Strategies for the Total Asymmetric Synthesis of Heliannuols K and L: Scope and Limitations

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Kulinkovich reactions of oxa-esters bearing terminal double bonds afford cyclopropanols by intramolecular cyclization. These can undergo Saegusa oxidation to provide β-chlorooxacycloalkanones and can then be then dehydrohalogenated into oxacycloalkenones. Through a judicious choice of starting esters, diverse aryl-fused benzoxocinones possessing the basic skeleton of sesquiterpenes, such as heliannuols, can be obtained. Although the syntheses of certain compounds in racemic form seem accessible, however, improvements through new strategies are still required for the total asymmetric synthesis. This article describes the first synthesis of enantiomerically enriched OMe-heliannuol K and the first stereo- and enantioselective synthesis of heliannuol L, and new approaches and studies of their limitations in the preparation of these products are detailed.

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Introduction

The preparation of natural and environmentally friendly bioactive products constitutes a synthetic challenge involving control over chemoselectivity, regioselectivity, and stereoselectivity. In this area, heliannuols,[1] isolated from sunflowers, represent a group of aryl derivatives showing allelopathic activities. Heliannuols K (**1**) and L (**2**) (Figure 1) appeared to us to be particularly attractive natural products in relation to our previous work on the construction of benzo-fused cyclic ethers.[2]

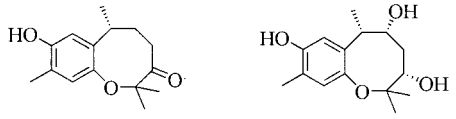

Figure 1. Heliannuols (+)-K (**1**) and (–)-L (**2**) from *Helianthus annuus*.

The intramolecular titanium-mediated cyclopropanation reaction[3] of the oxa-ω-alkenoic ester **3** gave a diastereomeric mixture of the cyclopropanols **4a** and **4b**, which, after oxidation and dehydrochlorination, yielded the benzoxocinone **5** (Figure 2).[4]

However, any asymmetric center present in the oxacycle would inevitably undergo racemization during the dehydrochlorination step.

To the best of our knowledge, the racemic synthesis of an O-Me heliannuol K precursor has previously been reported by Venkateswaran[5] as an intermediate in the formal

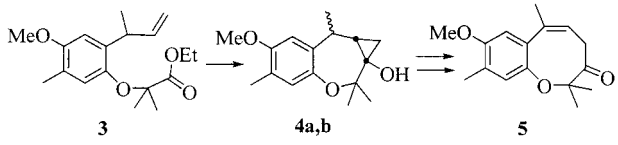

Figure 2. Synthesis of potential precursor **5**.

stereoselective synthesis of heliannuol A, whilst no total synthesis, racemic or asymmetric, of heliannuols K or L has been reported in the literature. In this article we report the scope and limitations of our procedure for the application of the asymmetric synthesis of heliannuols K (**1**) and L (**2**).

Results and Discussion

On the Synthesis of Heliannuol K

In order to preserve the integrity of the stereogenic carbon in the cyclopropanols **4a/4b**, it would be important to avoid dehydrohalogenation and rather to proceed by dehalogenation. To achieve this, it proved essential to determine experimental conditions to allow the radical **6** to be generated and trapped in situ by an appropriate reducing agent to furnish the benzoxocinone **8** (Scheme 1).

As shown in Table 1, oxidants such as ferric or cupric acetylacetonate[6] (Entries 1 and 2), manganese picolinate[7] (Entry 3), and vanadyl acetylacetonate[8] (Entry 4) in the presence of triethylsilane as hydrogen donor left the starting material unchanged. On the other hand, the Saegusa oxidation procedure[9] with one equivalent of ferric chloride and pyridine (Entry 5) gave a diastereomeric mixture (77:23) of the chlorides **7a** and **7b** (*trans*-**7a** as the major

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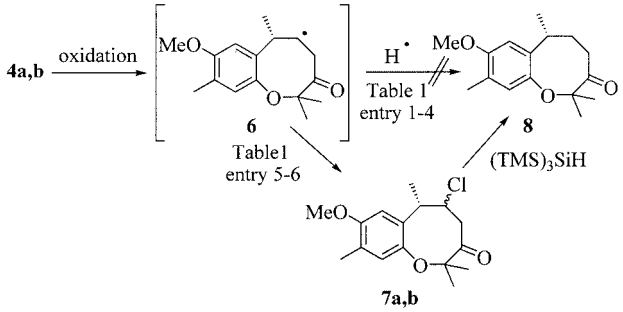


Scheme 1. Dechlorination without racemization.

isomer) even when ten equivalents of triethylsilane were used. However, treatment of these chlorides **7a** and **7b** with tris(trimethylsilyl)silane[10] afforded the expected oxacyclooctanone **8** (Entry 6).

The first strategy explored for the asymmetric synthesis of (+)-heliannuol K (**1**) involved the preparation of the enantiopure precursor **3**. This compound could in turn be derived from olefin **11**, which could be prepared by dehydration and reduction of triol **10**. Ketone **9** would therefore be an appropriate precursor in this retrosynthetic scheme (Figure 3).

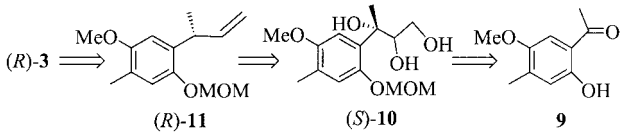
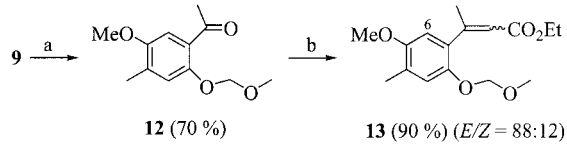


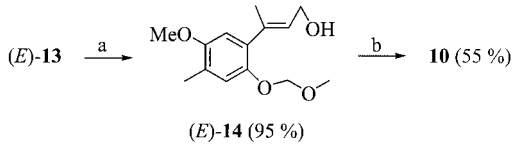
Figure 3. Retrosynthetic scheme for the synthesis of enantiopure oxa-ω-alkenoic ester **3**.

Ketone **9**, prepared from the commercially available 2-methylhydroquinone,[11] was thus protected as a MOM ether under classical conditions (protection as TBDMS ether was also effective, although in lower yield, indubitably due to large steric hindrance). Wittig–Horner treatment of the ketone **12** then yielded an (*E*/*Z*) mixture of the corresponding esters **13**, the configurations of which were attributed by observation of an nOe effect between the ethylenic hydrogen and the 6-hydrogen on the aryl moiety in the (*E*) isomer (Scheme 2).



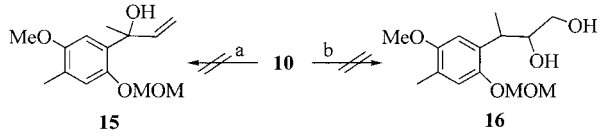
Scheme 2. a) $ClCH_2OCH_3$, *i*Pr_2Net, CH_2Cl_2, room temp. b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, reflux.

The ester (*E*)-**13**, separated from its (*Z*) isomer by silica gel chromatography, was readily reduced to the corresponding alcohol **14**. In order to test the feasibility of our procedure, nonasymmetric dihydroxylation of the double bond was then carried out to give the expected racemic triol **10** (Scheme 3).



Scheme 3. a) DIBAH, THF, 0 °C. b) OsO_4, NMO, *t*BuOH, H_2O, THF, 0 °C.

While conversion of *vic*-diols into olefins has been successfully reported by Garegg and Samuelson,[12] and by Lowary,[13] dehydration of the triol **10** did not give the expected alcohol **15**. Likewise, regioselective benzylic hydrogenolysis with Pearlman's catalyst[14] did not succeed in providing diol **16** (Scheme 4).



Scheme 4. a) I_2, PPh_3, imidazole, THF, reflux. b) H_2, $Pd(OH)_2/C$, EtOH, 20 °C.

Nevertheless, both enantiopure alcohol (*S*)-**15** and diol (*S*)-**16** could be considered as potential precursors in the asymmetric synthesis of intermediate **3**. Indeed, the chiral carbonate deriving from the alcohol (*S*)-**15** could undergo a palladium-catalyzed enantioselective reduction according to the Tsuji procedure[15] while dehydration[12,13] of the chiral diol (*S*)-**16** should afford the enantiopure olefin **3** (Figure 4).

Table 1. Attempts of synthesis of benzoxocinone 8 from cyclopropanols **4a**,**b**.

Entry	Oxidant (eq.)	Solvent	Reducing agent (equiv.)	Time	Temperature	Product (yield)
1	$Fe(acac)_3$ (0.1)	Et_2O	Et_3SiH (1.3)	100 h	20 °C	no reaction
2	$Cu(acac)_2$ (0.04)	EtOH	Et_3SiH (1.3)	72 h	20 °C	no reaction
3	$Mn(pic)_3$ (2.5)	DMF or Et_2O	Et_3SiH (2)	24 h	0 → 20 °C	no reaction
4	$VO(acac)_2$ (0.3)	EtOH	Et_3SiH (2)	24 h	20 °C	no reaction
5	$FeCl_3$[a] (2.2)	DMF	Et_3SiH (10)	24 h	0 °C	**7a**, **7b**[b] (73%)
6	$FeCl_3$[a] (2.2)	$PhCH_3$	$(TMS)_3SiH$ (1.2)	2 h	80 °C	**8**[b] (52%[c])

[a] One equivalent of pyridine was added. [b] As a diastereomeric mixture (77:23). [c] Overall yield over the two steps: chlorides **7a** and **7b** were isolated before reduction.

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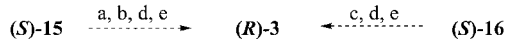


Figure 4. a) $ClCO_2Me$, pyridine. b) $Pd(acac)_2$, HCO_2H, NEt_3, nBu_3P. c) I_2, PPh_3, imidazole, THF, reflux. d) 6 N HCl, THF. e) NaH, DMPU, $Br(CH_3)_2CCO_2Et$, toluene, reflux.

Another approach toward enantiopure (*R*)-**3** would require oxidation and subsequent Wittig condensation of alcohol **18**, which might be derivable from diol **17** by stereoselective Raney nickel reduction as recently reported for the parent compound by Pan[16] (Figure 5).

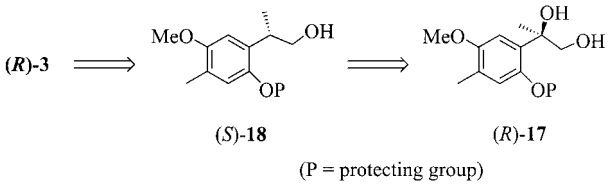
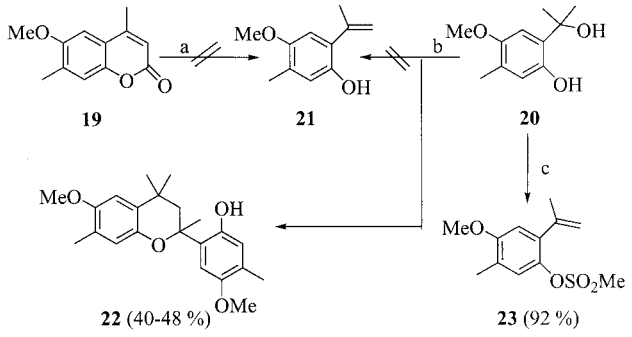


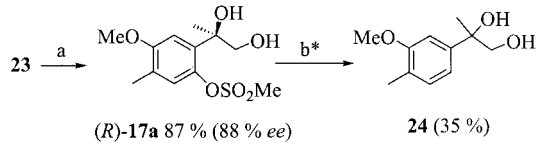
Figure 5. Alternative retrosynthetic scheme for the synthesis of enantiopure oxa-ω-alkenoic ester **3**.

In this regard, we were unable to reproduce the synthesis of the styrenol **21** either from 4,7-dimethyl-6-methoxycoumarin (**19**)[17] or by dehydration[18] of phenol **20** (prepared from the corresponding ketone **9**[19]), which only allowed the benzopyranyl derivative **22**[18a] to be isolated. Finally, treatment of phenol **20** with methanesulfonyl chloride under basic conditions[20] resulted in both dehydration of the tertiary alcohol function and esterification of the phenol to yield the mesylate **23** (Scheme 5).



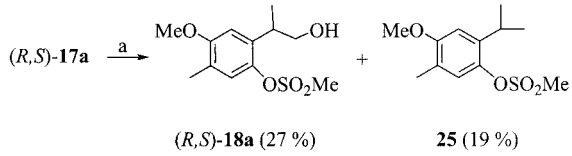
Scheme 5. a) KOH, ethane-1,2-diol, reflux. b) I_2, C_6H_6, reflux, or $MgSO_4$, C_6H_6, reflux or *p*-toluenesulfonic acid, CH_2Cl_2, reflux. c) $MeSO_2Cl$, NEt_3, DMAP.

Subsequent Sharpless asymmetric dihydroxylation[21] of mesylate **21** furnished the optically active diol (*R*)-**17a**, determination of the enantiomeric excess of which failed by HPLC, but was accomplished through the Mosher ester derivatives[22] (racemic diol **17a** was prepared by a sodium periodate/ruthenium chloride procedure[23]). However, application of the Pan procedure[16] to racemic mesylate **17a** only furnished the diol **24**, resulting from removal of the methanesulfonic group, a reaction already reported in the literature[24] (Scheme 6).



Scheme 6. a) AD-mix-β, *t*BuOH, H_2O, 0 °C. b*) H_2, $Pd(OH)_2/C$, EtOH, 20 °C (* reaction performed on the racemic mesylate).

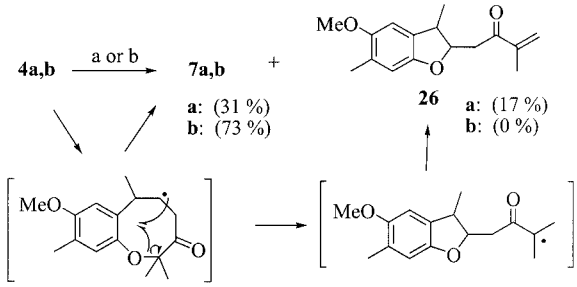
On the other hand, treatment of racemic mesylate **17a** with Pearlman's catalyst[14] gave the expected alcohol **18a** and the dehydroxylated sulfonate **25**, but in yields too low for this route to be viable (Scheme 7).



Scheme 7. a) H_2, $Pd(OH)_2/C$, EtOH, 20 °C.

Finally, to overcome these difficulties for the formation of an exploitable intermediate, the direct asymmetric hydrogenation of the benzoxocinone **5** was explored. This compound was prepared as outlined in Figure 2, as in our previous work.[4]

However, when the oxidation of the cyclopropanols **4a** and **4b** was carried out in ether, the benzofuran **26** was isolated in addition to the chlorides **7a** and **7b**. Its formation, not observed in DMF, follows a radical process, proceeding first by a classic homolytic scission of an internal cyclopropane bond (the chlorides **7a** and **7b** are formed by halogen trapping at this stage[25]). Homolytic rupture involving a new ring closure then occurs, with formation of enone **26** by base-induced proton elimination (Scheme 8).



Scheme 8. a) $FeCl_3$, pyridine, Et_2O, 0 °C. b) $FeCl_3$, pyridine, DMF, 0 °C.

In the light of research into the asymmetric hydrogenation of unactivated arylalkenes, the optically active iridium complexes [mainly the borate **27** (Figure 6)] proposed by Burgess[26] appeared to be the best candidates for chiral inductors for this type of compound.

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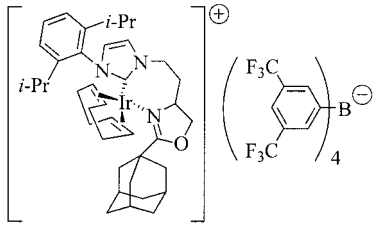
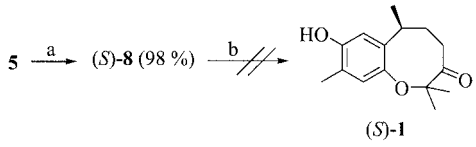


Figure 6. Iridium complex **27** used for asymmetric hydrogenation.

Hydrogenation of alkene **5** in the presence of catalyst **27** under atmospheric pressure achieved no reduction of the ethylenic carbon–carbon bond. After three hours at 50 bar, however, reduction had occurred to yield benzoxocinone **8**. Rotational analysis showed that only a weak asymmetric induction had been achieved. Moreover, a negative rotational value clearly indicated the unexpected (*S*) configuration for the major enantiomer, contrary to Burgess's prediction[26] (Scheme 9). In addition, demethylation effected under standard conditions (vide supra)[27] gave an inextricable mixture in which the presence of heliannuol K (**1**) was undetectable.

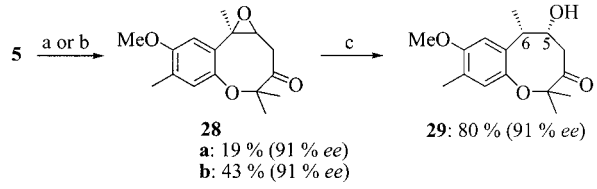


Scheme 9. a) H_2, Pd/C, 0.1 equiv. **27**, 50 bar, CH_2Cl_2, 20 °C. b) EtSNa, DMF, 140 °C.

Further exploration to improve this synthesis will therefore be necessary. Finally, the best method to achieve an efficient total enantioselective synthesis of heliannuol K should be the oxidation of the alcohol function of the oxacycle of heliannuol A (heliannuol A differs from heliannuol K only in the presence of a hydroxy function instead of the ketone). The asymmetric synthesis of both enantiomers of heliannuol A has been previously reported in the literature by Shishido.[28]

On the Synthesis of Heliannuol L

The asymmetric epoxidation of the benzoxocinone **5** was performed by both the Jacobsen[29] and the Shi[30] procedures and furnished the epoxide **28** in 19% and 43% yields, respectively. *Ee*s of 91% were determined by HPLC for both procedures, however. As reported in our previous work,[4] regioselective hydrogenolysis yielded the homobenzylic alcohol **29** as a single isomer, as observed by ^1H and ^{13}C NMR spectroscopy. Surprisingly, a 0.3 Hz coupling constant between the protons in position C-5 and C-6 of the oxacycle suggests a dihedral angle close to 90° (Scheme 10).



Scheme 10. a) (*S,S*)-Jacobsen manganese complex, *p*-phenylpyridine *N*-oxide, NaOCl, CH_2Cl_2, 4 °C. b) Shi procedure: D-fructose derivative, nBu_4NHSO_4, oxone, K_2CO_3, CH_3CN-DMM, 0 °C. c) H_2, Pd/C, MeOH, EtOAc, 20 °C.

Minimized molecular modeling calculation geometries[31] performed on the more stable conformation predicted a dihedral angle of 85° between 5-H and 6-H for the *cis* relationship, while an angle of 165°, with a ^3J coupling constant of 7 or 8 Hz, was predicted for the corresponding *trans* relationship (Figure 7). Moreover, cross correlation peaks between 5-H (δ = 4.08 ppm) and 6-H (δ = 3.41 ppm) in the NMR NOESY experiment clearly confirmed the *cis* relationship between these two hydrogens.

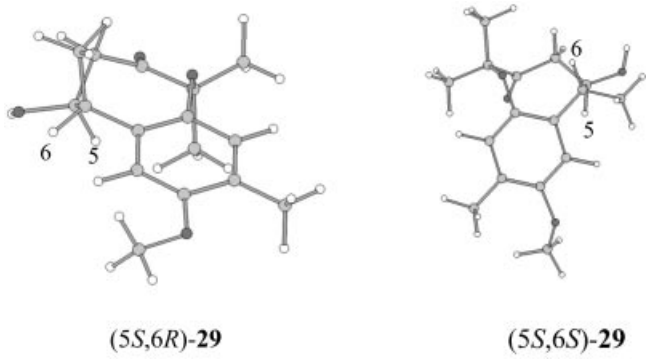
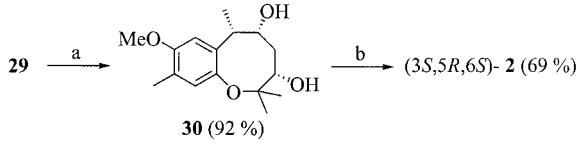


Figure 7. PM3-minimized geometries of (5*S*,6*R*)- and (5*S*,6*S*)-**29**.

Reduction of the ketone function of the oxacyclooctanone **29** with DIBAH at –78 °C furnished the diol **30** with total and expected stereoselectivity, while a weaker selectivity (77:23) occurred with sodium borohydride. Finally, demethylation[27] of ether **30** afforded (–)-heliannuol L (**2**) with retention of the integrity of all stereogenic centers (Scheme 11).



Scheme 11. a) DIBAH, THF, –78 °C. b) EtSNa, DMF, 140 °C.

Conclusions

We report in this article on our studies on some novel approaches in the total enantiomerically enriched synthesis of heliannuols K and L. The major difficulties encountered during this work are also reported. In the case of heliannuol K, a number of problems were encountered; firstly, es-

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tablishing the stereogenic center early did allow an acceptable yield of an enantiomerically enriched precursor of heliannuol K to be obtained, but the direct asymmetric hydrogenation of a potential precursor by use of chiral metallic complexes as would be predicted proved disappointing. Moreover, the impossibility of generating the phenolic function by removal of the methoxy group under classical methods requires that new procedures with other protecting groups have to be explored. In contrario, the first total racemic and enantiomeric synthesis of (–)-heliannuol L was fruitfully achieved from the same precursor as used in the first optically active synthesis of (–)-OMe-heliannuol K.

Experimental Section

General Remarks: Melting points (uncorrected) were determined with a Büchi B-545 apparatus. Polarimetric measurements were performed on a Perkin–Elmer 241 polarimeter. FT-IR: Perkin–Elmer spectrophotometer (Spectrum One). ^{1}H NMR: Bruker AM 250 (250 MHz), AM 360 (360 MHz), AC 250 (250 MHz), AC 200 (200 MHz), or DRX 400 (400 MHz): δ = 7.27 ppm for $CHCl_3$ as internal standard. ^{13}C NMR: Bruker AM 250 (63 MHz), AM 360 (90 MHz), AC 250 (63 MHz), AC 200 (50.3 MHz): δ = 77 ppm relative to the resonance of the solvent ($CDCl_3$). The DEPT-135 pulse was used for the determination of signal types. MS (Electronic Impact or Chemical Ionization): Nermag R-10 coupled with a OK1 DP 125 gas chromatograph. Relative percentages are shown in brackets; High Resolution Mass Spectra were recorded with a Finningan MAT 95S instrument (Electronic Impact or ElectroSpray). Elemental analysis were performed with a Perkin–Elmer 240C analyzer by the Service de Microanalyse, Institut de Chimie des Substances Naturelles, Gif-sur-Yvette (France). The enantiomeric excesses were determined by GPC (Cydex-B) or by HPLC (Chiracel OD-H column) or by ^{19}F NMR of Mosher esters or by ^{1}H NMR with the chiral shift reagent: (+)-europium tris[3-(heptafluoropropylhydroxymethylene)camphorate]. Solvents were dried by standard procedures. All reactions requiring anhydrous conditions were performed under argon.

Ethyl 2-[4-Methoxy-5-methyl-2-(1-methylprop-2-enyl)phenoxy]-2-methylpropanoate (3): DMPU (2.4 mL, 19.8 mmol) and 4-methoxy-5-methyl-2-(1-methylprop-2-enyl)phenol (prepared from the 2-methylanisole[32]) (1.9 g, 9.9 mmol) were successively added under argon at 20 °C to a solution of 60% sodium hydride suspension (514 mg, 12.8 mmol) in anhydrous toluene (105 mL). After the mixture had been stirred for 15 min, ethyl bromoisobutyrate (2.18 mL, 14.8 mmol) was added and the mixture was heated at reflux for 60 h. After cooling, filtration, and washing with toluene, the residue was concentrated and chromatographed on silica gel (eluent: petroleum ether/diethyl ether, 95:5 then 70:30) to furnish the oxaester **3** (2.4 g, 80%) as a pale yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.60 (s, 1 H), 6.56 (s, 1 H), 6.02 (ddd, $^{trans}J$ = 17.0 Hz, ^{cis}J = 11.0, ^3J = 5.5 Hz, 1 H), 5.06 (m, 2 H), 4.28 (q, ^3J = 7.1 Hz, 2 H), 3.95 (dq, ^3J = 6.8, ^3J = 5.5 Hz, 1 H), 3.77 (s, 3 H), 2.12 (s, 3 H), 1.56 (s, 3 H), 1.52 (s, 3 H), 1.31 (t, ^3J = 7.1 Hz, 3 H), 1.30 (d, ^3J = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 174.7, 152.8, 145.7, 142.9, 135.0, 124.2, 120.5, 112.7, 109.3, 79.2, 61.2, 55.4, 35.5, 25.6, 24.9, 19.0, 16.0, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 3082, 2981, 2936, 1735, 1501 cm^{-1}. MS EI, *m*/*z* = 306 $[M]^{+\cdot}$ (45), 193 (11), 192 (98), 191 (57), 178 (11), 177 (100), 159 (7). HRMS EI: found 306.1821; $C_{18}H_{26}O_4$ requires 306.1830.

6-Methoxy-2,2,5,8-tetramethyl-8,8a-dihydro-1*H*-benzo[*b*]cyclopropa-[*e*]oxepin-1a(2*H*)-ol (4a and 4b): $BrTi(OiPr)_4$ (0.3 mL, 0.98 mmol) and then, over a period of 4 h, a ethereal solution of cyclohexylmagnesium chloride (1.57 M, 2.5 mL, 3.9 mmol) were added successively to a solution of oxaester **3** (300 mg, 0.98 mmol) in THF (25 mL). After additional stirring for 1 h, the mixture was diluted with diethyl ether (25 mL), hydrolyzed at 0 °C with saturated aqueous NH_4Cl solution (3 mL), and vigorously stirred for 1 h. After filtration through Celite, drying over magnesium sulfate, and concentration, the residue was chromatographed on silica gel (toluene/diethyl ether, 98:2, then petroleum ether/diethyl ether, 80:20 then 50:50) to give the cyclopropanol **4a** (56 mg, 22%) and the cyclopropanol **4b** (54 mg, 21%) as colorless oils.

Isomer 4a: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.74 (s, 1 H), 6.59 (s, 1 H), 3.82 (s, 3 H), 2.79 (dq, ^3J = 7.3, ^3J = 6.7 Hz, 1 H), 2,16 (s, 3 H), 1.80 (s, 1 H), 1.50 (s, 3 H), 1.47 (d, ^3J = 7.3 Hz, 3 H), 1.35 (s, 3 H), 1.31–1.14 (m, 1 H), 0.99 (dd, ^{cis}J = 10.7 Hz, ^{gem}J = 5.2 Hz, 1 H), 0.74 (dd, $^{trans}J$ = 6.1 Hz, ^{gem}J = 5.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 154.1, 146.8, 137.6, 123.8, 126.3, 107.2, 77.5, 62.3, 55.6, 36.0, 34.2, 27.4, 25.4, 18.3, 15.7, 21.0 ppm. IR (neat): $\tilde{\nu}$ = 3391, 2960, 2934, 1505 cm^{-1}. MS EI, *m*/*z* = 262 $[M]^{+\cdot}$ (41), 260 (13), 229 (13), 206 (28), 191 (74), 178 (29), 177 (100); 165 (83), 164 (54), 163 (19), 149 (26), 149 (16), 91 (10). HRMS EI: found 262.1564; $C_{16}H_{22}O_3$ requires 262.1568.

Isomer 4b: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.66 (s, 1 H), 6.49 (s, 1 H), 3.79 (s, 3 H), 3.44 (dq, ^3J = 7.9, ^3J = 7.3 Hz, 1 H), 2.14 (s, 3 H), 1.94 (s, 1 H), 1.60 (m, 1 H), 1.48 (s, 3 H), 1.26 (s, 3 H), 1.22 (d, ^3J = 7.9 Hz, 3 H), 0.83 (dd, $^{trans}J$ = 7.3 Hz, ^{gem}J = 5.5 Hz, 1 H), 0.69 (dd, ^{cis}J = 11.0 Hz, ^{gem}J = 5.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 154.1, 145.9, 136.1, 124.5, 126.5, 110.1, 77.9, 64.7, 55.6, 33.1, 30.1, 26.6, 24.2, 22.7, 15.6, 13.3 ppm. IR (neat): $\tilde{\nu}$ = 3392, 2975, 2932, 1505 cm^{-1}. MS EI, *m*/*z* = 262 $[M]^{+\cdot}$ (46), 191 (23), 178 (18), 177 (100), 176 (36), 165 (32), 164 (17), 149 (22), 91 (7). HRMS EI: found 262.1576; $C_{16}H_{22}O_3$ requires 262.1568.

8-Methoxy-2,2,6,9-tetramethyl-2*H*-1-benzoxocin-3(4*H*)-one (5): Cyclopropanols **4a/4b** (71 mg, 0.27 mmol) in dimethylformamide (1 mL) were added dropwise under argon at 0 °C to a solution of anhydrous ferric(III) chloride (97 mg, 0,6 mmol) and pyridine (0.22 mL, 0.27 mmol) in dimethylformamide (3 ml). After stirring for 4 h at this temperature, the mixture was diluted with ethyl acetate (5 mL), H_2O (1 mL), and aqueous HCl solution (1 N, 1 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with H_2O (10 mL), dried over magnesium sulfate, and concentrated. DBU (0.085 mL, 0.54 mmol) was added dropwise at –10 °C to the crude residue dissolved in diethyl ether (10 ml), and the mixture was left to warm to room temperature and stirred overnight. After it had again been cooled to 0 °C, diethyl ether (5 mL) and H_2O (3 mL) was added. The aqueous phase was extracted with diethyl ether (3 × 10 mL), and the combined organic layers were washed with brine (5 mL), dried over magnesium sulfate, concentrated, and chromatographed on silica gel (eluent: petroleum ether/diethyl ether, 98:2) to give the expected ketone **5** (38.5 mg, 55%) as a white solid.[4]

***trans*- and *cis*-5-Chloro-8-methoxy-2,2,6,9-tetramethyl-5,6-dihydro-2*H*-1-benzoxocin-3(4*H*)-one (7):** The cyclopropanols **4a/4b** (74 mg, 0.28 mmol) in dimethylformamide (1 mL) were added dropwise under argon at 0 °C to a solution of ferric(III) chloride (100 mg, 0.62 mmol) and pyridine (0.024 mL, 0.28 mmol) in dimethylformamide (3 mL). After stirring for 3 h at the same temperature, the reaction mixture was diluted with H_2O (3 mL), aqueous HCl solution (1 N, 0.5 mL), and diethyl ether (5 mL). The organic phase was

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washed with H_2O (3 × 1 mL) and dried over anhydrous sulfate, and the solvents were evaporated. The crude residue was then purified by chromatography on silica gel (eluent: pentane/diethyl ether, 96:4 then 93:7) to furnish the *trans*-chloride **7a** (14 mg, 17%) and the *cis*-chloride **7b** (47 mg, (56%) as colorless oils.

***trans*-7a:** ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.78 (s, 1 H), 6.66 (s, 1 H), 4.41 (dt, ^3J = 4.0, ^3J = 11.1 Hz, 1 H), 3.83 (s, 3 H), 3.60–3.42 (m, 1 H), 2.97 (broad s, 1 H), 2.65 (dd, ^{gem}J = 11.5, ^3J = 4.0 Hz, 1 H), 2.18 (s, 3 H), 1.53 (d, ^3J = 9.5 Hz, 3 H), 1.50 (broad s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 207.4, 162.1, 145.8, 131.7, 125.9, 127.3, 110.9, 85.2, 62.9, 55.6, 44.2, 30.3, 23.7, 23.0, 15.9 ppm. IR (neat): $\tilde{\nu}$ = 2982, 2936, 1714, 1503 cm^{-1}. MS EI, *m*/*z* = 298 $[M]^{+\cdot}$ (9), 296 $[M]^{+\cdot}$ (30), 260 (26), 191 (47), 177 (25), 176 (27), 165 (100), 91 (5), 69 (7). HRMS EI: found 296.1170; $C_{16}H_{21}ClO_3$ requires 296.1179.

***cis*-7b:** ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.75 (s, 1 H), 6.51 (s, 1 H), 4.95 (t, ^3J = 8.5 Hz, 1 H), 3.78 (s, 3 H), 3.32–3.08 (m, 2 H), 2.82 (dd, ^{gem}J = 15.5, ^3J = 10.3 Hz, 1 H), 2.14 (s, 3 H), 1.55 (s, 3 H), 1.49 (d, ^3J = 6.9 Hz, 3 H), 1.46 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 207.8, 155.1, 145.3, 133.9, 125.8, 127.5, 110.9, 86.0, 61.9, 55.5, 47.6, 46.9, 25.1, 23.6, 21.7, 15.9 ppm. IR (neat): $\tilde{\nu}$ = 2977, 2934, 1714, 1504 cm^{-1}. MS EI, *m*/*z* = 298 $[M]^{+\cdot}$ (7), 296 $[M]^{+\cdot}$ (25), 260 (19), 191 (32), 177 (31), 176 (100), 165 (71), 161 (18). HRMS EI: found 296.1173; $C_{16}H_{21}ClO_3$ requires 296.1179.

8-Methoxy-2,2,6,9-tetramethyl-5,6-dihydro-2*H*-1-benzoxocin-3(4*H*)-one (8)

a) From the Chlorides 7a/7b: AIBN (5 mg, 0.026 mmol) and tris(trimethylsilyl)silane (0.1 mL, 0.31 mmol) were added successively at 20 °C to a solution of the chloro ketones **7a/7b** (78 mg, 0.26 mmol) in anhydrous toluene (1 mL). The mixture was heated at 80 °C for 2 h, and then cooled. The residue was concentrated and chromatographed on neutral alumina (eluent: petroleum ether/diethyl ether, 98:2 then 95:5) to give the expected ketone **8** (44 mg, 80%) as a white solid.[4]

b) From the Benzoxocinone 5: Pd/C (10%, 5 mg) was added to a solution of enone **5** (20 mg, 0.07 mmol) in ethyl acetate (1 mL) and the mixture was stirred at 20 °C for 3 days under hydrogen atmosphere. After filtration through Celite and concentration, the residue was chromatographed on silica gel (eluent: petroleum ether/diethyl ether, 93:7) to furnish the expected ketone **8** (20 mg, 98%).

c) Asymmetric Route: Iridium complex **27** (1.1 mg, 0.077 μmol) was added to a solution of enone **5** (20 mg, 0.07 mmol) in chloroform (2 mL), and the test tube was placed in a bomb, which was pressurized to 50 bar with hydrogen. After its contents had been stirred at 20 °C for 3 h, the bomb was vented and the mixture was evaporated and chromatographed on silica gel as previously reported to give the enantiomerically enriched benzoxocinone (*S*)-**8** (19 mg, 95%) with an enantiomeric excess of 14% as determined by use of europium chiral reagent. The enantiomeric purity determination was carried out by ^{1}H NMR in the presence of increasing amounts (from 10 mol% to 100 mol%) of the shift reagent [(+)-Eu(hfc)$_3$]. The singlet of the methoxy protons gave a double set of signals in the racemic benzoxocinone **8**. $[\alpha]_D^{20}$ = –5.2 (*c* = 0.95, $CHCl_3$).

1-[5-Methoxy-2-(methoxymethoxy)-4-methylphenyl]ethanone (12): *N*,*N*-Diisopropylethylamine (1.94 mL, 11.1 mmol) and chloromethoxymethane (0.85 mL, 11.1 mmol) were added dropwise and successively under argon at 0 °C to a solution of 2-hydroxy-5-methoxy-4-methylacetophenone (**9**, 1 g, 5.55 mmol) in dichloromethane (15 mL). After stirring for 5 d at 20 °C, the mixture was diluted with dichloromethane (20 mL) and treated with aqueous NaOH solution (6 N, 2 × 10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, evaporated, and flash chromatographed on silica gel (petroleum ether/diethyl ether, 92:8 then 70:30) to give pure MOM-ether **12** (0.87 g, 70%) as a yellow solid, m.p. 39–40 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.24 (s, 1 H), 7.00 (s, 1 H), 5.22 (s, 2 H), 3.83 (s, 3 H), 3.52 (s, 3 H), 2.65 (s, 3 H), 2.24 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 198.6, 152.3, 150.8, 133.5, 126.2, 117.8, 110.3, 94.9, 56.2, 55.5, 31.8, 16.5 ppm. $C_{12}H_{16}O_4$ requires 224.1048; calcd. C 64.27, H 7.19; found 64.05, H 7.24.

Ethyl (2*E*)- and (2*Z*)-3-[5-Methoxy-2-(methoxymethoxy)-4-methylphenyl]but-2-enoate (13): Triethyl phosphonoacetate (0.22 mL, 1.12 mmol) was added dropwise under argon at 0 °C to a solution of sodium hydride suspension (60%, 42 mg, 1.03 mmol) in tetrahydrofuran (1.5 mL). After the mixture had been stirred for 10 min, the ketone **12** (193 mg, 0.86 mmol) in tetrahydrofuran (1 mL) was added dropwise at the same temperature. After having been heated for 3 h, the mixture was cooled to 0 °C and diethyl ether (10 mL) and H_2O (3 mL) were added. The aqueous phase was extracted with diethyl ether (3 × 20 mL) and the combined organic layers were washed with brine (5 mL), dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (eluent: petroleum ether/diethyl ether, 93:7 then 70:30) to give ester (*E*)-**13** (200 mg, 79%) as a white solid and ester (*Z*)-**13** (27 mg, 11%) as a colorless oil.

Isomer (2*E*)-13: M.p. 35–36 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.94 (s, 1 H), 6.62 (s, 1 H), 5.91 (s, 1 H), 5.09 (s, 2 H), 4.22 (q, ^3J = 7.1 Hz, 2 H), 3.80 (s, 3 H), 3.48 (s, 3 H), 2.52 (s, 3 H), 2.21 (s, 3 H), 1,32 (t, ^3J = 7.1 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 166.5, 156.4, 152.4, 147.2, 131.7, 127.6, 119.0, 118.5, 110.4, 95.3, 59.5, 55.8, 55.5, 19.9, 16.0, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2979, 2829, 1714, 1634, 1505 cm^{-1}. MS EI, *m*/*z* = 294 $[M]^{+\cdot}$ (26), 262 (16), 233 (50), 219 (21), 216 (37), 204 (100), 189 (40), 176 (68), 161 (59), 45 (86). HRMS EI: found 294.1471, $C_{16}H_{22}O_5$ requires 294.1467; calcd. C 65.29, H 7.53; found 64.76, H 7.57.

Isomer (2*Z*)-13: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.94 (s, 1 H), 6.50 (s, 1 H), 5.96 (s, 1 H), 5.05 (s, 2 H), 4.00 (q, ^3J = 7.1 Hz, 2 H), 3.77 (s, 3 H), 3.46 (s, 3 H), 2.20 (s, 3 H), 2.17 (s, 3 H), 1.08 (t, ^3J = 7.1 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 165.5, 153.0, 152.9, 146.3, 129.2, 126.7, 118.9, 118.5, 109.8, 95.7, 59.5, 55.8, 55.7, 26.3, 16.2, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2953, 2854, 1728, 1715, 1646, 1505 cm^{-1}. MS EI, *m*/*z* = 294 $[M]^{+\cdot}$ (47), 262 (13, 233 (41), 219 (21), 216 (31), 205 (42), 204 (100), 189 (28), 176 (68), 161 (59), 45 (44). HRMS EI: found 294.1471, $C_{16}H_{22}O_5$ requires 294.1467.

(2*E*)-3-[5-Methoxy-2-(methoxymethoxy)-4-methylphenyl]but-2-en-1-ol (14): A DIBAH solution in toluene (1 M, 1.75 mL, 1.75 mmol) was added dropwise at 0 °C under argon to a solution of ester (*E*)-**13** (223 mg, 0.76 mmol) in anhydrous tetrahydrofuran (1 mL). After stirring for 2 h at the same temperature, the mixture was quenched by addition of an aqueous HCl solution (2 N, 1 mL) and diluted with ethyl acetate (15 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were washed with brine (3 mL), dried over magnesium sulfate, evaporated, and flash chromatographed on silica gel (eluent: petroleum ether/diethyl ether, 80:20 then 70:30) to yield the expected allylic alcohol **14** (181 mg, 95%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.91 (s, 1 H), 6.63 (s, 1 H), 5.70 (dt, ^3J = 6.8, ^4J = 1.5 Hz, 1 H), 5.09 (s, 2 H), 4.35 (d, ^3J = 6.8 Hz, 2 H), 3.80 (s, 3 H), 3.48 (s, 3 H), 2.20 (s, 3 H), 2.06 (s, 3 H), 1.57 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 152.5, 147.3, 137.8, 132.7, 126.2, 128.2, 118.5, 111.4, 95.5, 60.0, 55.9, 55.6, 17.4,

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16.0 ppm. IR (neat): $\tilde{\nu}$ = 3418, 2952, 1652, 1505 cm^{-1}. MS EI, *m*/*z* = 252 $[M]^{+\cdot}$ (7), 234 (25), 202 (35), 201 (25), 190 (54), 189 (100), 176 (23), 175 (84), 115 (11), 45 (28). HRMS EI: found 252.1356, $C_{14}H_{20}O_4$ requires 252.1361.

3-[5-Methoxy-2-(methoxymethoxy)-4-methylphenyl]butane-1,2,3-triol (10): NMO (151 mg, 1.28 mmol) and an aqueous OsO_4 solution (4%, 0.054 mL, 0.22 mmol) were successively added at 20 °C to a solution of allylic alcohol (*E*)-**14** (108 mg, 0.43 mmol) in a *tert*-butanol/THF/H_2O mixture (7:2:1, 4.2 mL). After this mixture had been stirred for 3 days at the same temperature, a saturated aqueous $Na_2S_2O_3$ solution (5 mL) was added. The aqueous phase was then extracted with AcOEt (3×15 mL), and the combined organic layers were successively washed with an aqueous $Na_2S_2O_3$ solution (0.1 M, 10 mL), an aqueous HCl solution (0.1 M, 10 mL), and H_2O (10 mL). After drying over magnesium sulfate and concentration the residue was purified by flash chromatography on silica gel (eluent: petroleum ether /ethyl acetate, 20:80 then 0:100) to give the triol **10** (73 mg, 55%) as a yellow solid, m.p. 72–73 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 6. 92 (s, 1 H), 6.65 (s, 1 H), 5.72 (t, ^3J = 4.2 Hz, 1 H), 5.13 (s, 2 H), 4.38 (d, ^3J = 4.2 Hz, 2 H), 3.85 (s, 3 H), 3.51 (s, 3 H), 2.27 (s, 3 H), 2.08 (s, 3 H), 1.61 (broad s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 152.4, 146.6, 130.9, 126.3, 117.0, 108.9, 94.6, 77.1, 73.7, 63.8, 56.0, 55.8, 25.3, 15.9 ppm. IR (KBr): $\tilde{\nu}$ = 3419, 2936, 1505 cm^{-1}. MS ES, *m*/*z* = 309.1 $[M + Na]^+$. HMRS ES^+: found 309.13098; $C_{14}H_{22}O_6Na$ requires 309.13140; calcd. C 58.73, H 7.74; found 58.55, H 7.44.

4-Methoxy-2-(6-methoxy-2,4,4,7-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-yl)-5-methylphenol (22)

a) I_2/C_6H_6: A solution of phenol **20** (330 mg, 1.68 mmol) and iodine (5 mg, 0.2 mmol) in benzene (7 mL) was heated at reflux for 5 h. After cooling, the organic phase was successively washed with a saturated aqueous $Na_2S_2O_3$ solution (2×5 mL), H_2O (5 mL), and brine (5 mL), and then dried over magnesium sulfate and concentrated. After flash chromatography on silica gel (eluent: pentane ether/diethyl ether, 92:8 then 80:20), dimer **22** (140 mg, 47%) was obtained as a white solid.

Magnesium Sulfate/C_6H_6: A solution of phenol **20** (330 mg, 1.68 mmol) and magnesium sulfate (1.51 g, 12.6 mmol) in benzene (10 mL) was heated at reflux for 24 h. After cooling, the organic phase was filtered, evaporated, and flash chromatographed as previously to give dimer **22** (143 mg, 48%).

***p*-Toluenesulfonic Acid/CH_2Cl_2:** A solution of phenol **20** (98 mg, 0.5 mmol) and TsOH (60 mg, 0.5 mmol) in CH_2Cl2 (5 mL) was heated at reflux for 2 h. After filtration, the organic phase was washed with H_2O (5 mL) and brine (5 mL), dried over magnesium sulfate, and concentrated. The residue was then flash chromatographed as previously to give dimer **22** (36 mg, 40%), m.p. 102–103 °C (ref.[18a] 105–106 °C). ^1H NMR (360 MHz, $CDCl_3$): δ = 7.71 (s, 1 H), 6.74 (s, 1 H), 6.69 (s, 1 H), 6,64 (s, 1 H), 6,62 (s, 1 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 2.56 (d, ^2J = 14.5 Hz, 1 H), 2.17 (s, 3 H), 2.15 (s, 3 H), 2.04 (d, ^2J = 14.5 Hz, 1 H), 1.69 (s, 3 H), 1.43 (s, 3 H), 1.22 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 152.7, 150.8, 147.4, 143.9, 129.1, 127.2, 127.0, 126.1, 119.5, 119.4, 109.3, 107.9, 80.2, 55.9, 55.7, 47.1, 32.4, 32.3, 31.1, 28.1, 15.7, 15.5 ppm. IR (KBr): $\tilde{\nu}$ = 3399, 2956, 2925, 2832, 2864, 1499 cm^{-1}. MS EI, *m*/*z* = 356 $[M]^{+\cdot}$ (32), 203 (8), 179 (86), 178 (100), 163 (18). HRMS EI: found 356.1978, $C_{22}H_{28}O_4$ requires 356.1987.

2-Isoproprenyl-4-methoxy-5-methylphenylmethanesulfonate (23): A methylmagnesium bromide solution in tetrahydrofuran (3 M, 0.980 mol, 2.93 mmol) was added dropwise at 0 °C under argon to a solution of 2-hydroxy-5-methoxy-4-methylacetophenone[11] (211 mg, 1.17 mmol) in tetrahydrofuran (4 mL). The resulting solution was allowed to stir at 20 °C for two hours and was then cooled to 0 °C, diethyl ether (10 mL) was added, and the mixture was quenched by addition of a saturated aqueous NH_4Cl solution (2 mL). The aqueous phase was then extracted with ethyl acetate (3×5 mL), and the combined organic layers were washed with brine (7 mL), dried over magnesium sulfate, and concentrated. Triethylamine (0.98 mL, 7 mmol) and DMAP (11.5 mg, 0.09 mmol) were added at 20 °C under argon to the crude residue, diluted with 6 mL of diethyl ether. Methanesulfonyl chloride (0.4 mL, 3.5 mmol) was then added dropwise at 0 °C, and the solution was allowed to stir at 20 °C for one hour. After extraction of the aqueous phase with ethyl acetate (3×10 mL), the combined organic phases were washed with brine (5 M), dried over magnesium sulfate, concentrated, and chromatographed on silica gel (eluent: petroleum ether/ethyl acetate, 92:8 then 85:15) to give the expected mesylate **23** (198 mg, 66%) as a pale yellow oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.14 (s, 1 H), 6.70 (s, 1 H), 5.27 (broad s, 1 H), 5.16 (broad s, 1 H), 3.84 (s, 3 H), 3.05 (s, 3 H), 2.21 (s, 3 H), 2.14 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 156.1, 141.9, 138.8, 134.6, 127.0, 124.7, 116.9, 116.4, 54.4, 37.5, 23.1, 15.7 ppm. IR (neat): $\tilde{\nu}$ = 3084, 2938, 1501 cm^{-1}. MS EI, *m*/*z* = 256 $[M]^{+\cdot}$ (42), 177 (100), 149 (56), 119 (14), 91 (13). HRMS EI: found 256.0761; $C_{22}H_{28}O_4$ requires 256.0769.

(2*R*)-2-{5-Methoxy-4-methyl-2-[(methylsulfonyl)oxy]phenyl}-propane-1,2-diol (17a)

a) Racemic Procedure: A solution of sodium periodate (150 mg, 0.7 mmol) and ruthenium chloride hydrate (6.8 mg, 0.03 mmol) in water (1 mL) was added at 0 °C to a solution of sulfonate **23** (120 mg, 0.47 mmol) in an ethyl acetate/acetonitrile mixture (1:1, 5.5 mL). After the mixture had been stirred at this temperature for 1 h, a saturated aqueous $Na_2S_2O_3$ solution (7 mL) was added and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over magnesium sulfate, concentrated, and chromatographed on silica gel (eluent: pentane/ethyl acetate, 5:95) to furnish the expected racemic diol **17a** (87 mg, 64%) as a white solid.

b) Asymmetric Procedure: A solution of AD-mix-β (1.076 g) in a H_2O/*t*BuOH mixture (1:1, 7.7 mL) was allowed to stir at 20 °C for two hours. After the mixture had been cooled to 0 °C, the sulfonate **23** (197 mg, 0.77 mmol) was added and the solution was stirred at this temperature for 48 h. Sodium sulfite (1.15 g, 0.92 mmol) and ethyl acetate (5 mL) were then added and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over magnesium sulfate, concentrated, and chromatographed on silica gel (eluent: pentane/ethyl acetate, 35:65) to give the diol **17a** (194 mg, 87%) as a white solid with an enantiomeric excess of 88% as determined by ^{19}F NMR on the Mosher ester derivatives; m.p. 107–108 °C. $[\alpha]_D^{20}$ = +1.8 (*c* = 1.01, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.20 (s, 1 H), 7.16 (s, 1 H), 4.10 (d, ^{gem}J = 11.5 Hz, 1 H), 3.85 (s, 3 H), 3.70 (d, ^{gem}J = 11.5 Hz, 1 H), 3.27 (s, 3 H), 3.13 (broad s, 2 H), 2.20 (s, 3 H), 1.54 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 155.9, 138.9, 134.6, 127.3, 123.5, 109.8, 74.5, 69.3, 55.5, 38.7, 25.0, 15.7 ppm. IR (KBr): $\tilde{\nu}$ = 3521, 2939, 1505, 1499 cm^{-1}. MS EI, *m*/*z* = 290 $[M]^{+\cdot}$ (1), 259 (33), 181 (11), 180 (100), 165 (47), 151 (11). HRMS EI: found 290.0821; $C_{12}H_{18}O_6S$ requires 290.0824; calcd. C 49.64, H 6.25; found C 49.69, H 6.28.

2-(3-Methoxy-4-methylphenyl)propane-1,2-diol (24): Raney nickel (400 mg), previously washed with ethanol, was added at 20 °C to a solution of diol **17a** (167 mg, 0.57 mmol) in ethanol (7 mL). After having been heated at reflux for 48 h, the cooled mixture was con-

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centrated and then chromatographed on silica gel (eluent: petroleum ether/ethyl acetate, 1:1 then 20:80) to furnish the starting material (40 mg, 36%) and the diol **24** (39 mg, 35%) as a white solid, m.p. 81–82 °C. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.12 (d, ^3J = 7.9 Hz, 1 H), 7.02 (s, 1 H), 6.87 (d, ^3J = 7.9 Hz, 1 H), 3.86 (s, 3 H), 3.82 (d, ^{gem}J = 11.0 Hz, 1 H), 3.64 (d, ^{gem}J = 11,0 Hz, 1 H), 2.58 (s, 2 H), 2.21 (s, 3 H), 1.53 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 157.8, 143.9, 130.4, 125.5, 116.6, 107.1, 74.9, 71.1, 55.3, 26.1, 15.8 ppm. IR (KBr): $\tilde{\nu}$ = 3393, 2974, 2932, 1505 cm^{-1}. MS EI, *m*/*z* = 196 $[M]^{+\cdot}$ (5), 178 (31), 165 (57), 150 (11), 149 (100), 119 (9), 91 (20), 43 (46). HRMS EI: found 196.1102, $C_{11}H_{16}O_3$ requires 196.1099; calcd. C 67.32, H 8.22; found C 67.51, H 7.99.

2-(2-Hydroxy-1-methylethyl)-4-methoxy-5-methylphenyl Methanesulfonate (18a) and 2-Isopropyl-4-methoxy-5-methylphenyl Methanesulfonate (25): A mixture of the diol **17a** (39 mg, 0.13 mmol) and palladium hydroxide (39 mg) in ethanol (1 mL) was stirred at 20 °C under hydrogen atmosphere for 24 h. After filtration through Celite and concentration, the residue was chromatographed on silica gel (eluent: pentane/ethyl acetate, 60:40 then 10:90) to give the starting material (13 mg, 33%), the expected alcohol **18a** (10 mg, 27%) as a colorless oil, and the sulfonate **25** (6.6 mg, 19%) as a colorless oil.

Compound 18a: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.08 (s, 1 H), 6.74 (s, 1 H), 3.84 (s, 3 H), 3.75 (d, ^3J = 7.1 Hz, 2 H), 3.39 (qt, ^3J = 7.1, ^3J = 7.0 Hz, 1 H), 3.23 (s, 3 H), 2.19 (s, 3 H), 2.05 (s, 1 H), 1.25 (d, ^3J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 156.8, 140.1, 135.0, 126.5, 124.1, 108.3, 67.8, 55.6, 38.0, 35.2, 17.7, 15.9 ppm. IR (neat): $\tilde{\nu}$ = 3400, 2966, 2936, 1505 cm^{-1}. MS EI, *m*/*z* = 274 $[M]^{+\cdot}$ (31), 195 (18), 166 (19), 165 (100), 164 (19), 150 (8), 149 (10), 91 (7). HRMS EI: found 274.0879, $C_{12}H_{18}O_5S$ requires 274.0874.

Compound 25: ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.06 (s, 1 H), 6.74 (s, 1 H), 3.84 (s, 3 H), 3.31 (hp, ^3J = 6.7 Hz, 1 H), 3.18 (s, 3 H), 2.18 (s, 3 H), 1.25 (d, ^3J = 6.7 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 156.7, 139.6, 139.2, 125.6, 123.7, 108.0, 55.6, 37.9, 27.2, 23.3, 15.8 ppm. IR (neat): $\tilde{\nu}$ = 2964, 2930, 1503 cm^{-1}. MS EI, *m*/*z* = 258 $[M]^{+\cdot}$ (52), 180 (25), 179 (100), 151 (21), 139 (37), 136 (13), 119 (11), 91 (13). HRMS EI: found 258.0927; $C_{12}H_{18}O_4S$ requires 258.0925.

1-(5-Methoxy-3,6-dimethyl-2,3-dihydro-1-benzofuran-2-yl)-3-methylbut-3-en-2-one (26): The cyclopropanols **4a/4b** (79 mg, 0.3 mmol) in diethyl ether (1 mL) were added dropwise at 0 °C under argon to a solution of ferric(III) chloride (108 mg, 0.66 mmol) and pyridine (0.025 mL, 0.3 mmol) in diethyl ether (3 mL). After stirring for three hours at the same temperature, the reaction mixture was quenched by addition of H_2O (1 mL) and diluted with ethyl acetate (15 mL). The aqueous phase was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude residue was chromatographed on silica gel (eluent: pentane/diethyl ether, 96:4 then 93:7) to give chloro ketone **7a** (7 mg. 8%), chloro ketone **7b** (20 mg, 23%), and the enone **26** (13 mg, 17%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.65 (s, 1 H), 6.59 (s, 1 H), 5.98 (s, 1 H), 5.84 (s, 1 H), 4.75 (m, 1 H), 3.79 (s, 3 H), 3.30 (dd, ^{gem}J = 16.5, ^3J = 6.8 Hz, 1 H), 3.14 (dq, ^3J = 6.8, ^3J = 6.4 Hz, 1 H), 2.94 (dd, ^{gem}J = 16.5, ^3J = 6.0 Hz, 1 H), 2.18 (s, 3 H), 1.91 (s, 3 H), 1.36 (d, ^3J = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 199.4, 152.3, 152.1, 144.7, 129,1, 126.5, 125.6, 111.7, 106.9, 86.5, 56.3, 43.1, 42.8, 19.6, 17.4, 16.5 ppm. IR (neat): $\tilde{\nu}$ = 2959, 2926, 1675, 1491 cm^{-1}. MS EI, *m*/*z* = 260 $[M]^{+\cdot}$ (20), 177 (34), 176 (100), 175 (11), 161 (56), 145 (5), 91 (4), 77 (13). HRMS EI: found 260.1401, $C_{16}H_{20}O_3$ requires 260.1412.

Racemic and (–)-(1a*R*,9b*S*)-8-Methoxy-4,4,7,9b-tetramethyl-1a,9b-dihydro-2*H*-oxireno[*e*][1]benzoxocin-3(4*H*)one (28)

a) Racemic Route: *m*-Chloroperbenzoic acid (70%, 52 mg, 0.2 mmol) was added at 0 °C to a solution of the ketone **5** (36 mg, 0.14 mmol) in dichloromethane (0.4 mL). After stirring at this temperature for 4 h, the resulting solution was diluted with dichloromethane (5 mL) and washed with an aqueous NaOH solution (2 N, 2 × 2 mL) and then with a saturated aqueous $Na_2S_2O_3$ solution (2 mL). After drying over magnesium sulfate, the organic phase was chromatographed on silica gel (eluent: pentane/diethyl ether, 90:10 then 87:13) to give the epoxide **28** (34 mg, 89%) as a white solid.[4]

b) Asymmetric Route by Jacobsen's Procedure: (*S,S*)-Jacobsen catalyst[28] (6 mg, 0.009 mmol) and then 4-phenylpyridine *N*-oxide (6 mg, 0.03 mmol) were added successively at 0 °C to a solution of ketone **5** (40 mg, 0.15 mmol) in dichloromethane (0.5 mL). After the mixture had been stirred for 5 min at this temperature, a Na_2HPO_4 buffer solution (0.05 N, 0.5 mL, pH = 11.3) was added, followed by an aqueous NaOCl solution (0.65 M, 0.5 mL, 0.3 mmol) over a 90 min period. After stirring for 24 h at 0 °C, the mixture was diluted with dichloromethane (5 mL) and brine (1 mL). The aqueous phase was extracted with dichloromethane (3 × 5 mL) and the combined organic layers were washed with H_2O (5 mL) and dried over magnesium sulfate. The residue was flash chromatographed (eluent: pentane/diethyl ether, 90:10 then 87:13) to furnish the expected optically active epoxide **28** (8 mg, 19%) as a white solid. The enantiomeric excess determined by HPLC was 91%.

c) Asymmetric Route by Shi's Procedure: A buffer solution of $Na_2B_4O_7 \cdot 10\,H_2O$ (0.005 N) in a $Na_2EDTA \cdot 2\,H_2O$ solution (4×10^{-4} N, 1.35 mL), nBu$_4$NHSO$_4$ (1.9 mg, 0.005 mmol), and Shi catalyst (1,2;4,5-di-*O*-isopropylene-d-*erythro*-2,3-hexodiulo-2,6-pyranose;[29] 10.5 mg, 0.04 mmol) were added successively at 20 °C to a solution of ketone **5** (35 mg, 0.13 mmol) in an acetonitrile/dimethoxymethane mixture (1:2, 2 mL). A solution of oxone (114 mg, 0.18 mmol) in ETDA (4×10^{-4} N, 0.9 mL) and a solution of K_2CO_3 (108 mg, 0.78 mmol) in H_2O (0.9 mL) were then added, at the same time but separately, at 0 °C over a 2 h period. After stirring for 1 h at this temperature, the mixture was diluted with H_2O (2 mL) and diethyl ether (10 mL). After extraction of the aqueous phase with diethyl ether (3 × 10 mL), the combined organic layers were washed with brine (5 mL), dried over magnesium sulfate, and concentrated. The residue was isolated as previously to give optically active epoxide **28** (16 mg, 43%) with an enantiomeric excess of 91% as determined by HPLC, together with starting material (19 mg, 50%). HPLC (Chiralcel OD-H; hexane/EtOH: 99:1; $t_{R\,=}$ 5.3 min for (–)-**28** and 5.6 min for (+)-**28**. $[a]_D^{20}$ = –39 (*c* = 0.65, $CHCl_3$).

(+)-(5*R*,6*S*)-5-Hydroxy-8-methoxy-2,2,6,9-tetramethyl-5,6-dihydro-2*H*-1-benzoxocin-3(4*H*)one (29): Pd/C (10%, 15 mg) was added to a solution of epoxy ketone (–)-**28** (50 mg, 0.18 mmol) in ethyl acetate (0.6 ml) and anhydrous methanol (0.020 mL) and the mixture was stirred under H_2 at 20 °C for 6 h. After filtration through Celite and concentration, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether/diethyl ether, 45:55) to give the alcohol (*5R*,*6S*)-**29** (49.3 mg 98%) as a colorless oil.

The enantiomeric purity determination was carried out by ^{1}H NMR in the presence of increasing amounts (from 10 mol% to 100 mol%) of the shift reagent [(+)-Eu(hfc)$_3$]. The singlets of the aro-

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matic protons in the racemic benzoxocinone **29** were already giving a double set of signals with 10 mol% of Eu(hfc)$_3$. $[\alpha]_D^{20}$ = +6.4 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79 (s, 1 H), 6.61 (s, 1 H), 4,08 (ddd, ^3J = 7.6, ^3J = 7.1, ^3J = 0.3, 1 H), 3.81 (s, 3 H), 3.41 (dp, ^3J = 6.8, ^3J = 0.3 Hz, 1 H), 2.92 (dd, ^2J = 10.6, ^3J = 7.6 Hz, 1 H), 2.67 (dd, ^2J = 10.6, ^3J = 7.1 Hz, 1 H), 2.17 (s, 3 H), 1.76 (broad s, 1 H), 1.54 (s, 3 H), 1.42 (d, ^3J = 6.8 Hz, 3 H), 1.41 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 209.6, 154.8, 146.1, 131.9, 127.4, 125.3, 110.5, 85.7, 72.0, 55.5, 43.9, 39.4, 24.7, 22.6, 16.6, 15.9 ppm. IR (neat): $\tilde{\nu}$ = 3445, 2989, 2938, 1709, 1505 cm^{-1}. MS EI, *m*/*z* = 278 $[M]^{+\cdot}$ (17), 194 (10), 191 (13), 177 (11), 176 (17), 166 (29), 165 (100), 164 (15), 149 (12). HRMS EI: found 278.1513, $C_{16}H_{22}O_4$ requires 278.1517.

(–)-(3*R*,5*R*,6*S*)-8-Methoxy-2,2,6,9-tetramethyl-3,4,5,6-tetrahydro-2*H*-1-benzoxocine-3,5-diol (30): A DIBALH solution in toluene (1 M, 0.24 mL, 0.53 mmol) was added at –78 °C under argon to a solution of benzoxocinone (5*R*,6*S*)-**29** (65 mg, 0.23 mmol) in anhydrous tetrahydrofuran, and the mixture was stirred at this temperature for 1 h. Ethyl acetate (5 mL) was then added, and the mixture was hydrolyzed at –78 °C with an aqueous HCl solution (3 N, 1 mL) and left to warm to room temperature. The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica gel (eluent: dichloromethane/methanol, 92:8 then 90:10) to furnish diol **30** (60 mg, 92 %) as a white solid.

The enantiomeric excesses were determined on a GC chiral column (Cydex B, 165 °C, 0.8 bar): t_R = 113.7 min for (–)-**30** and 114.6 min for (+)-**30**. $[\alpha]_D^{20}$ = –44 (*c* = 0.2, $CHCl_3$), m.p. 156–157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.76 (s, 1 H), 6.60 (s, 1 H), 4.06–3.90 (m, 1 H), 3.82 (s, 3 H), 3.77–3.62 (m, 1 H), 3.62–3.44 (m, 1 H), 2.17 (s, 3 H), 1.89–1.69 (m, 2 H), 1.50 (broad s, 2 H), 1,38 (d, ^3J = 7.3 Hz, 3 H), 1.27 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.1, 146.4, 132.1, 126.8, 124.5, 109.1, 81.7, 74.7, 73.2, 55.5, 39.7, 34.4, 28.8, 18.3, 15,8 ppm. IR (neat): $\tilde{\nu}$ = 3418, 2976, 2938, 1505 cm^{-1}. MS EI, *m*/*z* = 280 $[M]^{+\cdot}$ (21), 262 (31), 192 (13), 191 (25), 177 (22); 176 (19), 166 (66), 165 (100), 164 (11), 151 (23), 115 (13), 71 (15). HRMS EI: found 280.16563; $C_{16}H_{24}O_4$ requires 280.16744; calcd. C 68.55, H 8.63; found C 68.31, H 8.43.

(–)-Heliannuol L (2): Ethanethiolate (25 mg, 0.4 mmol) and then diol (3*R*,5*R*,6*S*)-**30** (4 mg, 0.014 mmol) were added under argon at 0 °C to a solution of sodium hydride suspension (60%, 16 mg, 0.4 mmol) in dimethylformamide (2 mL) and the resulting solution was heated at 140 °C for 16 h. After cooling at 40 °C, the dimethylformamide was directly evaporated under vacuum and the residue was stirred with ethyl acetate (5 mL) and H_2O (0.05 mL). Subsequent filtration through magnesium sulfate, evaporation, and chromatography on silica gel (eluent: ethyl acetate) give 2.6 mg (69%) of (–)-heliannuol L (**2**) as a colorless oil.[1e] $[\alpha]_D^{20}$ = –37 (*c* = 0.1, $CHCl_3$). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 150.7, 132.3, 126.9, 125.1, 122.0, 114.1, 81.7, 73.4, 39.8, 34.4, 31.9, 29.6, 18.6, 15.6. MS ES, *m*/*z* = 289 $[M + Na]^+$.

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