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Formal total synthesis of ottelione using iridium-catalyzed oxidative desymmetrization

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ABSTRACT

A catalytic asymmetric synthesis of a key intermediate for ottelione has been achieved using oxidative desymmetrization as the critical step. This oxidative desymmetrization was efficiently promoted by an iridium diamine complex to give the desired hydroxy ketone in >99% ee and 60% yield.

1. Introduction

Catalytic asymmetric synthesis is an ideal method for synthesizing optically active compounds. Today, this technology is widely used in the pharmaceutical and flavor industries.[1]

As shown in Scheme 1, Eq. 1, asymmetric reduction is an efficient method for the preparation of chiral alcohols compared to the oxidative kinetic resolution of racemic secondary alcohols, since the maximum conversion of the latter process is only 50% (Scheme 1, Eq. 2).

However, the reductive strategy is not effective for the preparation of hydroxy ketones due to overreduction (Scheme 1, Eq. 3). On the other hand, oxidative desymmetrization can be a powerful pathway for preparation of hydroxy ketones if the chiral recognition of the catalyst is excellent (Scheme 1, Eq. 4).

Recently we developed an efficient oxidative desymmetrization of *meso* diols using a chiral Ir complex. Specifically we found two different Ir catalysts that are effective in mediating the oxidative desymmetrization of *meso* 1,3-indandiol (Scheme 2).[2]

Furthermore, we applied the oxidative desymmetrization to the synthesis of ottelione. Otteliones A and B (**1a** and **1b**, Fig. 1) were first isolated in 1998 by Ayyad and Hoye et al. from the freshwater plant *Ottelia alismoides*, which was collected from the Nile Delta in Egypt.[3] Ottelione A and B have attracted much attention as they exhibit prominent biological properties such as antitumor activity.[4] It has also been reported that **1a** inhibits tubulin polymerization into microtubules (IC_{50}=1.2 μM).[4] The presence of the novel bicyclic hydrindane skeleton with four contiguous stereogenic centers and highly rare 4-methylene-2-cyclohexenone substructure together with the important biological properties and difficulty in obtaining the compound from its natural source (only 0.0009% of the dried weight of the sample)[4] make ottelione a challenging target for synthetic chemists.

In 2002, Mehta's group accomplished the first elegant total synthesis of racemic (±)-ottelione A.[5a] In 2003, Mehta[5b] and Katoh's[6] group independently succeeded in the enantioselective total synthesis of otteliones A and B. Recently Clive,[7a,b] Ryu[7c] and Sha[7d] also reported the enantioselective synthesis of otteliones A and B. Our previous route[6] started from (−)-quinic acid. Recently we succeeded in developing a catalytic asymmetric synthesis of a key intermediate to otteliones A, B and *epi*-ottelione A (Scheme 3).

Herein we describe the details of our catalytic asymmetric synthesis of ottelione.

2. Results and discussion

2.1. Synthesis of *meso* diols

As depicted in Scheme 3, we anticipated the synthesis of common key intermediate **2** by oxidative desymmetrization of 1,4-diols **5a**–**c**. Moreover, we surmised that variation of the R^1 and R^2

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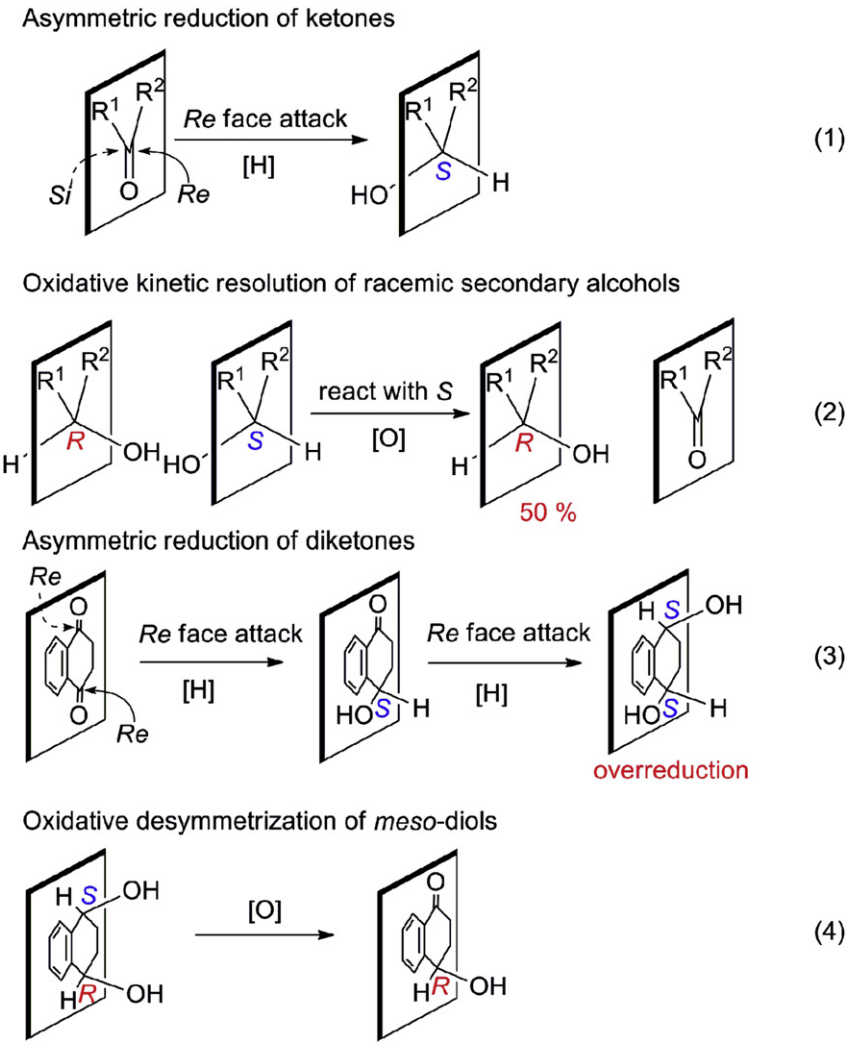
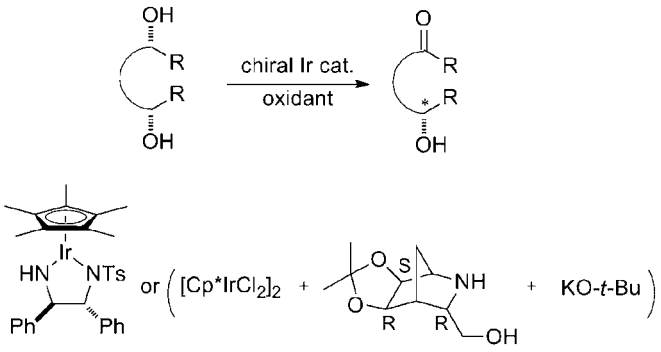


Scheme 1. Comparison of synthetic methods for preparation of chiral alcohols.



Scheme 2. Oxidative desymmetrization of secondary diols.

protecting groups in **5** could allow for tuning of the reactivity and selectivity in the oxidative desymmetrization step.

Our initial attempts toward the synthesis of **5** with osmium tetroxide-catalyzed dihydroxylation of **4** (derived from cyclopentadiene and *p*-benzoquinone) resulted in the formation of an undesired regio isomer, which was confirmed after treatment with 2,2-dimethoxypropane (Scheme 4). The structure and stereochemistry of adduct **6** were unambiguously determined by single X-ray crystallographic analysis as depicted in Figure 2.

To avoid this problem, the norbornene double bond in **4**[8] was protected through intramolecular bromoetherification[9] to give **7** (Scheme 5). Dihydroxylation of the cyclohexene double bond in **7** proceeded smoothly from the *exo-face* to furnish triol **8** in 73% yield. Protection of the *cis* diol moiety as the isopropylidene acetal afforded **9a** in 85% yield, and reductive cleavage of the bromo ether

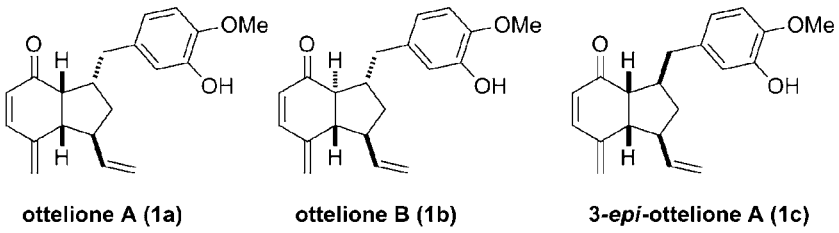
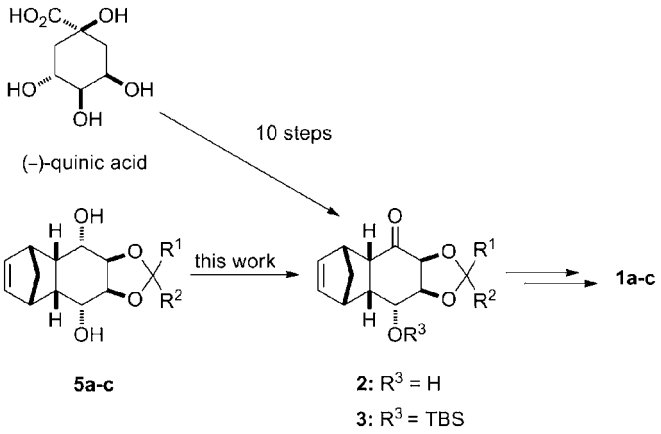


Figure 1. Structures of ottelione A, ottelione B and 3-*epi*-ottelione A.



Scheme 3. Our synthetic route to the otteliones.

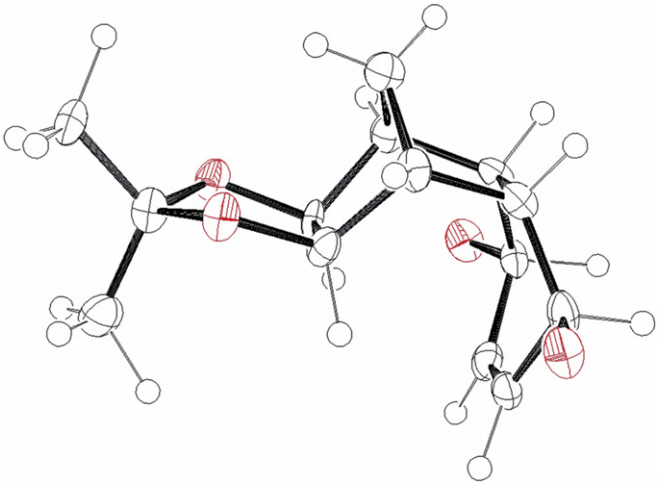


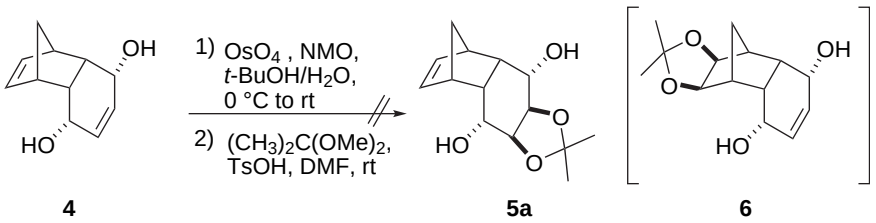
Figure 2. X-ray crystal structure of **6**.

gave the requisite *meso* diol **5a** in 88% yield. In a similar manner, *meso* diols **5b** and **5c** with ethylidene or cyclohexylidene acetal groups, respectively, were obtained in good yields. In the case of the ethylidene acetal, a 3.3:1 diastereomeric mixture of **5b** was produced, which was then separated after reductive cleavage by flash column chromatography. The stereochemistry of the adducts **5b**α and **5b**β were determined based on NOE experiments (see Supplementary data).

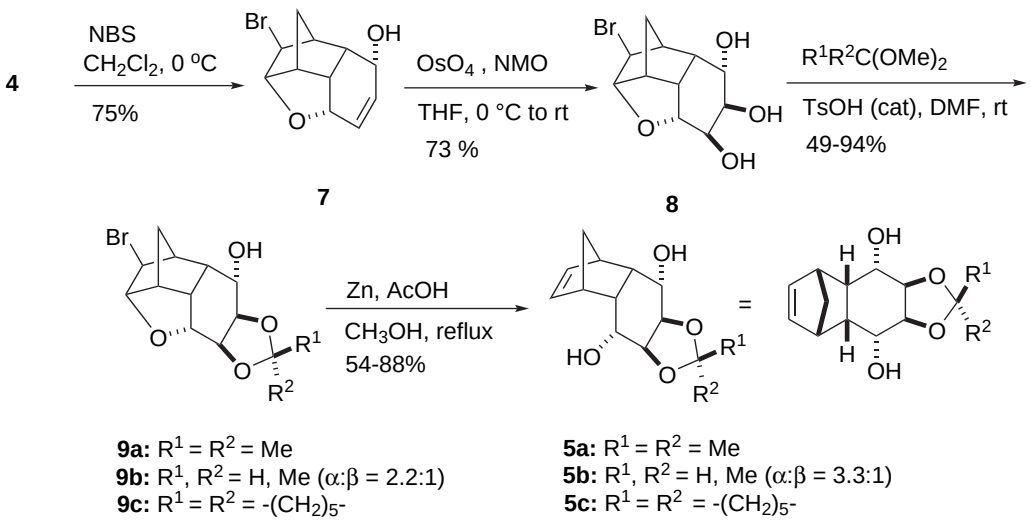
2.2. Oxidative desymmetrization of *meso* diols

After successfully establishing routes for the synthesis of these *meso* diols, efforts were then directed to oxidative desymmetrization of compounds **5a**–**c** using an Ir catalyst. For initial optimization of the reaction conditions, **5a** was chosen as the model substrate. The results are summarized in Table 1. The catalyst derived from amino alcohol ligand **11** afforded the desired compound **2a** in 20% ee (entry 1). Screening of other ligands revealed that *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN) gave the best result, providing **2a** in 60% yield with >99% ee (entry 4). The choice of hydrogen acceptor was then examined. It is known that cyclohexanone is a stronger acceptor than acetone.[10] Replacement of cyclohexanone with acetone thus not surprisingly led to lower conversions (entry 4 vs 5).

It is important to note, however, that no overoxidation products were detected in the reaction mixture. Increasing the amount of cyclohexanone to 60 equiv in order to drive the equilibrium toward

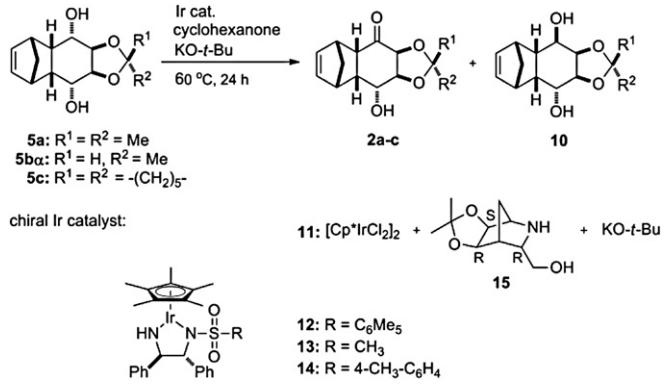


Scheme 4. Attempt for the synthesis of **5**.



Scheme 5. Synthesis of *meso* diols **5**.

Table 1
Optimization of reaction conditions for oxidative desymmetrization of *meso* diols[a]



Entry	Diol	Catalyst	Hydroxy ketone			**10**[d] (%)
			No.	Yield[b] (%)	ee[c] (%)	
1[e,f]	**5a**	**11**	**2a**	66	20	4
2	**5a**	**12**	**2a**	7	—	—
3	**5a**	**13**	**2a**	51	92	30
4	**5a**	**14**	**2a**	60	>99	13
5[g]	**5a**	**14**	**2a**	5	90	57
6	**5bα**	**14**	**2bα**	51	95	ND[h]
7	**5c**	**14**	**2c**	63	97	ND[h]

[a] Unless otherwise noted, the reaction was carried out with *meso* diol (0.08 mmol), Ir catalyst (10 mol %), cyclohexanone (30 equiv), and KO-*t*-Bu (8 mol %) at 60 °C for 24 h.
[b] Isolated yield after flash chromatography on the silica gel.
[c] Determined by HPLC on a chiral stationary phase.
[d] Determined by ^{1}H NMR.
[e] In situ prepared catalyst in CH_2Cl_2 was used.
[f] The absolute configuration of **2a** was determined to be 5R.[2] All others were assigned by analogy.
[g] Acetone was used as oxidant.
[h] ND=not determined.

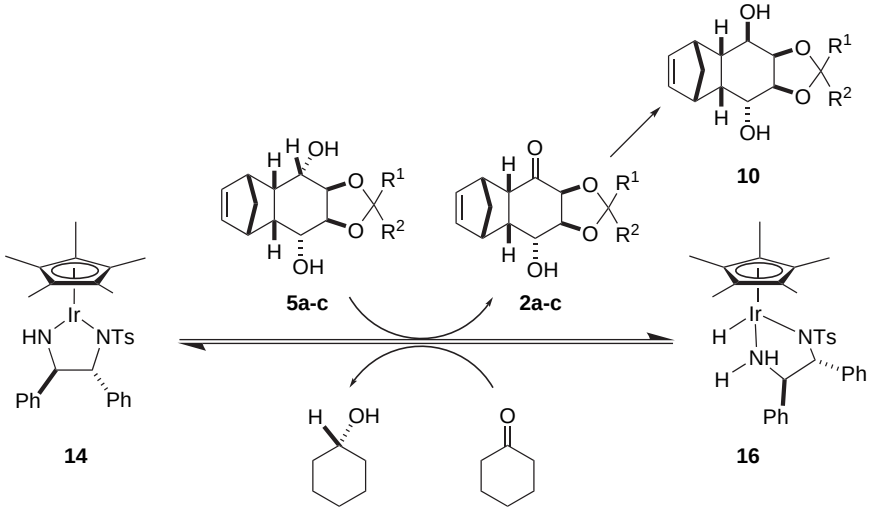
complete oxidation of the alcohol resulted in a slight decrease in the optical purity of **2a** without significant increase in yield, while a lower yield was observed with a lesser amount of cyclohexanone (15 equiv). Examination of a range of bases such as KOH, Na_2CO_3, and K_2CO_3 showed that KO-*t*-Bu was superior with respect to chemical yield and enantiomeric excess. In the absence of base, low conversion to the desired compound was observed. Lowering the reaction temperature or catalyst loading also led to a reduction in the yield of the target compound.

Similar to compound **5a**, reaction of **5b**α and **5c** proceeded smoothly and afforded the corresponding products in excellent enantiomeric excess (entries 6 and 7). These results indicate that the substitution pattern on the protected diol has no effect on the enantioselectivity.[11]

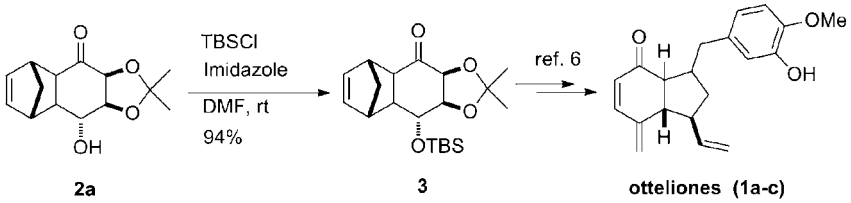
Notably, byproduct diol **10** was also observed in these reactions. The mechanistic rationale for formation of **10** is provided in Scheme 6. In the catalytic reaction, the amido Ir complex **14** dehydrogenates *meso* diols leading to formation of the amine hydride Ir complex **16**. It is well known that alcohol dehydrogenation takes place reversibly via a six-membered pericyclic transition state.[12] The Ir hydride complex reacts with cyclohexanone to transfer the hydride and proton to the C=O functionality, producing cyclohexanol. As the conversion increases, the rate of the reverse reaction becomes higher and **2** can also act as a hydrogen acceptor. Thus, hydrogen transfer between the product and the Ir hydride complex provides the hydrogenated *cis* and *trans* alcohols and regenerates the active catalyst.

2.3. Completion of the formal total synthesis of otteliones

Finally, treatment of **2a** (>99% ee) with TBSCl and imidazole in DMF at rt resulted in clean conversion to the desired TBS-protected alcohol **3** in 94% yield. The optical rotation and the spectral data of **3** were in accordance with literature.[17] The synthesis of (+)-ottelione A, (−)-ottelione B, and (+)-3-epi-ottelione A from the intermediate **3** has been reported by Katoh.[6] Thus, a formal total synthesis of otteliones has been accomplished (Scheme 7).



Scheme 6. Possible mechanism for the Ir-mediated oxidative desymmetrization.



Scheme 7. Synthesis of ottelione intermediate **3**.

3. Conclusion

In conclusion, we have accomplished an efficient catalytic asymmetric synthesis of a key intermediate **3** for the preparation of ottelione A in eight steps and 22% overall yield using the inexpensive and abundant starting materials cyclopentadiene and *p*-benzoquinone. A special feature of the synthesis is the use of an Ir catalyst for selective oxidation of one of the hydroxyl groups in *meso* alcohols. It is likely that our approach to the formal synthesis of ottelione may be extended to prepare analogues of these unique and biologically active natural compounds.

4. Experimental

4.1. General

Melting points were obtained with a Yanagimoto Micro Melting Point Apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO FT/IR 4100 spectrometer. ^{1}H NMR spectra were recorded on a JEOL EX-270 NMR, JEOL JNM-LA400 NMR, or JEOL JNM-LA600 NMR spectrometer with tetramethylsilane used as an internal standard. The chemical shifts are reported in parts per million on the δ scale downfield from tetramethylsilane, and signal patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. ^{13}C NMR spectra were measured on a JEOL EX-270 NMR or JEOL JNM-LA400 NMR spectrometer at 67.7 or 100 MHz. FAB mass spectra were recorded on a JEOL JMS-700 and JMS-M600 spectrometer; *m*-nitrobenzyl alcohol was used as the matrix. ESI-TOF mass spectra were recorded on a JEOL JMS-T100LC. Elemental analysis was performed on PERKIN–ELMER 2400. Optical rotations were measured with HORIBA SEPA-300 polarimeter. HPLC analyses were performed on JASCO HPLC system (JASCO PU 2080 pump and MD-2010 UV/Vis detector). Anhydrous THF and toluene were purchased from Kanto Chemicals and used without any purification. Other solvents were purified prior to use by standard techniques. Column chromatography was conducted on Kishida Silica Gel 60 (63–200 μm). Catalysts **12**,[13] **13**,[14] **14**,[15] and ligand **15**[16] were prepared according to literature procedures. The spectral data of **2a**, **5a**, **7**, **8**, **9a**, **10** and determination of the absolute configuration of the *trans*-diol **10** have been reported in a previous paper.[2]

Crystallographic data for the structures **6** have been deposited at the Cambridge Crystallographic Data Center and allocated the deposit number CCDC 780747.

4.2. General procedure for the oxidative desymmetrization of *meso* alcohols with (*R*,*R*)-14

A 1 mL test tube equipped with a magnetic stirring bar was charged with 15.4 mg (22.2 μmol) of (*R*,*R*)-**14**, 65 mg (0.22 mmol) of *meso* diol, and 2 mg (17.7 μmol) of KO-*t*-Bu. Then 69 μL (6.66 mmol, 30 mol equiv) of cyclohexanone was added to the above mixture and stirred at 60 °C for 24 h. The mixture was passed through a short silica gel column (30% MeOH in ethyl acetate) to remove the catalyst. Concentration under reduced pressure gave the crude mixture, which was purified by silica gel column chromatography to give the desired product.

*4.2.1. (1R,4S,4aR,5R,6S,7S,8aS)-5-Hydroxy-6,7-O-ethylidenedioxy-1,4,4a,5,6,7,8,8a-octahydro-endo-1,4-methano-naphthalen-8-one (**2b**α).* IR ν_{max}/cm^{-1} (neat): 3472, 2936, 1714, 1412, 1339; ^{1}H NMR (CD_3OD) δ: 6.23 (1H, dd, *J*=5.5, 3.0 Hz), 6.14 (1H, dd, *J*=5.5, 3.0 Hz), 4.98 (1H, q, *J*=4.9 Hz), 4.56 (1H, s), 4.20 (1H, dd, *J*=8.5, 7.1 Hz), 4.09 (1H, d, *J*=8.5 Hz), 3.96 (1H, dd, *J*=6.6, 5.5 Hz), 3.19 (1H, dd, *J*=10.2, 3.9 Hz), 3.10 (1H, s), 2.99 (2H, ddd, *J*=10.2, 5.5, 3.3 Hz), 1.52 (1H, d, *J*=8.1 Hz), 1.41 (1H, d, *J*=8.1 Hz), 1.36 (3H, d, *J*=4.9 Hz); ^{13}C NMR (CD_3OD) δ: 210.6, 137.6, 134.9, 102.9, 81.8, 79.7, 71.0, 52.4, 50.9, 47.6, 46.7, 46.3, 19.4; FAB-HRMS (*m*/*z*): [M+H]$^+$ calculated for $C_{13}H_{17}O_4$: 237.1127; found: 237.1145; $[\alpha]_D^{25}$ +75.1 (*c* 1.18, MeOH) (95% ee); enantioselectivity was determined by chiral stationary phase HPLC (Daicel CHIRALCEL AD-H, 0.46 cm)×25 cm, detection 210 nm, *n*-hexane/*i*-PrOH=9:1, flow rate=0.5 mL/min, t_R=41 min (major), t_R=49 min (minor).

*4.2.2. (1R,4S,4aR,5R,6S,7S,8aS)-5-Hydroxy-6,7-O-cyclohexylidenedioxy-1,4,4a,5,6,7,8,8a-octahydro-endo-1,4-methano-naphthalen-8-one (**2c**).* Mp 146–150 °C; IR ν_{max}/cm^{-1} (KBr): 3487, 2939, 1721, 1103; ^{1}H NMR (CD_3OD) δ: 6.20 (1H, dd, *J*=5.6, 2.9 Hz), 6.12 (1H, dd, *J*=5.6, 2.9 Hz), 4.35 (1H, dd, *J*=8.1, 6.6 Hz), 4.15 (1H, d, *J*=8.1 Hz), 3.99 (1H, t, *J*=5.9 Hz), 3.22 (1H, dd, *J*=10.4, 3.9 Hz), 3.02 (3H, m), 1.66–1.38 (13H, m); ^{13}C NMR (CD_3OD) δ: 211.4, 137.5, 134.8, 112.2, 80.6, 79.0, 71.4, 52.2, 50.3, 47.2, 46.4, 46.3, 37.3, 34.4, 26.2, 24.5, 24.7; FAB-HRMS (*m*/*z*): [M+H]$^+$ calculated for $C_{17}H_{23}O_4$: 291.1596; found: 291.1583; $[\alpha]_D^{22}$ +86.6 (*c* 0.75, $CHCl_3$) (97% ee); enantioselectivity was determined by chiral stationary phase HPLC (Daicel CHIRALCEL AD-H, 0.46 cm)×25 cm, detection 215 nm, *n*-hexane/*i*-PrOH=9:1, flow rate=0.5 mL/min, t_R=28 min (major), t_R=35 min (minor).

4.3. (1*R*,4*S*,4a*R*,5*R*,6*S*,7*S*,8a*S*)-5-*tert*-Butyldimethylsiloxy-6,7-*O*-isopropylidenedioxy-1,4,4a,5,6,7,8,8a-octahydro-*endo*-1,4-methano-naphthalen-8-one (3)

To a solution of **2a** (10.6 mg, 0.042 mmol) in DMF (40 mL) were added imidazole (11.9 mg, 0.17 mmol) and TBSCl (18.95 mg, 0.126 mmol) at rt. After stirring of the mixture for 9 h at rt, HCl (1 M) was added and the mixture was extracted with EtOAc (3×25 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (4:1 hexane/EtOAc) to give **3** (14.5 mg, 94%) as a white solid. ^{1}H NMR ($CDCl_3$) δ: 6.20 (1H, dd, *J*=5.6, 3.1 Hz), 6.12 (1H, dd, *J*=5.6, 3.1 Hz), 4.22 (1H, dd, *J*=8.3, 6.9 Hz), 4.12 (1H, d, *J*=8.3 Hz), 3.99 (1H, t, *J*=6.3 Hz), 3.18 (1H, dd, *J*=10.1, 3.9 Hz), 3.11 (1H, s), 3.08 (1H, s), 2.93–2.86 (1H, m), 1.54 (1H, d, *J*=8.4 Hz), 1.47 (3H, s), 1.37 (1H, d, *J*=8.4 Hz), 1.30 (3H, s), 0.89 (9H, s), 0.08 (3H, s), 0.07 (3H, s); ^{13}C NMR (CD_3OD) δ: 208.7, 137.0, 133.1, 109.9, 79.7, 78.1, 71.6, 51.6, 49.6, 46.6, 45.7, 45.2, 26.5, 25.8, 24.0, 18.0, −4.5, −4.9; $[\alpha]_D^{20}$ +46.3 (*c* 1.01, $CHCl_3$) (lit.[17] $[\alpha]_D^{20}$ +46.7 (*c* 1.01, $CHCl_3$)).

4.4. (1*R**,4*S**,4a*R**,5*R**,6*S**,7*R**,8*S**,8a*S**)-(*O*-Ethylidenedioxy)-1,4,4a,5,6,7,8,8a-octahydro-1,4-methano-naphthalene-5,8-diols (5bα and 5bβ)

A mixture of **9b** (140 mg, 0.44 mmol) and activated Zn (1.15 g, 17.65 mmol) in MeOH (4 mL) and AcOH (0.75 mL) was stirred at 65 °C for 5 h and then filtered through Celite.

The filtrate was poured into saturated aqueous $NaHCO_3$ solution and extracted with ether. The organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2:1 hexane/EtOAc) to give the *meso* diols **5b**α (43 mg, 41%) and **5b**β (14 mg, 13%) as white solids.

*4.4.1. Compound **5b**α.* Mp 192–194 °C; IR ν_{max}/cm^{-1} (KBr): 3263, 2977, 2926, 2869, 1409, 1125, 1051; ^{1}H NMR (CD_3OD) δ: 6.09–6.03 (2H, m), 4.81 (1H, q, *J*=4.8 Hz), 3.85–3.68 (4H, m), 3.02–2.95 (2H, m), 2.73–2.66 (2H, m), 1.47 (1H, d, *J*=8.1 Hz), 1.34–1.27 (4H, m); ^{13}C NMR (CD_3OD) δ: 135.6, 100.9, 80.3, 72.2, 52.5, 45.7, 45.3, 19.6; FABMS (*m*/*z*): 239 [M+H]$^+$. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.34; H, 7.83.

*4.4.2. Compound **5b**β.* Mp 208–209 °C; IR ν_{max}/cm^{-1} (KBr): 3287, 2983, 1153, 1051; ^{1}H NMR (CD_3OD) δ: 6.11–6.02 (2H, m), 5.09 (1H, q,

J=4.8 Hz), 3.97–3.84 (4H, m), 3.08–2.97 (2H, m), 2.77–2.65 (2H, m), 1.46 (1H, d, J=8.1 Hz), 1.33–1.21 (4H, m); ^{13}C NMR (CD_3OD) δ: 136.0, 99.3, 80.9, 70.1, 52.2, 45.7, 44.4, 19.3; FABMS (m/z): 239 $[M+H]^+$. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.36; H, 7.86.

4.5. (1*R**,4*S**,4a*R**,5*R**,6*S**,7*R**,8*S**,8a*S**)-(*O*-Cyclohexylidenedioxy)-1,4,4a,5,6,7,8,8a-octahydro-1,4-methano-naphthalene-5,8-diol (5c)

A mixture of **9c** (336 mg, 0.9 mmol) and activated Zn (2.4 g, 36.2 mmol) in MeOH (9.6 mL) and AcOH (1.5 mL) was stirred at 65 °C for 2 h and then filtered through Celite. The filtrate was poured into saturated aqueous $NaHCO_3$ solution and extracted with ether. The organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2:1 hexane/EtOAc) to give the *meso* diol **5c** (183 mg, 69%) as a white solid. Mp 214–216 °C; IR ν_{max}/cm^{-1} (KBr): 3491, 2956, 1072, 944; ^{1}H NMR (CD_3OD) δ: 6.07 (2H, m), 4.60 (2H, s), 3.86–3.80 (4H, m), 2.99 (2H, s), 2.70 (2H, s), 1.62–1.61 (4H, m), 1.53–1.52 (4H, m), 1.46 (1H, d, J=8.1 Hz), 1.39 (2H, s), 1.30 (1H, d, J=8.1 Hz); ^{13}C NMR (CD_3OD) δ: 135.7, 109.8, 79.0, 72.8, 52.5, 45.8, 45.2, 37.9, 34.3, 26.5, 25.0, 24.6; FABMS (m/z): 293 $[M+H]^+$. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.56; H, 8.48.

4.6. (1*R**,2*S**,3*R**,4*S**,4a*R**,5*R**,8*S**,8a*S**)-(*O*-Isopropylidenedioxy)-1,2,3,4,4a,5,8,8a-octahydro-1,4-methano-naphthalene-5,8-diol (6)

To a stirred solution of **4** (100 mg, 0.56 mmol) in H_2O/*t*-BuOH (1:3, 6.2 mL) was added NMO (328 mg, 2.8 mmol) and stirred for 10 min. After cooling the reaction mixture to 0 °C, OsO_4 (0.04 M in *t*-BuOH, 0.42 mL, 0.017 mol) was added drop wise over 30 min. The reaction was warmed to rt and stirred for a further 13 h. The reaction mixture was carefully quenched by addition of Na_2SO_3 (60 mg). After separation of Na_2SO_3, volatile materials were evaporated, and then the residue was extracted with EtOAc (3×25 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give crude product, which was used directly in the next step of reaction without further purification.

To a stirred solution of crude product (50 mg) and 2,2-dimethoxypropane (0.58 mL, 4.72 mmol) in DMF (0.1 mL) was added *p*-toluenesulfonic acid (17.9 mg, 0.094 mmol) and the reaction mixture was stirred for 24 h at rt. The reaction was quenched by addition of 1 mL water. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (1:2 hexanes/EtOAc) yields product **6** (37 mg, 62%) as a white solid.

IR ν_{max}/cm^{-1} (KBr): 3285, 1647, 1058; ^{1}H NMR (CD_3OD) δ: 5.59 (2H, s), 4.56 (1H, s), 4.33–4.25 (4H, m), 2.50–2.44 (2H, m), 2.41–2.36 (2H, m), 1.84 (1H, d, J=10.0 Hz), 1.34 (3H, s), 1.18 (3H, s), 1.13 (1H, d, J=10.0 Hz); ^{13}C NMR (CD_3OD) δ: 132.1, 108.8, 79.9, 66.5, 43.7, 40.8, 34.8, 25.5, 24.3; FABMS (m/z): 253 $[M+H]^+$. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.53; H, 8.13.

4.7. (1*R**,2*S**,3*S**,4*S**,4a*R**,5*S**,6*R**,7*R**,8*R**,8a*R**)-3-Bromo-2,8-epoxy-6,7-(*O*-ethylidenedioxy)decahydro-1,4-methano-naphthalen-5-ol (9b)

To a stirred solution of **8** (1.00 g, 3.4 mmol) and 1,1′-dimethyl ethane (7.3 mL, 68.7 mmol) in DMF (1.85 mL) was added *p*-toluenesulfonic acid (261 mg, 1.4 mmol) and the reaction mixture was stirred for 41 h at rt. The reaction was quenched by addition of 10 mL water. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (4:1 to 3:2 hexanes/EtOAc) yields product **9b** (534 mg, 49%) as mixture of two stereoisomers in 2.2:1 ratio.

*4.7.1. Compound **9b**α (major isomer).* ^{1}H NMR ($CDCl_3$) δ: 5.18 (1H, q, J=5.0 Hz), 4.53 (1H, d, J=5.0 Hz), 4.35 (1H, dd, J=5.0, 2.3 Hz), 4.24 (1H, dd, J=4.6, 2.3 Hz), 4.08–4.01 (2H, m), 3.80 (1H, d, J=2.3 Hz), 2.99–2.95 (1H, m), 2.68–2.46 (3H, m), 2.22 (1H, d, J=11.0 Hz), 1.64 (1H, d, J=11.0 Hz), 1.41 (3H, d, J=5.0 Hz); ^{13}C NMR ($CDCl_3$) δ: 21.4, 36.0, 36.2, 43.5, 43.9, 49.1, 56.0, 72.1, 76.8, 76.9, 78.1, 88.1, 102.4.

*4.7.2. Compound **9b**β (minor isomer).* ^{1}H NMR ($CDCl_3$) δ: 5.41 (1H, q, J=5.0 Hz), 4.53 (1H, d, J=5.0 Hz), 4.36 (1H, dd, J=5.0, 2.3 Hz), 4.24 (1H, dd, J=4.6, 2.3 Hz), 4.17 (1H, dd, J=8.2, 4.6 Hz), 4.08–4.01 (1H, m), 3.70 (1H, d, J=2.3 Hz), 2.99–2.95 (1H, m), 2.66 (1H, s), 2.59–2.54 (2H, m), 2.22 (1H, d, J=11.0 Hz), 1.64 (1H, d, J=11.0 Hz), 1.34 (3H, d, J=5.0 Hz); ^{13}C NMR ($CDCl_3$) δ: 21.4, 35.9, 36.2, 43.5, 44.3, 49.2, 55.9, 68.2, 75.1, 77.2, 78.3, 88.2, 101.2.

Mp (mixture of isomers) 74–77 °C; IR ν_{max}/cm^{-1} (KBr): 3411, 2961, 2877, 1413, 1135, 1082; FAB-HRMS (m/z): $[M+H]^+$ calculated for $C_{13}H_{18}BrO_4$: 317.0388; found: 317.0351.

4.8. (1*R**,2*S**,3*S**,4*S**,4a*R**,5*S**,6*R**,7*R**,8*R**,8a*R**)-Bromo-2,8-epoxy-6,7-(*O*-cyclohexylidenedioxy)decahydro-1,4-methano-naphthalen-5-ol (9c)

To a stirred solution of **8** (300 mg, 1.03 mmol) and 1,1′-dimethoxy cyclohexane (3.13 mL, 20.6 mmol) in DMF (0.55 mL) was added *p*-toluenesulfonic acid (78.3 mg, 0.4 mmol) and the reaction mixture was stirred for 13 h at rt. The reaction was quenched by addition of 5 mL water. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc) yields product **9c** (361 mg, 94%) as a white solid. IR ν_{max}/cm^{-1} (KBr): 3431, 2942, 2878, 1452, 1327, 1109, 1053; ^{1}H NMR ($CDCl_3$) δ: 4.52 (1H, d, J=5.0 Hz), 4.38–4.34 (2H, m), 4.12–4.04 (2H, m), 3.76 (1H, d, J=2.3 Hz), 2.99–2.93 (1H, m), 2.67–2.48 (3H, m), 2.30 (1H, s), 2.21 (1H, d, J=11.0 Hz), 1.74–1.52 (9H, m), 1.47–1.28 (2H, m); ^{13}C NMR ($CDCl_3$) δ: 110.1, 88.2, 77.3, 76.9, 75.6, 71.7, 56.1, 49.1, 44.0, 43.6, 38.3, 36.3, 36.0, 35.2, 24.9, 24.0, 23.7; FAB-HRMS (m/z): $[M+H]^+$ calculated for $C_{17}H_{24}BrO_4$: 371.0858; found: 371.0855.

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Supplementary data

^{1}H and ^{13}C NMR spectra for **2b**α, **2c**, **3**, **5b**α, **5b**β, **5c**, **6**, **9b**, and **9c**. Crystallographic information files (CIFs) for compound **6**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.07.047. These data include MOL files and InChIKeys of the most important compounds described in this article.

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