by vacuum distillation to give the title compound **5** (0.90 g, 89%) as a colourless oil, bp 87–89°C (0.5 mm Hg); ν_{max}/cm^{-1} (NaCl plate) 3496–2925, 1681, 1643; δ_H (400 MHz, $CDCl_3$) 7.98 (1H, d, J=7.5 Hz, Ar*H*), 7.48 (1H, dd, J=7.5, 7.5 Hz, Ar*H*), 7.27 (1H, dd, J=7.5, 7.5 Hz, Ar*H*), 7.15 (1H, d, J=7.5 Hz, Ar*H*), 6.43 (1H, d, J=9.7 Hz, ArC*H*), 6.03 (1H, d, J=9.7 Hz, C*H*), 1.19 (6H, s, 2×CH_3); δ_C (100 MHz, $CDCl_3$) 204.0, 141.6, 138.8, 134.7, 131.8, 128.1, 127.6, 127.5, 122.9, 45.6, 26.3; *m/z* (APCI) 173.2 (MH^+); HRMS (ES): MH^+, found 173.0965. $C_{12}H_{13}O$ requires 173.0965.

4.1.3. (−)-(3*S*,4*R*)2,2-Dimethyl-1a,7b-dihydro-2*H*-1-oxacyclopropa[α]naphthalene-3-one (−)-6. A solution of **5** (0.5 g, 2.91 mmol) and (*R*,*R*)-(−)-*N*,*N*′-bis-(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-manganese(III) chloride (92 mg, 0.15 mmol) in dichloromethane (10 mL) was stirred at 0°C for 5 min. A buffer solution of $NaHPO_4$ (0.05 M, 5.8 mL) and NaOCl (4.5%, 9.7 mL) stirring at 0°C (pH 11) was then added and the reaction mixture was stirred at 0°C for 3 days. After the reaction was complete by TLC (R_f (40% dichloromethane/light petroleum) 0.3) brine (50 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3×50 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated to give a dark oil which was purified by flash column chromatography (40% dichloromethane/light petroleum) to give the title compound (−)-**6** (0.41 g, 75%) as a colourless solid, mp 111–112°C; $[\alpha]_D^{20}$=−50.9 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} (NaCl plate) 3482–2926, 1682, 1590, 1270; δ_H (400 MHz, $CDCl_3$) 7.86 (1H, d, J=7.6 Hz, Ar*H*), 7.48 (2H, m, Ar*H*), 7.39 (1H, m, Ar*H*), 4.00 (1H, d, J=4.0 Hz, ArC*H*), 3.52 (1H, d, J=4.0 Hz, C*H*), 1.45 (3H, s, CH_3), 1.06 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 200.7, 138.7, 133.6, 130.9, 130.0, 129.9, 128.9, 61.4, 53.1, 43.8, 24.0, 21.8; *m/z* (APCI) 189.1 (MH^+); HRMS (CI, NH_3): MNH_4^+, found 206.1181. $C_{12}H_{16}N_1O_2$ requires 206.1182.

4.1.4. (±)-2,2-Dimethyl-1a,7b-dihydro-2*H*-1-oxacyclopropa[α]naphthalene-3-one (±)-6. A solution of **5** (209 mg, 1.21 mmol) in dichloromethane (3 mL) was cooled to 0°C under nitrogen. The solution was treated with *meta*-chloroperoxybenzoic acid (50%, 448 mg, 1.3 mmol) in one portion and allowed to warm to room temperature overnight. When the reaction was complete by TLC (R_f (40% dichloromethane/light petroleum) 0.3) the reaction mixture was extracted with diethyl ether (2×20 mL), washed with sodium bicarbonate solution (2×10 mL), water (10 mL) and brine (10 mL), dried over magnesium sulfate and concentrated to give a colourless oil. The product was purified by flash column chromatography (40% dichloromethane/light petroleum) to give the title compound (±)-**6** (213 mg, 94%), which was identical to an authentic sample. GC-FID analysis on a chiral stationary phase with a chrompack column (CP7532): injection/detection 250°C/300°C isothermal, separated an authentic racemic sample (t_1=41.7 min; t_2=41.9 min).

4.1.5. (−)(1*R*,3*R*)-2,2-Dimethyl-1,2,3,4-tetrahydronaphthalene-1,3-diol (−)-1. To 10% Pd/C catalyst (35 mg) was added a solution of (−)-**6** (350 mg, 1.86 mmol) in ethyl acetate (3 mL) and methanol (75 μL, 1.86 mmol). The reaction mixture was stirred under an atmosphere of hydrogen for 10 min. On completion by TLC (R_f (40% diethyl ether/light petroleum) 0.1) the reaction mixture was filtered through Celite® and concentrated to give an orange oil. The crude reaction mixture was then stirred with di-*iso*butylaluminium hydride (1 M in hexanes, 4.74 mL, 4.74 mmol) in tetrahydrofuran (10 mL) at −78°C for 30 min. After quenching with hydrochloric acid (2N, 5 mL) the organic phase was partitioned between diethyl ether (10 mL) and water (10 mL) and the organic phase was washed with sodium bicarbonate solution (10 mL), dried over magnesium sulfate and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (40% diethyl ether/light petroleum) gave the title compound (−)-**1** (267 mg, 75 %) as a colourless solid, mp 64.4–65.4°C; $[\alpha]_D^{20}$=−77.0 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} (NaCl plate) 3650–3200, 3391–2931; δ_H (400 MHz, $CDCl_3$) 7.33 (1H, m, Ar*H*), 7.19 (2H, m, Ar*H*), 7.08 (1H, m, Ar*H*), 4.21 (1H, s, ArC*H*OH), 3.83 (1H, dd, J=3.9, 4.6 Hz, ArC*H*H), 3.08 (1H, dd, J=17.7, 4.6 Hz, ArCH*H*), 2.89 (1H, dd, J=17.7, 3.9 Hz, ArCH$_2$C*H*OH), 2.51 (2H, s, 2×O*H*), 1.19 (3H, s, CH_3), 0.88 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 138.0, 132.2, 130.3, 129.7, 128.4, 127.1, 77.3, 75.0, 38.2, 35.8, 24.2, 21.1; *m/z* (APCI) 193.1 (MH^+); HRMS (EI): MH^+, found 192.1149. $C_{12}H_{16}O_2$ requires 192.1150.

Crystal data. $C_{12}H_{16}O_2$, crystallises from diethyl ether/light

petroleum as colourless prisms. Monoclinic, space group $P2(1)n$, a=10.420(4), b=10.073(2), c=10.842(5) Å, α=90.00, β=115.30(3), γ=90.00°, U=1028.8(7) Å^3, Z=4, D_c=1.241 mg m^{-3}, M=192.258, T=293(2) K. 2196 reflections collected, 2081 independent (R_{int}=0.0098) which were used in calculations. R_1=0.0362, wR_2=0.0937 for observed unique reflections [$F^2>2\sigma(F^2)$] and R_1=0.0470, wR_2=0.1005 for all 2081 unique reflections. The max. and min. residual electron densities on the final difference Fourier map were 0.321 and −0.211 e Å^{-3}, respectively. Cambridge Crystallographic Data Centre (CCDC) reference number 206519.

4.1.6. 2,2-Dimethyl-1,2,3,4-tetrahydronaphthalene-1,3-diol phenyl boronic acid adduct (12). *Crystal data*. $C_{18}H_{19}B_1O_2$, crystallises from diethyl ether as colourless blocks. Monoclinic, space group $P2(1)/c$, a=10.139(9), b=13.664(10), c=12.044(10) Å, α=90.00, β=112.92(2), γ=90.00°, U=1537(2) Å^3, Z=4, D_c=1.202 mg m^{-3}, M=278.159, T=293(2) K. 6180 reflections collected, 3018 independent (R_{int}=0.04081) which were used in calculations. R_1=0.0357, wR_2=0.0909 for observed unique reflections [$F^2>2\sigma(F^2)$] and R_1=0.0542, wR_2=0.0999 for all 3018 unique reflections. The max. and min. residual electron densities on the final difference Fourier map were 0.224 and −0.147 e Å^{-3}, respectively. Cambridge Crystallographic Data Centre (CCDC) reference number 206520.

4.1.7. (−)(1*R*,3*R*)-2,2-Dimethyl-1,2,3,4-tetrahydronaphthalene-1,3-diol-bis-4-iodobenzoyl ester (−)-11. The diol (−)-**1** (50 mg, 0.26 mmol) was added to a stirred solution of triethylamine (0.5 mL), 4-iodobenzoylchloride (173.2 mg, 0.65 mmol) and *N*,*N*-dimethylaminopyridine (4 mg) in dichloromethane (5 mL), and the resulting mixture was stirred at reflux for 16 h. After cooling to room temperature, the reaction mixture was separated between diethyl ether (5 mL) and water (5 mL). The aqueous phase was extracted with diethyl ether (3×5 mL) and the combined organic phases were dried over magnesium sulfate, filtered and concentrated to give a pale yellow oil. The crude material was purified by flash column chromatography (10% diethyl ether/light petroleum) to give the title compound (−)-**11** (130 mg, 76%) as a colourless solid. X-Ray quality crystals were grown from diethyl ether, mp 121–122°C; $[\alpha]_D^{20}$=−5.0 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} (NaCl plate) 3027, 1722, 1548; δ_H (400 MHz, $CDCl_3$) 7.68 (8H, m, Ar*H*), 7.10 (4H, m, Ar*H*), 6.15 (1H, s, ArC*H*O), 5.26 (1H, dd, *J*=7.7, 5.8 Hz, $ArCH_2CH$), 3.28 (1H, dd, *J*=17.3, 5.8 Hz, ArC*H*), 3.03 (1H, dd, *J*=17.3, 7.7 Hz, ArC*H*), 1.13 (3H, s, CH_3), 1.07 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 164.9, 164.7, 136.9, 136.8, 132.5, 131.3, 130.3, 130.2, 130.1, 128.7, 128.4, 127.9, 127.1, 126.9, 125.8, 124.9, 75.9, 73.9, 37.6, 30.9, 22.9, 16.3; *m*/*z* (APCI) 652.9 (MH$^+$); HRMS (CI, NH_3): MNH_4^+, found 669.9943. $C_{26}H_{26}N_1O_4I_2$ requires 669.9951.

Crystal data. $C_{26}H_{22}I_2O_4$, crystallises from diethyl ether as colourless needles. Monoclinic, space group $P2(1)$, a=8.148(2), b=5.8840(10), c=25.697(5) Å, α=90.00, β=90.01(3), γ=90.00°, U=1232.0(4) Å^3, Z=2, D_c=1.758 mg m^{-3}, M=652.268, T=293(2) K. 2445 reflections collected, 2394 independent (R_{int}=0.0282) which were used in calculations. R_1=0.0439, wR_2=0.1051 for observed unique reflections [$F^2>2\sigma(F^2)$] and R_1=0.0947, wR_2=0.1353 for all 2394 unique reflections. The max. and min. residual electron densities on the final difference Fourier map were 1.223 and −0.875 e Å^{-3}, respectively. Cambridge Crystallographic Data Centre (CCDC) reference number 206521.

4.1.8. (−)(*R*)-2,2-Dimethyl-1,2,3,4-tetrahydronaphthalene-3-ol (−)-8. The epoxide (−)-**6** (0.5 g, 2.66 mmol) was stirred with 10% palladium on carbon (50 mg) in methanol (10 mL), under an atmosphere of hydrogen for 16 h. The reaction mixture was filtered through Celite® and concentrated to give the title compound (−)-**8** (421 mg, 90%) as a colourless oil; $[\alpha]_D^{20}$=−25.0 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} (NaCl plate) 3655–3200, 3395–2935, 1087; δ_H (400 MHz, $CDCl_3$) 7.04 (4H, m, Ar*H*), 3.65 (1H, dd, *J*=5.5, 7.6 Hz, $ArCH_2CHOH$), 3.04 (1H, dd, *J*=17.1, 5.5 Hz, ArCH*H*CHOH), 2.71 (1H, dd, *J*=17.1, 7.6 Hz, ArC*H*HCHOH), 2.65 (1H, d, *J*=16.5 Hz, ArC*H*H), 2.49 (1H, d, *J*=16.5 Hz, ArCH*H*), 0.98 (3H, s, CH_3), 0.88 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 135.4, 133.6, 129.5, 129.4, 125.9, 125.7, 74.2, 41.3, 34.9, 34.3, 26.3, 21.5; *m*/*z* (APCI) 177.1 (MH$^+$); HRMS (ES): MH$^+$, found 177.1278. $C_{12}H_{16}O_1$ requires 177.1279.

4.1.9. (−)(1*S*,3*R*)-*trans*-2,2-Dimethyl-1,2,3,4-tetrahydronaphthalene-1-3-diol (−)-9. To a solution of the epoxide (−)-**6** (200 mg, 1.06 mmol) in anhydrous tetrahydrofuran (5 mL) at 0°C was added di*iso*butylaluminium hydride (1 M in hexanes, 5.3 mL, 5.3 mmol) dropwise. After stirring at this temperature for 2 h, the reaction mixture was quenched by cautious dropwise addition of HCl (2 M). The reaction mixture was diluted with diethyl ether (10 mL) and washed with brine (10 mL). After drying over magnesium sulfate, the product was concentrated to give a pale oil. The crude material was purified by crystallisation from diethyl ether to give the title compound (−)-**9** (172 mg, 85%) as a colourless crystalline solid, mp 66.5–67.5°C; $[\alpha]_D^{20}$=−15.0 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} (NaCl plate) 3650–3200, 3390–2930; δ_H (400 MHz, $CDCl_3$) 7.32 (1H, m, Ar*H*), 7.15 (2H, m, Ar*H*), 7.05 (1H, m, Ar*H*), 4.93 (1H, s, ArC*H*OH), 4.20 (1H, dd, *J*=8.7, 6.0 Hz, $ArCH_2CHOH$), 3.15 (1H, dd, *J*=17.0, 6.0 Hz, ArCH*H*), 2.67 (1H, dd, *J*=17.0, 8.7 Hz, ArC*H*H), 1.56 (2H, s, O*H*), 1.18 (3H, s, CH_3), 0.96 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 135.7, 133.8, 130.0, 129.1, 128.2, 126.6, 70.4, 69.6, 39.4, 34.8, 23.8, 19.7; *m*/*z* (APCI) 193.1 (MH$^+$); HRMS (EI): MH$^+$, found 193.1148. $C_{12}H_{14}O_2$ requires 193.1150.

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