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Tetrahedron
Tetrahedron 60 (2004) 9725–9733

# Application of sulfur ylide mediated epoxidations in the asymmetric synthesis of β-hydroxy-δ-lactones. Synthesis of a mevinic acid analogue and (+)-prelactone B

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Received 21 June 2004; revised 4 July 2004; accepted 6 July 2004

Available online 21 August 2004

**Abstract**—Catalytic and stoichiometric asymmetric sulfur ylide reactions were employed to prepare alkyl–aryl epoxide intermediates in a convergent manner. These epoxides were utilized in efficient syntheses of the mevinic acid analogue **1** and prelactone B.


## 1. Introduction

The asymmetric synthesis of epoxides from carbonyl compounds using sulfur ylide intermediates has emerged as a powerful method for not only creating C–C bonds with control of asymmetry but also for generating functionality suitable for further manipulation.[1] We have reported an efficient catalytic asymmetric process for the conversion of aldehydes into epoxides[2] and a complementary stoichiometric process for a range of problematic substrates, which had either given low yields or low selectivities in our catalytic process.[3] The broad substrate scope of the combined catalytic and stoichiometric processes now allows the sulfur ylide disconnection to be applied with confidence in total synthesis. The practicality of these methods have been demonstrated in the concise synthesis of CDP 840.[3] Most studies of asymmetric epoxidation of carbonyl compounds to date have focused on methodology development[4] rather than their use, but the power of new methodology is best illustrated with applications in synthesis. In this paper, we describe the application of catalytic and stoichiometric asymmetric sulfur ylide mediated epoxidation methodology in the synthesis of the β-hydroxy-δ-lactones which are present in a large number of biologically important molecules (Fig. 1).[5]

## 2. Results and discussion

Our general retrosynthetic analysis of β-hydroxy-δ-lactones **A1/A2** is shown in Scheme 1. The target lactone **A1/A2** could be generated from the corresponding hydroxy keto-ester via diastereoselective reduction. The hydroxy keto ester **B** could be obtained by sequential Birch reduction and ozonolysis of epoxide **D**,[6] which itself could potentially be obtained through our asymmetric sulfur ylide mediated epoxidation reaction employing sulfide **S**.[2] In this paper we report two successful syntheses of β-hydroxy-δ-lactones using this synthetic strategy.

We chose as our first target the β-hydroxy-δ-lactone **1**.[7] This lactone is a simplified structural analogue of the naturally occurring potent HMG-CoA reductase inhibitors, compactin and mevinolin.[8] Since their discovery, many synthetic approaches to these compounds as well as analogues have appeared[9] and it has been shown from SAR studies that the lactone moiety of the mevinic acids is essential for the biological activity.[10]

To synthesize lactone **1** we required epoxide **2**. In order to prepare epoxide **2**, we decided to employ the stoichiometric sulfur ylide reaction since we were aware that α-unsubstituted aldehydes gave epoxides with low diastereoselectivity (e.g. valeraldehyde, 3:1 *trans*/*cis*)[2] under catalytic conditions. Thus, sulfide **S** was converted into the required sulfonium salt and treated with 3-cyclohexane propanal (prepared from commercially available 3-cyclohexyl propanol) in the presence of the $EtP_2$[11,3] base. This furnished the desired epoxide **2** with almost perfect

*Keywords*: Sulfur ylide; Epoxides; Mevinic acid.
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doi:10.1016/j.tet.2004.07.044

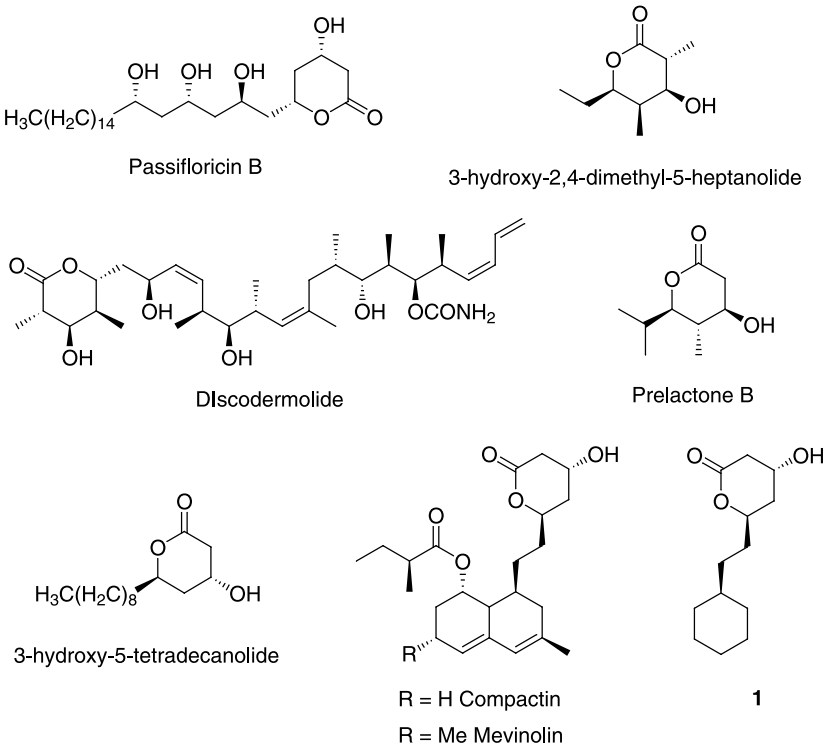
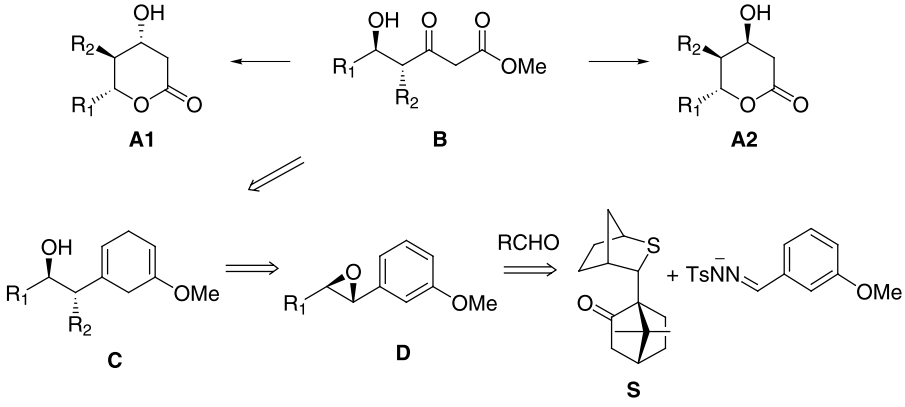



**Figure 1.** β-Hydroxy-δ-lactone structures in biologically important molecules.

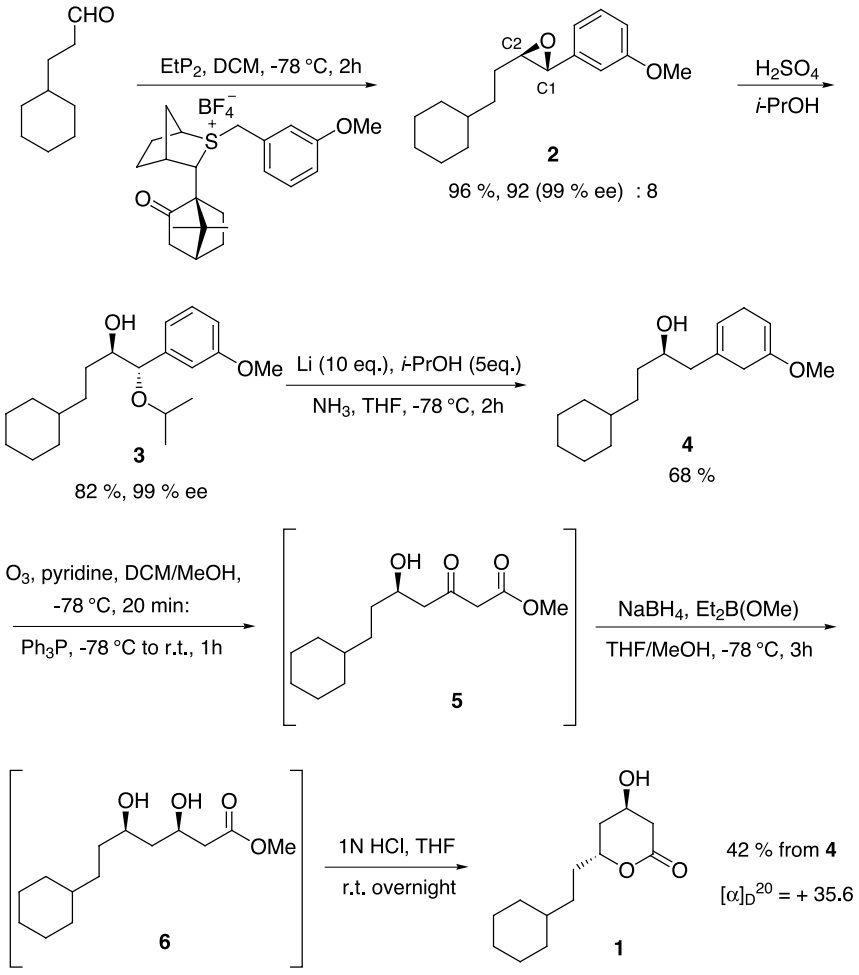



**Scheme 1.** Retrosynthetic analysis of β-hydroxy-δ-lactones **A1/A2**.

enantioselectivity (99% for *trans*) and good diastereoselectivity (92:8) in 96% yield (Scheme 2). Chiral sulfide **S** was recovered in 83% yield.

Separation of the *cis* and *trans* epoxides was required since they possess opposite stereochemistry at C2 and if they were both carried through would erode the enantioselectivity of the final product. However, all attempts to separate the two epoxides were unsuccessful. We therefore decided to open the epoxide with a suitable nucleophile to generate a separable diastereomeric mixture. Among a variety of possible nucleophiles, we considered alkoxides because such functionality could be easily removed during Birch reduction. Both methanol and *i*-PrOH were investigated and the isopropyl ether **3** gave a readily separable diastereomeric mixture. Thus, opening of epoxides with *i*-PrOH in the presence of catalytic concd $H_2SO_4$ gave two separable ethers from which the desired *anti* product **3** was isolated in 82% yield. Since the diastereomeric ratio of epoxide isomers correlated well with the ratio of ethers formed, it is believed that epoxide opening occurred with clean inversion.

Next, Birch reduction was carried out under standard conditions.[12] After a solution of alcohol **3** in $NH_3$ with 10 equiv of Li metal and 5 equiv of *i*-PrOH was refluxed for 2 h, diene **4** was generated in 68% yield. Ozonolysis of diene **4** afforded hydroxy keto ester **5** in moderate yield. However, the resulting keto ester **5** readily lactonized during purification on silica gel and decomposed in basic media. To avoid these problems, the crude material was quickly filtered through a silica gel pad, and used directly in the next step. *syn* Selective reduction of hydroxy keto ester **5** using $NaBH_4$ in the presence of $Et_2B(OMe)$ gave **6** with almost



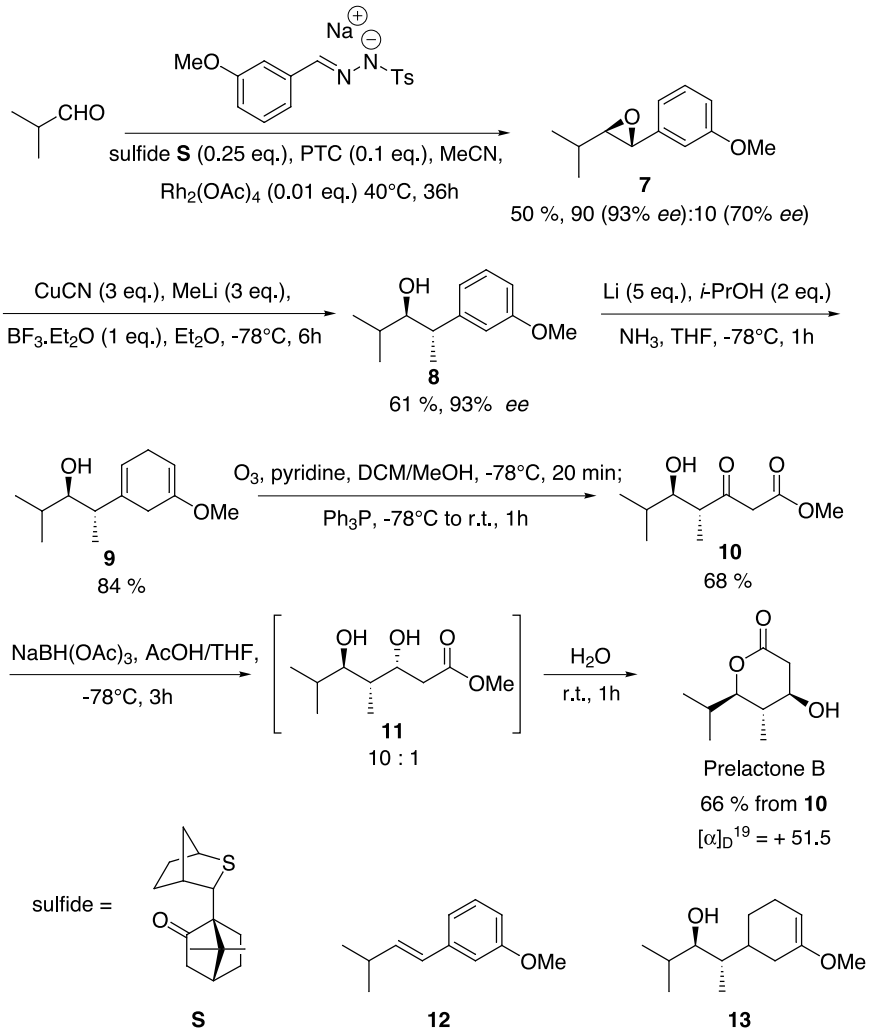

**Scheme 2.** Total synthesis of a mevinic acid analogue.

perfect diastereoselectivity (>98:2).[13] The *syn*-3,5-dihydroxy ester **6** slowly lactonized during purification on silica gel. We therefore treated the crude material with a few drops of 1 N HCl and this furnished the desired lactone **1** (42% over 3 steps). This material was identical to that reported in the literature (mp 70–72 °C, $[\alpha]_D^{20}=+35.6$ ($c=1.0$ in $CHCl_3$) [lit.[7a]: mp 69–70 °C, $[\alpha]_D^{20}=+34.1$ ($c=0.85$ in $CHCl_3$)]).

In the above synthesis, only one of the two stereogenic centers created in the epoxide was used, as the other was destroyed. We were keen to exemplify our methodology where both stereogenic centers were utilized and therefore turned our attention to the synthesis of the β-hydroxy-δ-lactone, (+)-prelactone B. This functionalized chiral δ-lactone was first isolated from bafilomycin-producing *Streptomyces griseus* by Zeeck and Bindseil in 1993, and it represents an early metabolite in the biosynthesis of polyketide antibiotics.[14]

Since the aryl epoxide required **7** bears branching at the α-position, we expected that our catalytic process would furnish the epoxide with good levels of diastereoselectivity. We therefore began our synthesis by treating isobutyraldehyde under our standard catalytic epoxidation conditions employing 25 mol% of the chiral sulfide **S**.[2] This furnished the desired epoxide in 50% yield as a 9:1 mixture of *trans* and *cis* isomers. The enantiomeric excesses for the two isomers were 93 and 70%, respectively.

Ring-opening reactions of the epoxide **7** with a variety of organometallic reagents was not straightforward. Neither MeLi nor Grignard reagents furnished the desired product even with $BF_3\cdot Et_2O$. Cuprates and Grignard reagents (MeMgBr or MeMgCl) with catalytic amount of various Cu salts under several different conditions were also examined[15] and despite partial success, yields were capricious and a significant amount of alkene **12** and unreacted starting epoxide were always observed. In addition, rearrangement of the epoxide to the corresponding ketone was occasionally observed. Trimethylaluminum was also tried[16] but in this case, the product was the undesired *syn* isomer regardless of the reaction conditions. Successful ring opening was finally achieved when the cuprate was employed in the presence of a Lewis acid.[17] Most importantly, careful control of the temperature and stoichiometry of the cuprate were critical to obtain reliable and reproducible results: 3 equiv of MeLi was slowly added to a suspension of 3 equiv of CuCN in $Et_2O$ at 0 °C. After 30 min at 0 °C, the mixture was cooled to −78 °C and a solution of epoxide was slowly added to the cuprate followed by addition of $BF_3\cdot OEt_2$. Under the optimized conditions, the ring-opening reaction of the mixture of chiral epoxides proceeded smoothly to give alcohol **8** in




**Scheme 3.** Total synthesis of (+) prelactone B.

61% yield with 93% ee. The *trans* epoxide was converted into the *anti* alcohol **8** while the *cis* epoxide was largely untouched (Scheme 3).

Under identical Birch reduction conditions as used previously, the desired diene **9** was obtained in only 46% yield with 42% of over-reduced side-product **13**. It was believed that the presence of the free alcohol in close proximity to the double bond resulted in further reduction of the diene to the cylcohexene **13**.[18] We attempted to suppress unwanted over-reduction by protecting the free alcohol but this resulted in considerably slower and lower yielding reactions. Best results were obtained when the reaction was carried out with 5 equiv of Li and 2 equiv *i*-PrOH. Under these conditions, the desired diene **9** was obtained in 84% yield with negligible amounts of the over-reduced side product **13**.

After ozonolysis, the hydroxy keto ester **10** was then reduced to dihydroxy ester **11**. Of the several reducing agents tested, sodium triacetoxyborohydride[19] was found to be optimum giving good yields and selectivities (10:1). As the resulting dihydroxy ester **11** was unstable on silica gel, this compound was directly treated with acid. Interestingly, when the reduction reaction was quenched with water and left to stir for an additional 1 h at room temperature, the *anti*-dihydroxy ester **11** was converted into (+)-prelactone B while the minor *syn* dihydroxy ester remained in solution. Using a few drops of aqueous 1 N HCl resulted in complete conversion of the 10:1 mixture of diols into the same mixture of lactones. The synthetic sample of (+)-prelactone B (93% ee) was spectroscopically identical to that reported in the literature (mp 96–98 °C, $[\alpha]_D^{19} = +51.5$ ($c = 1.0$ in $CH_3OH$) [lit.[14b]: mp 97–98 °C, $[\alpha]_D^{19} = +62.1$ ($c = 1.72$ in $CH_3OH$)]). The lower alpha D observed probably reflects the enantioselectivity obtained in the epoxidation step (93% ee).

## 3. Conclusions

In conclusion, we have successfully synthesized naturally occurring and biologically important β-hydroxy-δ-lactones from enantiomerically enriched epoxides. These syntheses demonstrate the utility of enantioselective sulfur ylide mediated reactions in the convergent preparation of epoxides and their subsequent diverse applications in organic synthesis.

## 4. Experimental

### 4.1. General methods

All oxygen or moisture sensitive reactions were carried out in oven-dried glassware under the positive pressure of argon. Sensitive liquids and solutions were transferred by syringe or cannula and introduced through rubber septa through which a high flow of nitrogen was maintained. Concentration of solution was accomplished by using a Buchi rotary evaporator with a water aspirator. This was generally followed by removal of residual solvents on a vacuum line held at 0.1–1 Torr. Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Chromatography grade hexane and ethyl acetate were technical grade and distilled before use. $Et_2O$ and THF were distilled from sodium benzophenone ketyl under nitrogen. Triethylamine was distilled from sodium. Dichloromethane was distilled from $P_2O_5$. Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel 60 $F_{254}$ plates. Visualization on TLC was achieved by use of UV light (254 nm), treatment with acidic anisaldehyde, potassium permanganate, 5% phosphomolybdic acid in ethanol, or ceric ammonium molybdate stain followed by heating. Flash column chromatography was undertaken on silica gel (Merck Kieselgel 60 $F_{254}$ 400–630 mesh). Proton nuclear magnetic resonance spectroscopy ($^1$H NMR) was recorded on Bruker FT AM 400 (400 MHz). Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0 ppm for TMSCl. The following abbreviations were used to describe peak patterns when appropriate: br=broad, s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet. Coupling constant, $J$ was reported in Hertz unit (Hz). Carbon 13 nuclear magnetic resonance spectroscopy ($^{13}$C NMR) was recorded on Brucker FT AM 400 (100 MHz) and was fully decoupled by broad band decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.0 ppm of chloroform-*d*. Infrared (IR) spectra were recorded neat in 0.5 mm path length sodium chloride cells on Bruker EQUINOX 55. Frequencies are given in reciprocal centimeters ($cm^{-1}$) and only selected absorbances are reported. Optical rotations were measured on an Autopol III of Rudolph instrument or a Perkin–Elmer 241 polarimeter at598 nm (Na D-line) with a path length of 1 dm. Concentrations ($c$) are quoted in g/100 mL. Low resolution mass spectra ($m/z$) were recorded on a VG Platform or VG Prospec with only (M+) and major peaks being reported with intensities being quoted as percentages of the base peak. High resolution mass spectra were recorded on a VG Prospec by using direct insertion probe (DIP) and EI or FAB method. High performance liquid chromatography (HPLC) data were obtained by using Agillent with chiralcel OD, OD-H, OJ or chiralpak AS-H column.

**4.1.1. 3-Cyclohexylpropanal.**[20] Neat DMSO (1.0 mL, 14 mmol) was added dropwise to a stirred solution of oxalyl chloride (440 μL, 5.0 mmol) in dichloromethane (20 mL) at −78 °C under argon atmosphere. After 15 min 3-cyclopropanol (610 μL, 4.0 mmol) was slowly added while the temperature was maintained at −78 °C. The solution was stirred for 1 h, during which the solution became cloudy. Triethylamine (5.0 mL) was added to the solution and the solution was warmed to room temperature slowly. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3×20 mL). The crude mixture was purified by flash chromatography (EtOAc/hexane=1/10). Colorless oil (500 mg, 89%); $R_f$=0.50 (EtOAc/hexane=1/10); $^1$H NMR (300 MHz, $CDCl_3$) 0.80–0.92 (2H, m, C$H_2$), 1.04–1.26 (4H, m, C$H_2$×2), 1.49 (2H, q, $J$=7.5 Hz, C$H_2$CH), 1.57–1.71 (5H, m, C$H_2$×2+C$H$), 2.40 (2H, dt, $J$=2.0, 7.5 Hz, C$H_2$CHO), 9.73 (1H, t, $J$=2.0 Hz, C$H$O); $^{13}$C NMR (75 MHz, $CDCl_3$) 26.2, 26.4, 29.3, 33.0, 37.2, 41.5, 203.1.

**4.1.2. 2-(3-Methoxybenzyl)-3-[(1*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]-(3*S*)-2-thionia-bicyclo [2.2.1]-heptane tetrafluoroborate.** To a rapidly stirred solution of chiral sulfide **S** (500 mg, 2.0 mmol) and 3-methoxybenzyl bromide (420 μL, 3.0 mmol) in dichloromethane (2 mL) was added silver tetrafluoroborate (778 mg, 4.0 mmol) in the dark under an argon atmosphere at room temperature. The reaction stirred for 48 h and 10 mL of $CH_2Cl_2$ was added. Silver bromide precipitate was filtered and the filtrate was concentrated in vacuo. The residual brown oil was purified by flash chromatography (0–5% MeOH/$CH_2Cl_2$) to give an off white foam. This was recrystallized from $CH_2Cl_2$ and $Et_2O$ to give a white precipitate. (572 mg, 77%); $R_f$= 0.36 (MeOH/$CH_2Cl_2$=1/10); $\nu_{max}/cm^{-1}$ (neat) 2957, 1739, 1587, 1492, 1456, 1267, 1055; mp 168−169 °C; $[\alpha]_D^{19}$= −40.0 ($c$=1.0 in $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) 1.08 (3H, s, C$H_3$), 1.18 (3H, s, C$H_3$), 1.29 (2H, d, $J$=8.6 Hz, C$H_2$), 1.60 (2H, m, C$H_2$), 1.87–2.22 (7H, m, 2×C$H_2$+ CH$H$CO+SCHCH$H$), 2.54 (1H, ddd, $J$=2.6, 5.2, 18.8 Hz, CH$H$CO), 2.85 (1H, d, $J$=12.9 Hz, SCHCH$H$), 3.20 (1H, br s, SCHC$H$), 3.80 (3H, s, OC$H_3$), 4.11 (1H, d, $J$=5.0 Hz, SC$H$CH$_2$), 4.39 (1H, d, $J$=13.5 Hz, SCH$H$Ar), 4.42 (1H, d, $J$=2.7 Hz, SC$H$CH), 4.62 (1H, d, $J$=13.5 Hz, SCH$H$Ar), 6.88 (1H, dd, $J$=2.6, 8.6 Hz, Ar$H$), 6.97 (1H, br s, Ar$H$), 6.99 (1H, d, $J$=2.0 Hz, Ar$H$), 7.26 (1H, t, $J$=8.2 Hz, Ar$H$); $^{13}$C NMR (100 MHz, $CDCl_3$) 19.2, 21.9, 24.4, 26.7, 26.8, 33.3, 41.1, 43.5, 44.1, 45.1, 47.8, 49.9, 55.6, 57.6, 60.1, 68.9, 115.2, 116.2, 122.3, 129.8, 130.7, 160.5, 215.7; $m/z$ (FAB) 371 ($M^+-BF_4^-$, 100%), 217 (30), 121 (43), 55 (33); (Found: $M^+-BF_4^-$ 371.2044 $C_{23}H_{31}SO_2$ requires $m/z$ 371.2045).

**4.1.3. 2-(2-Cyclohexylethyl)-3-(3-methoxyphenyl)oxirane (2).** To a stirred solution of 2-(3-methoxybenzyl)-3-[(1*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]-(3*S*)-2-thioniabicyclo-[2.2.1]-heptane tetrafluoroborate (465 mg, 1.0 mmol) in dichloromethane (5.0 mL) was added *N*,*N*,*N*′,*N*′,-tetramethyl-*N*″-[tris(dimethylamino)phos-phoralidene]phosphoric triamide ethylimine (415 μL, 1.25 mmol) at −78 °C under argon. After 30 min, 3-cyclohexylpropanal (175 mg, 1.25 mmol) was added to the solution. After 2 h stirring, the mixture was warmed up to room temperature and then saturated NaCl solution (10 mL) was added. The organic layer was separated and the aqueous layer extracted with EtOAc (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography (EtOAc/hexane=1/50) to give a mixture of *trans*/*cis*=92:8 epoxides (249 mg, 96%) and chiral sulfide (259 mg, 83%); $R_f$=0.30 (EtOAc/hexane=

1/20); $\nu_{max}/cm^{-1}$ (neat) 2923, 1604, 1493, 1455, 1260, 1154, 1047, 891, 782; $^1H$ NMR (400 MHz, $CDCl_3$) 0.66–0.80 (*cis*, 2H, m, $CH_2$), 0.84–0.94 (*trans*, 2H, m, $CH_2$), 1.04–1.30 (4H, m, $CH_2\times2$), 1.30–1.44 (2H, m, $CH_2$), 1.62–1.74 (7H, m, $CH_2\times3+CH$), 2.89 (*trans*, 1H, dt, $J=2.2$, 5.7 Hz, C*H*(O)CHAr), 3.15 (*cis*, 1H, dt, $J=4.3$, 5.7 Hz, C*H*(O)CHAr), 3.57 (*trans*, 1H, d, $J=2.2$ Hz, CH(O)C*H*Ar), 3.78 (*trans*, 3H, s, $OCH_3$), 3.79 (*cis*, 3H, s, $OCH_3$), 4.03 (*cis*, 1H, d, $J=4.3$ Hz, CH(O)C*H*Ar), 6.77 (1H, m, Ar*H*), 6.81 (1H, ddd, $J=1.0$, 2.4, 8.0 Hz, Ar*H*), 6.85 (1H, m, Ar*H*), 7.23 (1H, t, $J=7.8$ Hz, Ar*H*); $^{13}C$ NMR (100 MHz, $CDCl_3$) *trans* isomer: 26.3 (2), 26.6, 29.6, 33.1, 33.3, 33.4, 37.3, 55.2, 58.6, 63.4, 110.4, 113.7, 118.0, 129.4, 139.7, 159.8 *cis* isomer: 24.0, 26.1, 26.2, 26.5, 33.0, 33.5, 33.7, 57.5, 59.0, 111.7, 113.2, 118.8, 129.0, 137.4, 159.3; *m/z* (EI) 260 ($M^+$, 70%), 177 (10), 163 (44), 149 (72), 136 (81), 121 (100), 109 (70), 95 (53), 91 (58), 81 (62), 67 (60), 55 (65); (Found $M^+$ 260.1786 $C_{17}H_{24}O_2$ requires *m/z* 260.1776); Chiracel OD-H, hexane/*i*-PrOH (99.5/0.5), 1.0 mL/min, 10 °C, major 9.9 min (2*R*,3*R*), minor 10.6 min (2*S*,3*S*) for *trans* isomer and major 9.2 min (2*R*,3*S*), minor 7.0 min (2*S*,3*R*) for *cis* isomer.

**4.1.4. (1*S*,2*R*)-4-Cyclohexyl-1-isopropoxy-1-(3-methoxyphenyl)butan-2-ol (3).** A solution of 2-(2-cyclohexylethyl)-3-(3-methoxyphenyl)oxirane (260 mg, 1.0 mmol) in *i*-PrOH (10 mL) was treated with catalytic amount of conc. $H_2SO_4$ at 0 °C. After 30 min, *i*-PrOH was removed under reduced pressure in the presence of $NaHCO_3$. The residue was dissolved with ether, and then after filtration of the mixture, the filtrate was concentrated in vacuo. The crude mixture was purified by flash chromatography (EtOAc/hexane=1/10) to give a colorless oil (262 mg, 82%); $R_f=0.22$ (EtOAc/hexane=1/10); $\nu_{max}/cm^{-1}$ (neat) 3568, 2923, 1488, 1453, 1263, 1050; $[\alpha]_D^{20}=+57.4$ ($c=1.0$ in $CH_3OH$); $^1H$ NMR (400 MHz, $CDCl_3$) 0.82 (2H, m, $CH_2$), 1.05–1.50 (8H, m, $CH_2\times4$), 1.09 (3H, d, $J=6.1$ Hz, $CH(CH_3)_2$), 1.13 (3H, d, $J=6.1$ Hz, $CH(CH_3)_2$), 1.55–1.70 (5H, m, $CH_2\times3+CH$), 1.79 (1H, br s, O*H*), 3.51 (1H, septet, $J=6.1$ Hz, $CH(CH_3)_2$), 3.62 (1H, m, C*H*OH), 3.78 (3H, s, $OCH_3$), 4.27 (1H, d, $J=5.3$ Hz, C*H*O(*i*-Pr)), 6.81 (1H, m, Ar*H*), 6.89 (1H, m, Ar*H*), 7.24 (1H, t, $J=8.1$ Hz, Ar*H*); $^{13}C$ NMR (100 MHz, $CDCl_3$) 21.2, 23.4, 26.4 (2), 26.9, 29.4, 33.2, 33.5 (2), 37.8, 55.2, 69.5, 75.1, 82.0, 113.0, 113.1, 120.1, 129.2, 141.4, 159.6; *m/z* (FAB) 343 ($M^+$+Na, 98), 261 (100), 180 (47), 137 (65), 121 (58), 109 (28), 55 (16); (Found $M^+$+Na 343.2251 $C_{20}H_{32}O_3Na$ requires *m/z* 343.2249); Chiracel OD-H, hexane/*i*-PrOH (98/2), 0.5 mL/min, 20 °C, major 12.8 min (1*S*,2*R*), minor 11.7 min (1*R*,2*S*).

**4.1.5. (2*R*)-4-Cyclohexyl-1-(5-methoxycyclohexa-1,4-dienyl)-butan-2-ol (4).** Well-dried $NH_3$ over Na was transferred to a two-neck flask containing Li (69 mg, 10.0 mmol). A solution of (1*S*,2*R*)-4-cyclohexyl-1-isopropoxy-1-(3-methoxyphenyl)butan-2-ol (385 mg, 1.2 mmol) in THF (1 mL) was added to the blue $NH_3$ solution via cannula followed by addition of *i*-PrOH (500 μL, 6.0 mmol). The mixture was refluxed for 2 h and cooled to −78 °C, and then treated sequentially with 2 mL of benzene and 850 mg of ammonium acetate. $NH_3$ was allowed to evaporate and the residue was partitioned between brine (10 mL) and ethyl acetate (10 mL). The mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (EtOAC/hexane=1/20) to give a colorless oil (214 mg, 67%); $R_f=0.18$ (EtOAc/hexane=1/10); $\nu_{max}/cm^{-1}$ (neat) 3418, 2994, 1696, 1665, 1449, 1390, 1221, 1136; $^1H$ NMR (400 MHz, $C_6D_6$) 0.80–0.95 (2H, m, $CH_2$), 1.05–1.45 (9H, m, $CH_2\times4+OH$), 1.60–1.75 (5H, m, $CH_2\times2+CH$), 1.99 (2H, d, $J=6.3$ Hz, $CHOHCH_2CH=C$), 2.70–2.90 (4H, m, $=CCH_2C=\times2$), 3.28 (3H, s, $OCH_3$), 3.51 (1H, m, C*H*OH), 4.44 (1H, br s, $CH=COCH_3$), 5.43 (1H, br s, $CH=C(CH_2)_2$); $^{13}C$ NMR (100 MHz, $C_6D_6$) 26.7, 26.8, 27.1, 27.2, 32.3, 33.6, 33.7, 33.8, 35.0, 38.1, 45.9, 53.6, 69.1, 90.2, 121.9, 132.1, 153.4; *m/z* (EI) 264 ($M^+$, 20%), 135 (31), 122 (100), 109 (37), 91 (14), 55 (17); (Found $M^+$ 264.2090 $C_{17}H_{28}O_2$ requires *m/z* 264.2089).

**4.1.6. 6-(2-Cyclohexylethyl)-4-hydroxy-tetrahydropyran-2-one (1).**[7a] Round-bottomed flask equipped with $CaCl_2$ drying tube was filled with a solution of (2*R*)-4-cyclohexyl-1-(5-methoxycyclohexa-1,4-dienyl)-butan-2-ol (110 mg, 0.42 mmol) and pyridine (100 μL) in 10 mL of dichloromethane and 2 mL of methanol at −78 °C. $O_3$ was bubbled until saturated, at which point blue color was persisted. The solution was degassed with $O_2$ until blue color disappeared. Triphenylphosphine (110 mg, 0.42 mmol) was added and stirring continued for 1 h at room temperature. NaCl solution was added and two layers were separated. The aqueous layer extracted with dichloromethane (3×10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated to give the desired product as a colorless oil, which was used in next step without further purification; $R_f=0.35$ (EtOAc/hexane=1/2); $\nu_{max}/cm^{-1}$ (neat) 3421, 2923, 2851, 1747, 1715, 1651, 1448, 1324; $^1H$ NMR (400 MHz, $CDCl_3$) 0.82–0.95 (2H, m, $CH_2$), 1.00–1.50 (10H, m, $CH_2\times5$), 1.55–1.78 (5H, m, $CH_2\times2+CH$), 2.61 (1H, dd, $J=8.8$, 17.4 Hz, $CHOHCH_2CO$), 2.70 (1H, dd, $J=3.1$, 17.4 Hz, $CHOHCH_2CO$), 3.46 (2H, s, $COCH_2CO_2CH_3$), 3.71 (3H, s, $OCH_3$), 4.00 (1H, m, C*H*OH); $^{13}C$ NMR (100 MHz, $C_6D_6$) 26.3 (2), 26.6, 33.0, 33.2, 33.3, 33.8, 37.5, 49.6 (2), 52.4, 67.8, 167.3, 203.6; *m/z* (FAB) 257 ($M^+$+H, 100), 239 (49), 189 (35), 137 (60), 117 (44), 81 (43), 55 (40); (Found $M^+$+H 257.1750 $C_{14}H_{25}O_4$ requires *m/z* 257.1753).

To a cooled (−78 °C) solution of resulting (5*R*)-7-cyclohexyl-5-hydroxy-3-oxo-heptanoic acid methyl ester in 5 mL of THF and 1 mL of methanol was added a solution of diethylmethoxyborane (1.0 M in THF, 420 μL). The reaction mixture stirred at −78 °C for 15 min and then sodium borohydride (77 mg, 2.0 mmol) was added in a portion. The mixture stirred for 2 h and quenched by adding 1 mL of 1 N HCl. Stirring continued 1 h and $NaHCO_3$ solution was added to neutralize the mixture. The aqueous layer extracted with ethyl acetate (3×5 mL). The combined organic layer were dried ($MgSO_4$), filtered and concentrated. Flash chromatography with EtOAc/hexane=1/2 gave the desired product as a white solid (40 mg, 42%); $R_f=0.15$ (EtOAc/hexane=1/2); mp 70–72 °C [lit.: 69–70 °C][7a]; $[\alpha]_D^{20}=+35.6$ ($c=1.0$ in $CHCl_3$) [lit.: $[\alpha]_D^{20}=+34.1$ ($c=0.85$ in $CHCl_3$)][7a]; $^1H$ NMR (300 MHz, $CDCl_3$) 0.75–0.95 (2H, m, $CH_2$), 1.05–1.95 (16H, m, $CH_2\times7+CH+OH$), 2.60 (1H, ddd, $J=1.5$, 3.8, 22.6 Hz, $CH_2CO_2$), 2.65

(1H, dd, $J=5.0$, 22.6 Hz, C$H_2$CO$_2$), 4.36 (1H, m, C*H*OH), 4.63 (1H, m, C*H*OCO).

**4.1.7. *m*-Methoxybenzaldehyde tosylhydrazone.** To a rapidly stirred suspension of *p*-toluenesulfonyl hydrazide (5.7 g, 30.0 mmol) in methanol (20 mL) was added *m*-anisaldehyde (3.75 mL, 30 mmol) dropwise. A mildly exothermic reaction ensued and the hydrazide dissolved. Within 5–10 min *m*-methoxybenzaldehyde tosylhydrazone began to precipitate. After approximately 30 min the mixture was cooled to 0 °C and the product removed by filtration, washed with a small quantity of ice-cold methanol. Recrystallization from methanol gave a white solid (8.25 g, 90%); $\nu_{max}/cm^{-1}$ (neat) 3463, 3158, 1597, 1327, 1270, 1171, 1064, 899, 665; mp 106–107 °C; $^1$H NMR (400 MHz, $CDCl_3$) 2.37 (3H, s, C$H_3$), 3.78 (3H, s, OC$H_3$), 6.88 (1H, dd, $J=2.5$, 8.2 Hz, Ar*H*), 7.08 (1H, d, $J=7.6$ Hz, Ar*H*), 7.12 (1H, s, Ar*H*), 7.22 (1H, t, $J=8.0$ Hz, Ar*H*), 7.28 (2H, d, $J=8.2$ Hz, Ar*H*), 7.73 (1H, s, C*H*=N), 7.86 (2H, d, $J=8.2$ Hz, Ar*H*), 8.32 (1H, br s, N*H*); $^{13}$C NMR (100 MHz $CDCl_3$) 21.6, 55.3, 111.5, 116.7, 120.5, 127.9, 129.6, 129.7, 134.5, 135.2, 144.3, 147.7, 159.7; *m*/*z* (EI) 304 ($M^+$, 20%), 156 (18), 148 (100), 139 (13), 134 (46), 120 (97), 105 (15), 91 (81), 77 (31), 65 (28), 51 (22); (Found $M^+$ 304.0886 $C_{15}H_{16}N_2O_3S$ requires *m*/*z* 304.0882).

**4.1.8. *m*-Methoxybenzaldehyde tosylhydrazone sodium salt.** A 1.0 M sodium methoxide solution was prepared by adding sodium (635 mg, 27.5 mmol) to anhydrous methanol (27.5 mL) with external cooling. Once all of the metal had dissolved, *m*-methoxybenzaldehyde tosylhydrazone (8.25 g, 27 mmol) was added and the mixture stirred until the solid had dissolved. After stirring for a further 15 min, methanol was removed under reduced pressure at room temperature to yield hydrazone salt in quantitative yield. Solid hydrazone salt was then ground using a pestle and mortar to give a free flowing powder; $\nu_{max}/cm^{-1}$ (neat) 3459, 2959, 1600, 1237, 1129, 1084, 1031, 910; $^1$H NMR (400 MHz, $(CD_3)_2SO$) 2.27 (3H, s, CH3), 3.71 (3H, s, OCH3), 6.65 (1H, dd, $J=2.3$, 8.1 Hz, Ar*H*), 6.92 (2H, m, Ar*H*), 7.12 (1H, t, $J=7.2$ Hz, Ar*H*), 7.15 (2H, d, $J=8.2$ Hz, Ar*H*), 7.54 (1H, s, C*H*=N), 7.58 (2H, d, $J=8.2$ Hz Ar*H*); $^{13}$C NMR (100 MHz, $(CD_3)_2SO$) 20.8, 54.8, 109.5, 111.6, 117.6, 126.5, 128.1, 129.1, 136.2, 138.4, 139.9, 143.9, 159.2; *m*/*z* (FAB) 327 ($M^+ +1$, 21%), 201 (100), 176 (17); (Found: $[M+H]^+$ 327.0781 $C_{15}H_{16}O_3N_2SNa$ requires *m*/*z* 327.0779).

**4.1.9. 2-Isopropyl-3-(3-methoxyphenyl)oxirane (7).** A round bottomed flask was fitted with chiral sulfide (125 mg, 0.5 mmol), rhodium(II) acetate dimer (9 mg, 0.02 mmol), benzyl triethylammonium chloride (46 mg, 0.2 mmol), isobutyraldehyde (180 μL, 2.0 mmol) in anhydrous acetonitrile (6.0 mL) under nitrogen atmosphere. *m*-Methoxybenzaldehyde tosylhydrazone sodium salt (667 mg, 2.0 mmol) was added and the reaction mixture was stirred vigorously at room temperature for 10 min, then at 40 °C. Same amount of *m*-methoxybenzaldehyde tosylhydrazone sodium salt was added again after 12 and 24 h. After an additional 12 h stirring, the reaction was quenched by the addition of water (15 mL). The aqueous layer was washed with ethyl acetate (3×10 mL) and the combined organic phases dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified on silica gel ($Et_2O$/hexane=1/20) to give a desired product with some unknown impurities. Further purification was carried out by Kugelrohr distillation (6 Torr, 140 °C) to afford a pure mixture of *trans*/*cis*=90:10 (190 mg, 50%) as a colorless oil; $R_f=0.30$ ($Et_2O$/hexane=1/10); $\nu_{max}/cm^{-1}$ (neat) 2963, 1604, 1464, 1260, 1046; $^1$H NMR (400 MHz, $CDCl_3$) 0.70 (*cis*, 3H, d, $J=6.7$ Hz, C$H_3$), 1.01 (*trans*, 3H, d, $J=6.8$ Hz, C$H_3$), 1.08 (*trans*+*cis*, 3H, d, $J=6.8$ Hz, C$H_3$), 1.24 (*cis*, 1H, m, C$H$(C$H_3$)$_2$), 1.66 (*trans*, 1H, octet, $J=6.8$ Hz, C$H$(C$H_3$)$_2$), 2.72 (*trans*, 1H, dd, $J=2.1$, 6.8 Hz, CO*H*CH), 3.63 (*trans*, 1H, d, $J=2.1$ Hz, ArCO*H*), 2.83 (*cis*, 1H, dd, $J=4.4$, 9.2 Hz, CO*H*CH), 3.78 (*trans*, 3H, s, OC$H_3$), 3.79 (*cis*, 3H, s, OC$H_3$), 4.06 (*cis*, 1H, d, $J=4.4$ Hz, ArCO*H*), 6.76–6.92 (3H, m, Ar*H*), 7.23 (1H, t, $J=7.9$ Hz, Ar*H*); $^{13}$C NMR (100 MHz $CDCl_3$) *trans* isomer: 18.4, 19.0, 30.9, 55.2, 57.5, 68.3, 110.4, 113.7, 117.9, 129.4, 139.7, 159.8; *cis* isomer: 17.9, 19.9, 25.9, 55.2, 57.7, 65.1, 111.7, 112.9, 118.7, 129.0, 137.5, 159.3; *m*/*z* (EI); 192 ($M^+$, 79%), 176 (13), 161 (25), 149 (95), 136 (100), 121 (40), 109 (19), 91 (45), 77 (28), 71 (12), 55 (12); (Found $M^+$ 192.1152 $C_{12}H_{16}O_2$ requires *m*/*z* 192.1150); Chiracel OJ-H, hexane/*i*-PrOH (99.5/0.5), 1.0 mL/min, 10 °C, major 12.0 min (2*R*,3*R*), minor 13.1 min (2*S*,3*S*) for *trans* isomer and major 7.4 min (2*R*,3*S*), minor 8.1 min (2*S*,3*R*) for *cis* isomer.

**4.1.10. (2*S*,3*R*)-2-(3-Methoxyphenyl)-4-methyl-pentan-3-ol (8).** To a stirred suspension of CuCN (464 mg, 5.2 mmol) in $Et_2O$ (20 mL) was quickly added MeLi (1.6 M in $Et_2O$, 3.25 mL) at 0 °C. After 20 min the mixture was cooled to −78 °C. A solution of 2-isopropyl-3-(3-methoxyphenyl)oxirane (322 mg, 1.73 mmol) in $Et_2O$ (5 mL) was added followed by $BF_3\cdot Et_2O$ (220 μL, 1.73 mmol). Temperature was raised to room temperature after 6 h and 50 mL of $NH_3Cl/NH_4OH$ solution (4/1) was added. The aqueous layer was washed with ethyl acetate (3×50 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (EtOAc/hexane=1/20) to furnish a pale yellow oil (232 mg, 64%); $R_f=0.25$ (EtOAc/hexane=1/10); $\nu_{max}/cm^{-1}$ (neat) 3476, 2962, 1602, 1487, 1262; $[\alpha]_D^{17}=-19.1$ ($c=1.0$ in $CH_3OH$); $^1$H NMR (400 MHz, $CDCl_3$) 0.92 (3H, d, $J=6.8$ Hz, (C$H_3$)$_2$CH), 1.01 (3H, d, $J=6.8$ Hz, (C$H_3$)$_2$CH), 1.20 (1H, br s, O*H*), 1.22 (3H, d, $J=7.0$ Hz, C$H_3$CHAr), 1.79 (1H, d-septet, $J=4.2$, 6.8 Hz, C$H$(C$H_3$)$_2$), 2.80 (1H, quintet, $J=7.2$ Hz, CH$_3$C*H*Ar), 3.41 (1H, dd, $J=4.2$, 7.6 Hz, COHC*H*), 3.79 (3H, s, OC$H_3$), 6.80 (3H, m, Ar*H*), 7.22 (1H, t, $J=7.7$ Hz, Ar*H*); $^{13}$C NMR (100 MHz $CDCl_3$) 15.2, 18.5, 20.4, 29.9, 43.5, 55.1, 80.3, 111.7, 114.0, 120.5, 129.5, 145.8, 159.7; *m*/*z* (EI) 208 ($M^+$, 22%), 165 (12), 136 (100), 121 (63), 104 (14), 91 (11), 77 (8), 55 (9); (Found $M^+$ 208.1464. $C_{13}H_{20}O_2$ requires *m*/*z* 208.1463); Chiracel OD-H, hexane/*i*-PrOH (95/5), 0.5 mL/min, 20 °C, major 14.8 min (2*S*,3*R*), minor 13.0 min (2*R*,3*S*).

**4.1.11. (2*S*,3*R*)-2-(5-Methoxycyclohexa-1,4-dienyl)-4-methylpentan-3-ol (9).** Well-dried $NH_3$ over Na was transferred to a two-neck flask containing Li (53 mg, 7.5 mmol). A solution of (2*S*,3*R*)-2-(3-methoxyphenyl)-4-methyl-pentan-3-ol (314 mg, 1.5 mmol) in THF (2 mL) was

added to the blue $NH_3$ solution *via* cannula followed by the addition of *i*-PrOH (250 μL, 3.0 mmol). The mixture was refluxed for 2 h and cooled to −78 °C, and then treated sequentially with 2 mL of benzene and 850 mg of ammonium acetate. $NH_3$ was allowed to evaporate and the residue was partitioned between brine (20 mL) and ethyl acetate (20 mL). The mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (EtOAC/hexane=1/20) to give a colorless oil (265 mg, 84%); $R_f$=0.30 (EtOAc/hexane=1/10); $\nu_{max}/cm^{-1}$ (neat) 3553, 2962, 1695, 1389, 1221, 1156; $[\alpha]_D^{16}$=+14.7 ($c$=1.0 in PhH); $^1$H NMR (400 MHz, $C_6D_6$) 0.79 (3H, d, $J$=7.1 Hz, C$H_3$CH), 0.88 (3H, d, $J$=6.8 Hz, (C$H_3$)$_2$CH), 1.04 (3H, d, $J$=6.8 Hz, (C$H_3$)$_2$CH), 1.39 (1H, br s, O$H$), 1.61 (1H, d-septet, $J$=3.2, 6.8 Hz, C$H$(CH$_3$)$_2$), 2.17 (1H, dq, $J$=7.1, 8.8 Hz, CH$_3$C$H$), 2.69 (2H, m, C$H_2$), 2.79 (2H, m, C$H_2$), 3.13 (1H, dd, $J$=3.2, 8.8 Hz, C$H$OH), 3.27 (3H, s, OC$H_3$), 4.41 (1H, br s, CH$_2$C$H$=C), 5.40 (1H, br s, CH$_2$C$H$=COCH$_3$); $^{13}$C NMR (100 MHz $C_6D_6$) 14.6, 15.5, 20.9, 27.0, 28.8, 29.6, 45.1, 53.6, 76.3, 90.1, 121.6, 136.9, 153.6; *m/z* (EI) 210 ($M^+$, 21%), 149 (43), 138 (100), 121 (47), 109 (82), 105 (19), 91 (30), 77 (12), 55 (9); (Found $M^+$ 210.1619. $C_{13}H_{22}O_2$ requires *m/z* 210.1620).

**4.1.12. (4*S*,5*R*)-5-Hydroxy-4,6-dimethyl-3-oxo-heptanoic acid methyl ester (10).** A two-neck flask equipped with $CaCl_2$ drying tube was filled with a solution of (2*S*,3*R*)-2-(5-methoxycyclohexa-1,4-dienyl)-4-methylpentan-3-ol (210 mg, 1.0 mmol) and pyridine (100 μL) in 10 mL of $CH_2Cl_2$ and 2 mL of methanol at −78 °C. $O_3$ was bubbled until saturated, at which point blue color persisted, and then the solution was degassed with $O_2$ until blue color disappeared. Triphenyl phosphine (785 mg, 3.0 mmol) was added and stirring continued for 1 h at room temperature. After solvent was removed under reduced pressure, flash chromatography (25% EtOAc in hexane) gave the desire product as a pale yellow oil (135 mg, 67%); $R_f$=0.36 (EtOAc/hexane=1/2); $\nu_{max}/cm^{-1}$ (neat) 3525, 2964, 1747, 1713, 1457, 1317, 1159, 996; $[\alpha]_D^{17}$=−16.6 ($c$=1.0 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) 0.84 (keto 3H, d, $J$=6.8 Hz, (C$H_3$)$_2$CH), 0.88 (enol 3H, d, $J$=6.7 Hz, (C$H_3$)$_2$CH), 0.91 (enol, 3H, d, $J$=6.7 Hz, (C$H_3$)$_2$CH), 0.92 (keto, 3H, d, $J$=6.8 Hz, (C$H_3$)$_2$CH), 1.06 (keto, 3H, d, $J$=7.1 Hz, CHC$H_3$), 1.14 (enol, 3H, d, $J$=7.1 Hz, CHC$H_3$), 1.68 (enol, 1H, m, C$H$(CH$_3$)$_2$), 1.74 (keto, 1H, d-septet, $J$=2.8, 6.8 Hz, C$H$(CH$_3$)$_2$), 1.90 (enol, 1H, br s, O$H$), 2.00 (enol, 1H, br s, O$H$), 2.31 (keto, 1H, d, $J$=5.9 Hz, O$H$), 2.37 (enol, 1H, quintet, $J$=7.0 Hz, C$H$CH$_3$), 2.81 (keto, 1H, quintet, $J$=7.4 Hz, C$H$CH$_3$), 3.32 (enol, 1H, m, C$H$OH), 3.45 (keto, 1H, m, C$H$OH), 3.55 (keto, 2H, d, $J$=3.4 Hz, COC$H_2$), 3.68 (enol, 3H, s, OC$H_3$), 3.69 (keto, 3H, s, OC$H_3$), 5.03 (enol, 1H, s, COH=C$H$); $^{13}$C NMR (100 MHz $CDCl_3$) keto: 13.5, 15.0, 19.8, 29.9, 49.1, 49.3, 52.2, 78.1, 167.7, 207.8 enol: 15.5, 16.2, 19.9, 30.8, 42.8, 51.2, 78.3, 89.9, 173.0, 180.3.

**4.1.13. Prelactone B ((3*R*,4*S*,5*R*)-3-hydroxy-4,6-dimethylheptanoic acid-δ-lactone).**[14b] Acetic acid (1.0 mL) was added to a suspension of NaBH(OAc)$_3$ (410 mg, 1.9 mmol) in THF (3 mL) at −78 °C under argon. After 10 min, a solution of (4*S*,5*R*)-5-hydroxy-4,6-dimethyl-3-oxo-heptanoic acid methyl ester (130 mg, 0.64 mmol) in THF (2 mL) was added. Reaction continued for 3 h, and then temperature was raised to room temperature. The reaction was quenched by adding water (5 mL) and two-phase mixture was stirred for an additional hour. After being neutralized by 20% NaOH solution, the aqueous layer extracted with ethyl acetate (3×10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Flash chromatography (EtOAc/hexane=1/1) gave Prelactone B as a white solid (73 mg, 66%); $R_f$=0.26 (EtOAc/hexane=1/1); mp 96–98 °C [lit.: 97–98 °C][14b]; $[\alpha]_D^{19}$=+51.5 ($c$=1.0 in $CH_3OH$)[lit.: $[\alpha]_D^{19}$=+62.1 ($c$=1.72 in $CH_3OH$)][14b]; $^1$H NMR (400 MHz, $CDCl_3$) 0.90 (3H, d, C$H_3$CH, $J$=6.9 Hz), 1.04 (3H, d, $J$=6.7 Hz, (C$H_3$)$_2$CH), 1.04 (3H, d, $J$=6.7 Hz, (C$H_3$)$_2$CH), 1.73 (1H, d-septet, $J$=2.2, 6.9 Hz, C$H$CH$_3$), 1.97 (1H, m, C$H$(CH$_3$)$_2$), 2.02 (1H, br s., O$H$), 2.46 (1H, dd, $J$=8.1, 17.3 Hz, C$H$HCO), 2.90 (1H, dd, $J$=5.9, 17.3 Hz, C$H$HCO), 3.74 (2H, m, C$H$OH+OC$H$CH); $^{13}$C NMR (100 MHz $CDCl_3$) 13.6, 14.0, 20.0, 28.9, 38.9, 39.0, 69.8, 86.2, 170.9.

## References and notes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