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Enzymatic desymmetrization/resolution of epoxydiols derived from 1,4-naphthoquinone, 5-hydroxy-1,4-naphthoquinone and 5,8-dihydroxy-1,4-naphthoquinone

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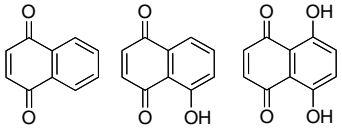
Abstract—The enzymatic desymmetrization/resolution of epoxydiols generated from the basic epoxidation and reduction of 1, 4-naphthoquoinone, 5-hydroxy-1,4-naphthoquinone and 5,8-dihydroxy-1,4-naphthoquinone is described. 2,3-Epoxy-1$^{\alpha}$,2$^{\alpha}$,3$^{\alpha}$,4$^{\alpha}$-tetrahydronaphthalene-1,4-diol and 5,8-diallyloxy-2,3-epoxy-1$^{\alpha}$,2$^{\alpha}$,3$^{\alpha}$,4$^{\alpha}$-tetrahydronaphthalene-1,4-diol were desymmetrized in the presence of isopropenyl acetate using *Burholderia cepacia* lipase and *Candida antartica* lipase B, respectively. An enzymatic resolution of 8-benzyloxy-2,3-epoxy-1$^{\alpha}$,2$^{\alpha}$,3$^{\alpha}$,4$^{\alpha}$-tetrahydronaphthalene-1,4-diol using *B. cepacia* lipase in isopropenyl acetate is also described.

1. Introduction

Our laboratory has been involved in a research program that utilizes simple, readily available, achiral starting material such as cyclopentadiene, benzene, *p*-benzoquinone and cycloheptatriene as the starting point in the synthesis of densely functionalized, enantiopure, bioactive molecules.[1] This strategy has led to the synthesis of numerous biologically interesting compounds such as: (+)- and (−)-bromoxone,[2] (+)- and (−)-harveynone,[3] (−)-tricholomen A,[3] LL-C10037α,[4] (−)-SS20846A,[5] the core ring system of zaragozic acid[6] and a variety of unnatural amino acids.[7] A feature common to each of these syntheses is an enzymatic resolution[8] or desymmetrization[8] to establish the absolute stereochemistry of a key intermediate.

Our interest in the production of enantiopure compounds using enzymatic transformations has led us to explore the previously overlooked 1,4-naphthoquinones. Herein we report the transformation of 1,4-naphthoquinone **1**, 5-hydroxy-1,4-naphthoquinone (juglone) **2**[9a] and 5,8-dihydroxy-1,4-naphthoquinone (naphthazarin) **3**,[9b] into highly oxygenated enantiopure compounds poised for further elaboration into bioactive target molecules.



1 **2** **3**

2. Results and discussion

2.1. 1,4-Naphthoquinone

The first step in the functionalization of **1** was the basic epoxidation of the quinone type alkene. Initial attempts towards the epoxidation of **1** (NaOH, H_2O_2 at 0 °C) resulted in the production of epoxide **4** along with the generation of aromatic impurities due to the decomposition of the target epoxide in the high pH medium. The decomposition of the **4** was avoided by substituting K_2CO_3 for NaOH. This simple modification of the reaction conditions delivered epoxide **4** in 80% yield. Subsequent reduction of **4** with $NaBH_4$ in methanol at −78 °C delivered *meso-syn,syn*-epoxydiol **5**.[10] The excellent diastereoselectivity of this reduction is probably due to the epoxide oxygen effectively blocking approach of the reducing species to the α-face, forcing reduction to occur exclusively from the less hindered β-face (Fig. 1). Desymmetrization of **5**, upon incubation with *Burholderia cepacia* lipase[11] (Amano Lipase PS) using isopropenyl acetate (IPA) as the acetate donor, produced acetate **6** (1*R*,2*R*,3*S*,4*S*) in 85% yield with >95% ee as

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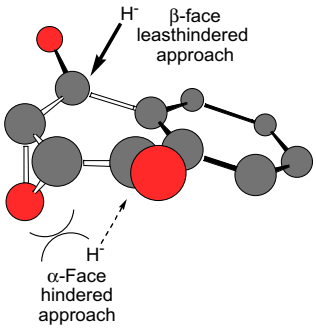


Figure 1. The β-face approach of the reducing species is favored due to the steric bulk of the epoxide on the α-face.

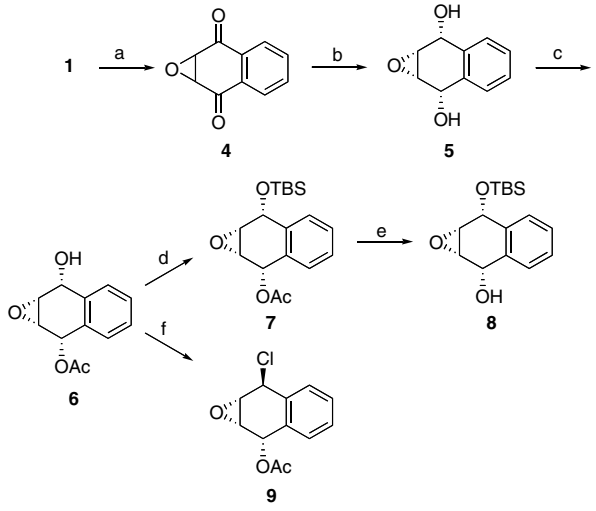
determined by F^{19} NMR of a Mosher's ester derivative.[12]

Protection of the (*R*)-alcohol of **6** with TBSCl/imidazole delivered silyl ether **7**. The latter upon subsequent hydrolysis with K_2CO_3 in methanol produced **8** with the (*S*)-alcohol unprotected (Scheme 1). This simple protection/deprotection strategy enables the liberation of each prochiral alcohol independent of the other and could be used to generate either enantiomer of a target compound from the same biocatalytic transformation.

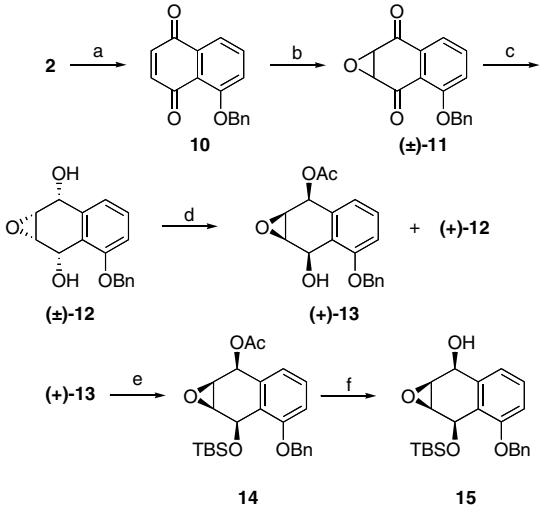
The relative stereochemistry of acetate **6** was confirmed by X-ray crystal structure analysis. The predicted absolute stereochemistry of **6** (1*R*,2*R*,3*S*,4*S*) was confirmed indirectly by X-ray crystal structure analysis of (1*S*,2*S*,3*S*,4*S*)-chloride **9**, generated upon incubation of **6** with mesyl chloride and triethylamine for 18 h (Scheme 1).

2.2. 5-Hydroxy-1,4-naphthoquinone

The elaboration and resolution of **2** followed the general protocol established for **1** with some minor variations. Initial attempts towards the basic epoxidation of **2** resulted in the complete decomposition of starting material. The decomposition of the starting material was minimized by simply protecting the phenol moiety of **2** as a benzyl ether. Incubating **2** with benzyl bromide/AgO produced benzyl ether **10**, which, upon exposure to K_2CO_3 and H_2O_2 delivered the desired epoxide **11** (Scheme 2).



Scheme 1. Reagents and conditions: (a) H_2O_2, K_2CO_3, H_2O/acetone, 0 °C, 80%; (b) $NaBH_4$, MeOH, −78 °C, 93%; (c) 200 wt% Amano Lipase PS, isopropenyl acetate, 50 °C, 24 h, 85%; (d) TBSCl, imidazole, 85%; (e) Na_2CO_3, methanol, 100%; (f) MsCl, TEA, 18 h, 97%.



Scheme 2. Reagents and conditions: (a) BnBr, AgO, CH_2Cl_2, 65%; (b) H_2O_2, K_2CO_3, H_2O/acetone, 0 °C, 87%; (c) K-Selectride, −78 °C, 60%; (d) 200 wt% Amano Lipase PS, isopropenyl acetate, 50 °C, 16 h, (+)-**13** 30%, ⩾95% ee, (+)-**12** 31%, ⩾95% ee; (e) TBSOTf, imidazole, CH_2Cl_2, 75%; (f) K_2CO_3, MeOH, 93%.

The reduction of diketone (±)-**11** was expected to produce the racemic *syn*,*syn*-epoxydiol (±)-**12**. However, $NaBH_4$ reduction of (±)-**11** produced a mixture of diol diastereomers. Fortunately, when (±)-**11** was exposed to the sterically demanding reducing agent K-Selectride, (±)-**12** was produced as the sole product. The selectivity of the reduction was examined in detail in the naphthazarin **3** case (vide infra). Incubation of (±)-**12** with Amano Lipase PS in the presence of IPA at 50 °C resulted in the generation of enantiopure acetate (+)-**13** (30% yield, >95% ee) and the recovery of enantiopure diol (+)-**12** (31% yield, >95% ee). The enantiomeric excess was determined using chiral shift analysis [300 MHz, (+)-Eu(hfc)$_3$].[13] The absolute stereochemistry for compounds **12** and **13** were established using the simple model for predicting the enantiomer (or prochiral alcohol) that will be acetylated preferentially in the reaction between a lipase and the secondary alcohol of a substrate (Fig. 2).[14] Using this simple model and the stereochemical data obtained for the structurally similar acetate **6** the absolute stereochemistry was determined to be (1*R*,2*R*,3*S*,4*S*) for (+)-**13** and (1*S*,2*S*,3*R*,4*R*) for (+)-

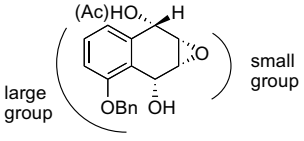
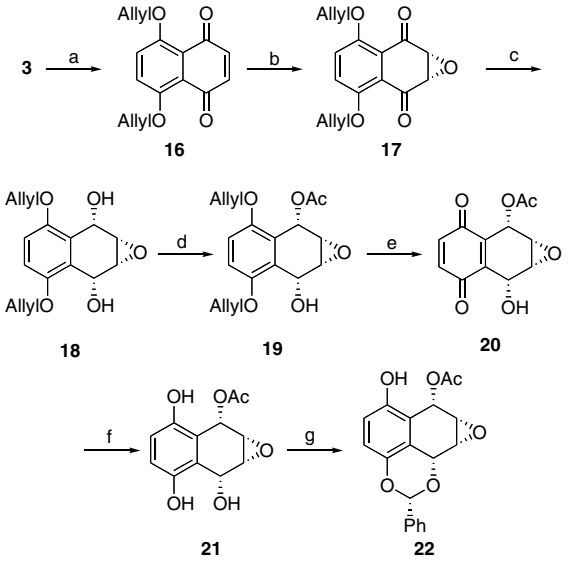


Figure 2. Simple model used to predict the enantioselective acylation of a secondary alcohol substrate.

12. Treatment of **13** with TBSOTf and imidazole delivered silyl ether **14**, which, upon hydrolysis with K_2CO_3, revealed alcohol **15**.

2.3. 5,8-Dihydroxy-1,4-naphthoquinone

The functionalization of naphthazarin followed the general scheme for 1,4-naphthoquinone **1** with some notable exceptions (Scheme 3). Naphthazarin **3** was conveniently prepared from 1,5-dinitronaphthalene by the Fierz–David and Stoeker[15] modification of Fieser's method.[16] Protection of the two phenols with allyl groups was accomplished using Ag_2O and allyl iodide to give **16**. The allyl protecting group was chosen for two reasons: (1) it was anticipated that it would be easily removed and (2) its relatively small size was not expected to interfere with the enzymatic desymmetrization. Epoxidation to give **17** with hydrogen peroxide and sodium bicarbonate proceeded in good yield as in the 1,4-naphthoquinone **1** case. However, reduction of the ketone moieties in **17** with sodium borohydride, which in the 1,4-naphthoquinone **1** example delivered the *meso-syn,syn*-epoxydiol **5** with excellent diastereoselectivity, gave in the naphthazarin **3** analogue a mixture of all possible diastereomers (Table 1). The reduction selectivity problem was solved by utilizing L-Selectride at −78 °C, which delivered *meso-syn,syn*-epoxydiol **18** as the only diastereomer, which could be detected by NMR. It was presumed that the diastereomer formed was *meso-syn,syn*-epoxydiol **18**, which was later confirmed by X-ray analysis after enzymatic acetylation (vide infra). The issue of stereochemical control in the double reduction is addressed below.

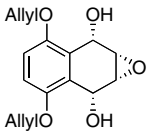
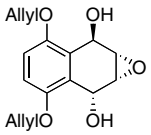
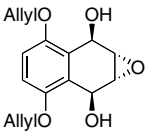


Scheme 3. Reagents and conditions: (a) allyl iodide, Ag_2O, 81%; (b) H_2O_2, Na_2CO_3, 96%; (c) L-Selectride, −78 °C, 82%; (d) 200 wt% Novo SP-435, isopropenyl acetate, toluene, 4 d, 93%, ⩾98% ee; (e) CAN, 98%; (f) H_2, Pd/C; (g) $PhCH(OMe)_2$, PTSA, 58% for two steps.

At this point, we attempted to desymmetrize *meso*-diol **18** by enzymatic acylation. The conditions, which were efficacious in the 1,4-naphthoquinone **1** series (Amano Lipase PS, isopropenyl acetate, 50 °C led to slow conversion to the monoacetate **19** with concomitant decomposition leading to an unidentified side product. After screening various enzymes, solvents and acetyl donors, we found that the reaction proceeded cleanly at room temperature with *Candida antartica* lipase B (Novo SP-435) in 4:1 toluene/vinyl acetate. The absolute stereochemistry of **19** was assigned based on the model as (1*R*,2*R*,3*S*,4*S*) using the simple model shown in Figure 2 and the results obtained in the 1,4-naphthoquinone example. The diacetate was not observed by TLC; the acetylation appeared to be highly enantioselective and this was confirmed by Mosher ester derivative analysis (>98% ee by ^{19}F NMR). The X-ray crystal analysis confirmed the relative stereochemistry but could not confirm absolute stereochemistry.

Removal of the allyl protecting groups proved to be difficult. Various conditions based on π-allyl formation or alkene isomerization followed by hydrolysis either showed no reaction or decomposition.[17] The decomposition is likely due to the instability of the hydroquinone **21** in the presence of acid, base or oxygen. Considering the electron rich nature of the allyl-protected hydroquinone **19**, we devised a two step deprotection strategy. First, the quinone **20** was formed by oxidation with ceric ammonium nitrate,[18] thereby removing the allyl groups. Reduction to hydroquinone **21** was accomplished under neutral catalytic hydrogenation conditions and required minimal work-up. Hydroquinone **21** proved to be very unstable to acid, base and oxygen and was therefore transformed immediately into the more stable benzylidene acetal **22** with the absolute configuration of (1*S*,2*S*,3*R*,4*R*). Fortunately, only one diastereomer was observed by NMR, which was shown by NOE to have the hydrogen on the β-face (Fig. 3), in agreement with calculations performed on the two diastereomers.[19,20]

Table 1. Diastereomeric ratios obtained in reductions of diketone **17**

Conditions	 **18**	 **23**	 **24**
$NaBH_4$, 0 °C, $MeOH/CH_2Cl_2$	12%	63%	25%
$NaBH_4$, −40 °C, $MeOH/CH_2Cl_2$	8%	57%	35%
L-Selectride, −78 °C, THF	>96%	<2%	<2%

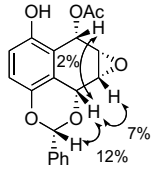


Figure 3. Observed NOE signals confirming the stereochemistry of benzylidene acetal **22**.

2.4. Examination of the reduction of 17

The diastereoselectivity of the reduction of diketone **17** was examined in detail. Table 1 shows the diastereomeric ratios for the reduction of diketone **17** under three different conditions: Sodium borohydride at 0 and 40 °C, and L-Selectride reduction at −78 °C. Three diastereomers are possible: *syn*,*syn*-**18**, *anti*-*syn*-**23** and *anti*,*anti*-**24**. The reduction with sodium borohydride favours attack by the hydride from the α-face, which, surprisingly, is on the same face as the epoxide. Recall that in the 1,4-naphthoquinone **1** series, reduction of the diketone **4** by sodium borohydride gave exclusively *syn*,*syn*-diol **5**. The reduction of **15** by L-Selectride, in contrast, only shows attack from the β-face, away from the bulk of the epoxide.

The results can be understood by examining the torsional strain involved in the reduction (Fig. 4). The allyloxy substituents, which are *peri* to the carbonyls, have considerable bulk and force the carbonyls out of the plane of the aromatic ring. In the case of diketone **4**, the hydrogens *peri* to the carbonyls have a much smaller effect. The calculated angle between the carbonyl and the plane of the ring is 32° for **17** and 16° for **4**,[19] where the carbonyl is bent away from the epoxide in both cases. Thus, in the case of **17**, there is considerably more torsional strain involved in reduction from the β-face because the carbonyl oxygen must be pushed past the allyloxy substituent. This leads to preferential α-face attack with the relatively small hydride source sodium borohydride. With the sterically demanding L-Selectride, the reduction from the α-face is prevented by the steric bulk of the epoxide, and the reduction is forced to proceed from the β-face. In the case of **4**, which has only minimal torsional strain, the bulk of the epoxide controls the reduction with sodium borohydride and gives the desired β-face attack.

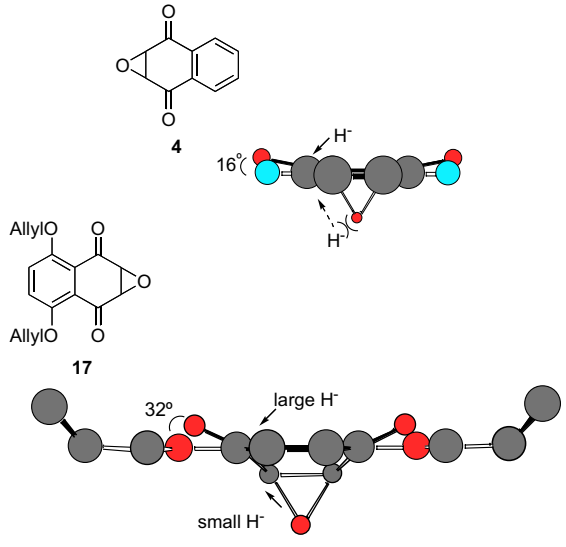


Figure 4. Torsional strain between the carbonyl oxygen and allyloxy moiety of **17** is responsible for the favourable approach of a small hydride source from the α-face.

3. Conclusion

The elaboration of 1,4-naphthoquinone **1**, 5-hydroxy-1,4-naphthoquinone **2** and 5,8-dihydroxy-1,4-naphthoquinones **3** has led to the development of three novel highly functionalized enantiopure intermediates. The absolute stereochemistry was established by an enzymatic resolution of racemic diol (±)-**12** and enzymatic desymmetrizations of *meso*-diols **5** and **18**. We anticipate that the highly functionalized, enantiopure intermediates presented in this work will be valuable for the asymmetric synthesis of a variety of bioactive natural and unnatural targets.

4. Experimental

4.1. 2,3-Epoxy-1,2$^{\beta}$,3$^{\beta}$,4-tetrahydronaphthalene-1,4-dione 4

To a cooled (0 °C) solution of 1,4-naphthoquinone **1** (8 g, 50.6 mmol) in acetone (500 mL) was added a solution of basic peroxide (30% solution in water H_2O_2, 2.58 g, 75.9 mmol; K_2CO_3, 10.5 g, 75.9 mmol). The reaction mixture was stirred for 2 h until the reaction was determined to be complete by TLC. The solution was quenched with aqueous $FeSO_4$ and extracted with ethyl acetate (4 × 300 mL). The combined organic layers were dried with $MgSO_4$, filtered, concentrated and purified by flash chromatography to afford 7.04 g (80%) of **4**: mp = 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.01 (s, 2H), 7.65–8.1 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.27, 127.20, 131.73, 134.70, 190.70; HRMS (EI) calculated for $C_{10}H_6O_3$ (M^+) 174.0317, found 174.0318.

4.2. 2,3-Epoxy-1$^{\alpha}$,2$^{\alpha}$,3$^{\alpha}$,4$^{\alpha}$-tetrahydronaphthalene-1,4-diol 5

To a cooled (−78 °C) solution of epoxide **4** (3.17 g, 18.2 mmol) in methanol (180 mL) was added sodium borohydride (692 mg, 18.2 mmol). The reaction mixture was stirred for 3 h until the reaction had reached room temperature and was determined to be complete by TLC. The reaction was quenched with H_2O (50 mL) and extracted with ethyl acetate (4 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, concentrated and purified by flash chromatography to afford 3 g (93%) of **5**: mp = 173–175 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 3.35, (s, 2H) 4.89 (s, 2H), 7.21 (m, 2H), 7.51 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 55.15, 66.78, 125.60, 127.29, 134.79; HRMS (EI) calculated for $C_{10}H_{10}O_3$ (M^+) 178.0630, found 178.0634.

4.3. (1*R*,2*R*,3*S*,4*S*)-4-Acetoxy-2,3-epoxy-1,2,3,4-tetrahydronaphthalen-1-ol 6

To a solution of diol **5** (100 mg, 0.562 mmol) in isopropenyl acetate (6 mL) was added Amano Lipase PS (200 mg, 200 wt%). This solution was stirred at 50 °C for 24 h until the reaction was determined to be complete by TLC. The solution was concentrated and the solid residue was recrystallized from methanol. The solid crystalline material was filtered, rinsed with pet. ether (2×10 mL) and concentrated to reveal 105 mg (85%) of **6**: $[\alpha]_D^{21} = +4.0$ (*c* 1.0, CH_2Cl_2); mp = 189–190 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (S, 3H), 3.74 (dd, 1H, $J = 1.8$, 1.8 Hz), 3.77 (dd, 1H, $J = 1.8$, 1.8 Hz), 4.93 (br s, 1H), 6.17 (br s, 1H), 7.18–7.20 (m, 1H), 7.29–7.40 (m, 2H), 7.62–7.65 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 52.77, 54.71, 66.84, 68.58, 125.57, 126.59, 128.07, 128.47, 129.343, 134.50, 171.07; HRMS (EI) calculated for $C_{12}H_{11}O_4$ (M^+) 220.0736, found 220.0733.

4.4. (1*S*,2*S*,3*S*,4*R*)-1-Acetoxy-4-(*tert*-butyldimethylsilyloxy)-2,3-epoxy-1,2,3,4-tetrahydronaphthalene 7

To a solution of acetate **6** (95 mg, 0.432 mmol) in CH_2Cl_2 (4 mL) was added imidazole (88 mg, 1.30 mmol) and TBSCl (71 mg, 0.475 mmol). This solution was stirred for 24 h until the reaction was determined to be complete by TLC. The reaction mixture was quenched with 1 M HCl (1×30 mL) and extracted CH_2Cl_2 (4×30 mL). The combined organic layers were dried with $MgSO_4$, filtered, concentrated and purified by flash chromatography to afford 121 mg (85%) of **7**: mp = 86–87 °C; $[\alpha]_D^{21} = -22.0$ (*c* 1.50, CH_2Cl_2); ^{1}H (300 MHz, $CDCl_3$): δ 3.06 (dd, 1H, $J = 1.2$, 5.1 Hz), 3.70 (dd, 1H, $J = 1.2$, 4.8 Hz), 5.03 (br s, 1H), 6.15 (br s, 1H), 7.18–7.53 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.81, −4.33, 18.20, 21.05, 25.81, 51.81, 54.40, 67.94, 68.88, 124.76, 125.83, 127.42, 128.03, 129.12, 134.34, 171.00; HRMS (EI) calculated for $C_{18}H_{26}O_4Si$ ($M^+-C_4H_9$) 277.0896, found 277.0894.

4.5. (1*S*,2*S*,3*S*,4*R*)-2,3-Epoxy-4-(*tert*-butyldimethylsilyloxy)-1,2,3,4-tetrahydronaphthalen-1-ol 8

To a solution of acetate **7** (956 mg, 2.90 mmol) in methanol (30 mL) was added sodium carbonate (100 mg). This solution was stirred for 1 h until the reaction was determined to be complete by TLC. The solution was concentrated and partitioned between H_2O and ethyl acetate. The aqueous layer was extracted with ethyl acetate (4×100 mL) and the combined organic layers were dried with $MgSO_4$, filtered, concentrated and purified by flash chromatography to afford 835 mg (100%) of **8** as a clear oil: $[\alpha]_D^{21} = -18$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.21 (s, 3H), 0.24 (s, 3H), 1.03 (s, 9H), 3.60 (dd, 1H, $J = 1.5$, 1.5 Hz), 3.63 (dd, 1H, $J = 1.5$, 1.5 Hz), 4.81 (br s, 1H) 4.99 (br s, 1H), 7.30–7.33 (m, 2H), 7.45–7.48 (m, 1H), 7.53–7.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.78, −4.29, 18.21, 25.83, 54.84, 55.45, 67.07, 67.91, 125.67, 125.75, 127.61, 127.79, 133.82; HRMS (EI) calculated for $C_{16}H_{24}O_3Si$ ($M^+-C_4H_9$) 235.0790, found 235.0791.

4.6. (1*S*,2*S*,3*S*,4*S*)-1-Acetoxy-4-chloro-2,3-epoxy-1,2,3,4-tetrahydronaphthalene 9

To a solution of alcohol **6** (250 mg, 1.14 mmol) in CH_2Cl_2 (10 mL) was added triethylamine (288 mg, 2.85 mmol) and methanesulfonyl chloride (260 mg, 2.27 mmol). The reaction mixture was stirred for 18 h until the reaction was determined to be complete by TLC. The solution was quenched with water and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried with $MgSO_4$, filtered, concentrated and purified by flash chromatography to afford 263 mg (97%) of **9**: mp = 145–145.5 °C; $[\alpha]_D^{21} = +109$ (*c* 1.27, CH_2Cl_2); ^{1}H (300 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.80 (d, 1H, $J = 1.2$ Hz), 3.81 (d, 1H, $J = 1.2$ Hz), 5.42 (br s, 1H), 6.39 (br s, m), 7.28–7.43 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.02, 52.15, 52.79, 55.02, 68.42, 126.02, 128.73, 129.73, 129.81, 130.27, 131.58, 170.79; HRMS (EI) calculated for $C_{12}H_{11}ClO_3$ (M^+) 238.0397, found 238.0395.

4.7. 8-Benzyloxy-2,3-epoxy-1,2$^{\alpha}$,3$^{\alpha}$,4-tetrahydronaphthalen-1,4-dione 11

To a cooled (0 °C) solution of **10** (792 mg, 3.0 mmol) in acetone (30 mL) was added a basic peroxide solution (H_2O_2, 459 mg, 13.5 mmol; K_2CO_3, 1.66 g, 12.0 mmol). The reaction mixture was stirred for 2 h at which time the solution was quenched with aqueous $FeSO_4$ and extracted with ethyl acetate (4×150 mL). The combined organic layers were dried with $MgSO_4$, filtered, concentrated and purified by flash chromatography to afford 731 mg (87%) of **11**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.99 (s, 2H), 5.20 (d, 1H, $J = 12.3$ Hz), 5.27 (d, 1H, $J = 12.3$ Hz), 7.26–7.65 (m, 8H); ^{13}C (125 MHz, $CDCl_3$): δ 55.21, 55.44, 70.91, 119.49, 119.60, 126.74, 128.06, 128.69, 135.00, 135.75, 189.95, 191.66; HRMS (EI) calculated for $C_{17}H_{12}O_4$ (M^+) 280.0736, found 280.0736.

4.8. 8-Benzyloxy-2,3-epoxy-1$^{\alpha}$,2$^{\alpha}$,3$^{\alpha}$,4$^{\alpha}$-tetrahydronaphthalene-1,4-diol 12

To a cooled (−78 °C) solution of epoxide **11** (296 mg, 1.06 mmol) in THF (10 mL) was added K-selectride (705 mg, 3.17 mmol). This solution was stirred for 3 h until the reaction had reached room temperature and was determined to be complete by TLC. The solution was quenched with H_2O and extracted with ethyl acetate (4×75 mL). The combined organic layers were dried with $MgSO_4$, filtered, concentrated and purified by flash chromatography to afford 161 mg (54%) of (±)-**12**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (dd, 1H, $J = 2.4$, 4.2 Hz), 3.80 (dd, 1H, $J = 3.0$, 4.8 Hz), 4.60 (br s, 1H), 4.86 (d, 1H, $J = 2.4$ Hz), 5.13 (s, 2H), 5.23 (d, 1H, $J = 2.4$ Hz), 6.89–6.95 (m, 1H), 7.26–7.42 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.67, 55.56, 64.45, 66.67, 70.86, 111.24, 120.76, 122.44, 127.65, 128.55, 128.91, 129.10, 135.74, 136.24, 156.71; HRMS (EI) calculated for $C_{17}H_{16}O_4$ (M^+) 284.1047, found 284.1047.

4.9. (1*R*,2*R*,3*S*,4*S*)-4-Acetoxy-8-benzyloxy-2,3-epoxy-1,2,3,4-tetrahydronaphthalen-1-ol 13

To a suspension of diol (±)-**12** (161 mg, 0.567 mmol) in isopropenyl acetate (6 mL) was added Amano Lipase PS (322 mg, 200% wt). The reaction mixture was stirred at 50 °C for 16 h until the reaction was determined to be 50% complete by HPLC. At which time the solution was cooled to room temperature and water (2 mL) was added. The resultant aqueous layer was extracted with ethyl acetate (4 × 20 mL) and the combined organic layers were dried with $MgSO_4$, filtered, concentrated and purified by flash chromatography to afford 56 mg (30%) of (+)-**13** and 50 mg (31%) of enantioenriched alcohol (+)-**12**: diol rotation $[\alpha]_D^{21} = +26.5$ (*c* 2.50, CH_2Cl_2); acetate data $[\alpha]_D^{23} = +58.4$ (*c* 0.46, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.76 (s, 2H), 5.14 (s, 2H), 5.26 (br s, 1H), 6.17 (br s, 1H), 6.90 (d, 1H, $J = 7.8$ Hz), 6.95 (d, 1H, $J = 8.4$ Hz), 7.38–7.42 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.12, 51.62, 54.23, 64.55, 68.63, 70.97, 111.65, 119.72, 127.69, 128.62, 128.95, 131.74, 135.20; HRMS (EI) calculated for $C_{19}H_{18}O_5$ (M^+) 326.1154, found 326.1149.

4.10. (1*S*,2*S*,3*S*,4*R*)-1-Acetoxy-8-benzyloxy-2,3-epoxy-4-(*tert*-butyldimethylsilyoxy)-1,2,3,4-tetrahydronaphthalene 14

To a solution of alcohol **13** (71 mg, 0.218 mmol) in CH_2Cl_2 was added imidazole (30 mg, 0.436 mmol) and TBSOTf (49 mg, 0.327 mmol). This mixture was stirred for 1 h until determined complete by TLC, at which time the solution was washed with dilute HCl (1 × 10 mL) and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The concentrate was purified by flash chromatography to deliver **14** (72 mg, 0.164 mmol) in a 75% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 3H), 0.12 (s, 3H), 0.92 (s, 9H), 2.25 (s, 3H), 3.69 (t, 1H, $J = 3.6$ Hz), 3.96 (dd, 1H, $J = 1.2$, 3.0 Hz), 5.19 (br s, 2H), 5.35 (d, 1H, $J = 3.6$ Hz), 6.12 (d, 1H, $J = 3.0$ Hz), 6.74–6.81 (m, 2H), 7.14–7.39 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.75, −4.20, 18.44, 21.09, 25.97, 52.51, 55.67, 63.49, 68.51, 69.55, 111.68, 119.22, 124.16, 126.90, 127.66, 128.45, 128.78, 132.20, 136.90, 157.60, 171.32; HRMS (EI) calculated for $C_{25}H_{22}O_5Si$ ($M^+ - C_4H_9$) 383.1315, found 383.1315.

4.11. (1*S*,2*S*,3*S*,4*R*)-8-Benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2,3-epoxy-1,2,3,4-tetrahydronaphthalen-1-ol 15

To a solution of acetate **14** (72 mg, 0.164 mmol) in methanol (2 mL) was added K_2CO_3 (10 mg). This reaction mixture was stirred for 24 h until the reaction was determined to be complete by TLC. The solution was diluted with H_2O (3 mL) and the reaction was extracted with ethyl acetate (4 × 5 mL) and the combined organic layers were dried with $MgSO_4$, filtered, concentrated and purified by flash chromatography to afford 61 mg (93%) of **15**. ^1H (300 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 2.61 (br s, 1H), 3.69–3.75 (m, 2H), 4.84 (br s, 1H), 5.18 (s, 2H), 5.36 (d, 1H, $J = 3.0$ Hz), 6.37–6.76 (m, 1H), 7.16–7.37 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.86, −4.30, 18.43, 25.98, 55.76, 57.06, 63.14, 66.29, 69.67, 111.37, 120.46, 123.51, 127.73, 128.47, 129.01, 136.92, 137.24, 157.20; HRMS (EI) calculated for $C_{23}H_{30}O_4Si$ ($M^+ - C_4H_9$) 341.1209, found 341.1211.

4.12. 5,8-Diallyloxy-1,4-naphthoquinone 16

A mixture of **3** (0.82 g, 4.3 mmol), allyl iodide (4.1 mL, 45 mmol) and silver(I)oxide (10 g, 44 mmol) was vigorously stirred under N_2 in a flask protected from light for 28 h. The mixture was filtered through a pad of Celite, concentrated in vacuo and placed under high vacuum to remove excess allyl iodide. The reddish brown solid was purified by flash chromatography (gradient from 3:1 to 1:1 hexanes/ethyl acetate) to provide **16** (0.95 g, 81%) as an orange solid: mp = 96–98 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (s, 2H), 6.78 (s, 2H), 6.10 (m, 2H), 5.61 (m, 2H), 5.35 (m, 2H), 4.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.7, 152.8, 138.3 (CH), 132.3 (CH), 122.1 (CH), 121.5, 118.0 (CH_2), 70.5 (CH_2); HRMS (EI) calcd for $C_{16}H_{14}O_4$ 270.0892, found 270.0897.

4.13. 5,8-Diallyloxy-2,3-epoxy-1,2$^{\beta}$,3$^{\beta}$,4-tetrahydronaphthalene-1,4-dione 17

To a solution of **16** (0.91 g, 3.4 mmol) in methanol (150 mL) at 0 °C was added 30% aqueous hydrogen peroxide solution (1.75 mL, 17 mmol) and 2 M aqueous sodium bicarbonate solution (3.3 mL, 6.6 mmol) and the solution stirred at 0 °C for 0.5 h. The solution was neutralized with 1 N HCl (8 mL), filtered through a pad of Celite and the filtrate was concentrated in vacuo. The yellow-orange residue was treated with saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate (3 × 70 mL). The combined organics were washed with brine (200 mL), dried with $MgSO_4$ and concentrated in vacuo to provide epoxide **17** (0.92 g, 96%), which was used without further purification. An analytically pure sample was obtained from another batch by flash chromatography on neutral Alumina (gradient form 4:1 to 2:1 hexanes/ethylacetate) to provide epoxide **17** as a yellow solid: mp = 92–93 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.19 (s, 2H), 6.04 (m, 2H), 5.49 (dd, $J = 17.2$, 1.5 Hz, 2H), 5.32 (dd, $J = 10.6$, 1.0 Hz, 2H), 4.66 (m, 2H), 4.54 (m, 4H), 3.97 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.7, 151.5, 132.3 (CH), 121.9, 120.9 (CH), 118.1 (CH_2), 70.6 (CH_2), 55.5 (CH); HRMS (EI) calcd for $C_{16}H_{14}O_5$ 286.0841, found 286.0841.

4.14. 5,8-Diallyloxy-2,3-epoxy-1$^{\beta}$,2$^{\beta}$,3$^{\beta}$,4$^{\beta}$-tetrahydronaphthalene-1,4-diol 18

To a solution of epoxide **17** (0.92 g, 3.2 mmol) in THF (50 mL) at −78 °C was added dropwise a solution of 1.0 M L-Selectride (13 mL, 14 mmol) and the solution stirred at −78 °C for 0.5 h. The excess L-Selectride was quenched with water (10 mL) and the solution was allowed to warm to 0 °C. Organoborane was oxidized by adding 30% aqueous hydrogen peroxide solution

(6.7 mL, 65 mmol) and stirring for 0.5 h at room temperature. The solution was diluted with ethyl acetate (50 mL) and washed with saturated ammonium chloride solution (1 × 100 mL), brine (1 × 100 mL), dried with $MgSO_4$ and concentrated in vacuo. The product was purified by flash chromatography (1:1 hexanes/ethyl acetate, then 19:1 dichloromethane/acetone, then 9:1 dichloromethane/acetone) to give diol **18** (0.76 g, 82%) as a white solid: mp = 145–147 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 6.94 (s, 2H), 6.07–6.19 (m, 2H), 5.44 (ddd, J = 17.1, 3.1, 1.8 Hz, 2H), 5.28 (ddd, J = 10.4, 3.1, 1.8 Hz, 2H), 5.14 (m, 2H), 4.58–4.71 (m, 4H), 4.29 (d, J = 3.7 Hz, 2H), 3.61 (dd, J = 6.1, 3.1 Hz, 2H); ^{13}C NMR (75 MHz, acetone-d_6): δ 151.3, 132.4 (CH), 124.7, 118.5 (CH), 111.7 (CH_2), 69.7 (CH_2), 64.2 (CH), 54.4 (CH); HRMS (EI) calcd for $C_{16}H_{18}O_5$ 290.1154, found 290.1154.

4.15. (1*R*,2*R*,3*S*,4*S*)-4-Acetoxy-5,8-diallyloxy-2,3-epoxy-1,2,3,4-tetrahydronaphthalen-1-ol 19

A mixture of diol **18** (2.67 g, 9.2 mmol) and Novo SP-435 enzyme (5.34 g) in toluene (400 mL) and isopropenyl acetate (100 mL) was gently stirred with an overhead stirrer for 90 h. The mixture was filtered and the enzyme was washed with benzene and hexanes. The filtrate was concentrated in vacuo. The product was purified by flash chromatography (2:1 hexanes/ethyl acetate) to provide acetate **19** (2.71 g, 93%) as a white solid: mp = 151–153 °C; $[\alpha]_D^{21} = -28.2$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD): δ 6.96 (d, J = 9.7 Hz, 1H), 6.88 (d, J = 9.7 Hz, 1H), 6.29 (d, J = 3.2 Hz, 1H), 5.96–6.15 (m, 2H) 5.42 (ddd, J = 17.0, 3.2, 1.6 Hz, 1H), 5.36 (ddd, J = 17.0, 3.2, 1.6 Hz, 1H), 5.27 (ddd, J = 10.5, 1.6, 1.6 Hz, 1H), 5.23 (ddd, J = 10.5, 1.6, 1.6 Hz, 1H), 5.21 (d, J = 4.1 Hz, 1H), 4.56–4.67 (m, 2H), 4.48 (m, 2H), 3.74 (m, 2H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 172.6, 152.7, 152.6, 135.00 (CH), 134.96 (CH), 127.6, 122.2, 118.1 (CH_2), 117.6 (CH_2), 114.4 (CH), 113.1 (CH), 70.9 (CH_2), 70.5 (CH_2), 66.5 (CH), 64.0 (CH), 56.4 (CH), 54.2 (CH), 21.1 (CH_3); HRMS (EI) calcd for $C_{16}H_{20}O_5$ 332.1260, found 332.1256.

4.16. (5*S*,6*S*,7*R*,8*R*)-5-Acetoxy-6,7-epoxy-5,6,7,8-tetrahydro-1,4-naphthoquinone-8-ol 20

To a solution of allyl-protected hydroquinone **19** (0.50 g, 1.5 mmol) in acetonitrile (15 mL) at 0 °C was added dropwise a solution of ceric ammonium nitrate (2.0 g, 3.6 mmol) in water (15 mL) and the resulting solution stirred for 10 min. The solution was diluted with water (10 mL) and the product was extracted with chloroform (5 × 20 mL). The combined extracts were dried with $MgSO_4$ and concentrated in vacuo to produce quinone **20** (369 mg, 98%) of a bright orange solid: mp = 135–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (d, J = 9.8 Hz, 1H), 6.77 (d, J = 9.8 Hz, 1H), 6.19 (m, 1H), 5.09 (m, 2H) 3.82 (d, J = 4.0 Hz, 1H), 3.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.9, 184.5, 170.0, 139.1, 137.5 (CH), 136.4 (CH), 135.4 (CH), 63.38 (CH), 63.33 (CH), 53.5 (CH), 51.8 (CH), 20.7 (CH_3); HRMS (EI) calcd for $C_{12}H_{10}O_6$ 250.0477, found 250.0475.

4.17. (1*S*,2*S*,3*R*,4*R*)-1-Acetoxy-4,5-benzylidenedioxy-2,3-epoxy-1,2,3,4-tetrahydronaphthalen-8-ol 22

A solution of **20** (350 mg, 1.4 mmol) in methanol (100 mL) was stirred with palladium on carbon (Degussa, 20 wt%) under an atmosphere of hydrogen for 52 h. The mixture was filtered through a pad of Celite and immediately concentrated in vacuo. To a solution of the resulting hydroquinone **21** (358 mg, 1.14 mmol) in THF (30 mL) was added p-toluene sulfonic acid (13 mg, 0.07 mmol) and benzaldehyde dimethyl acetal (8.5 mL, 57 mmol) and the solution stirred under nitrogen for 53 h. The solution was diluted with ethyl acetate (50 mL), washed with water (2 × 80 mL), dried with $MgSO_4$ and concentrated in vacuo. The product was purified by flash chromatography (hexanes, then 3:1 hexanes/ethyl acetate, then 2:1 hexanes/ethyl acetate) to provide benzylidene acetal **22** (278 mg, 58%) as an off white solid: mp = 126 °C (dec); $[\alpha]_D^{21} = -139$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (m, 2H), 7.45 (m, 3H), 6.82 (d, J = 9.1 Hz, 1H), 6.77 (d, J = 9.1 Hz, 1H), 6.39 (s, 1H), 6.18 (s, 1H), 5.83 (s, 1H), 5.34 (s, 1H), 3.87 (d, J = 5.1 Hz, 1H), 3.78 (d, J = 5.1 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 148.1, 146.1, 136.5, 129.8 (CH), 128.5 (CH), 126.5 (CH), 118.3 (CH), 117.6 (CH), 115.2, 113.2, 100.2, 72.9 (CH), 69.6 (CH), 51.0 (CH), 50.9 (CH), 21.1 (CH_3); HRMS (FAB) calcd for $C_{19}H_{16}O_6$ 340.0947, found 340.0949.

4.18. X-ray crystal structures

Crystallographic data for **6**, **9** and **19** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 246669, CCDC 246671 and CCDC 246965, respectively. Copies can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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