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Investigation of a new chiral auxiliary derived chemoenzymatically from toluene: Experimental and computational study

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Abstract

A tricyclic chiral auxiliary, prepared from the enzymatically derived *cis*-arene dihydrodiol metabolite of toluene, was investigated as a means of asymmetric induction in several different reactions. The auxiliary was converted to an oxaziridine and its utility in hydroxylation, providing low levels of enantiomeric excess, was compared with that of Davis's oxaziridine. Insight into the origin of stereoinduction in this reaction is provided and is based on computational Monte Carlo Multiple Minimum (MCMM) searches using the OPLS3 forcefield. The use of the auxiliary group in the alkylation of appended esters proved disappointing. Diels-Alder cycloaddition of an acrylate, derived from the auxiliary group, with cyclohexadiene furnished a mixture of diastereomeric adducts in essentially equal amounts. The adducts were separated and the corresponding enantiomeric residues were isolated with good enantiomeric excess. Evidence of reasonable levels of asymmetric induction in the above processes was lacking. Experimental and spectral data are provided for all key compounds.

Key Words

Chiral auxiliary, biocatalysis, computational study, Diels-Alder cycloaddition, Davis hydroxylation

Introduction

Almost two decades ago, we subjected several arene *cis*-dihydrodiols, namely **1**, **2**, and **3**, derived from styrene, toluene, and (2-bromoethyl)benzene, respectively to intramolecular Diels-Alder reactions. These efforts led to the total synthesis of zeylena (**5**)¹ and to an effective model study for the synthesis of morphine fragments **7**² and **9**,³ as shown in Figure 1.

The model studies toward morphine eventually led to a very efficient synthesis of *ent*-hydromorphone (**12**)⁴ by employing a similar intramolecular cycloaddition strategy, shown in Figure 1.

Initial model study towards morphine:

Advanced model study towards morphine:

Figure 1. Synthesis of zeylena (5) and *ent*-hydromorphone (12) via intramolecular [4+2] cycloaddition.

In addition, in 1992 we utilized compound **13**, Scheme 1, derived from the enzymatic metabolite of styrene, in a proof of absolute stereochemistry of new metabolites derived from *o*- and *m*-chlorostyrenes (**14**).⁵ We suggested in 1993⁶ that rigid structures of type **13** or **15** might be useful as auxiliary groups for

reactions such as Michael additions, alkylations, Diels-Alder cycloadditions, hydroxylations, and as organocatalysts.

Reagents and conditions: (i) NaH, allyl bromide, THF, $-20\text{ }^{\circ}\text{C}$; (ii) CCl_4 , $80\text{ }^{\circ}\text{C}$; (iii) H_2 , Pd/C, 45 psi.

Scheme 1: Proof of absolute stereochemistry of **14**.⁵

We did not return to the investigation of compounds such as **15** until two decades later, with expectations of useful levels of asymmetric induction that would be derived from its use as a chiral auxiliary. The efficient and easily scalable synthesis of **15** from toluene further supported our expectations. In this paper we report some rather disappointing results with regard to low level of asymmetric induction for several common processes.

Results and discussion

Synthesis of auxiliary groups. We reasoned that the hindered *exo*-face of **15** would result in rigid transition states and limited facial access for the functionalization of groups attached to the core. We chose to examine Davis hydroxylation, alkylation of enolate anions, and intramolecular Diels-Alder

cycloadditions. The reactions were designed to produce known substances for immediate comparison. The synthesis of the chiral auxiliary group, shown in Scheme 2, begins with the enzymatic dihydroxylation of toluene with *E. coli* JM109 (pDTG601A), a strain that over-expresses toluene dioxygenase.⁷

Scheme 2: Synthesis of oxaziridine **22**.

The synthesis started from enantiomerically pure *cis*-dihydrodiol **2** obtained from the enzymatic dihydroxylation of toluene.⁸ Diol **2** was selectively protected with a bulky dimethylthexylsilyl chloride (THSCl) on the less hindered 1-position to afford silyl ether **16** in 91% yield, as shown in Scheme 1. When *tert*-butyldimethylsilyl chloride was used instead of THSCl, migration of the protecting group was observed in the subsequent step. Alcohol **16** was then alkylated with allyl bromide, and the resulting allyl ether spontaneously underwent intramolecular Diels-Alder reaction upon work-up. To complete the conversion, the crude reaction mixture was dissolved in THF and heated to reflux. Column chromatography of the reaction mixture provided tricyclic silyl ether **18** in 83%

yield. The alkene in **18** was then reduced using 10% Pd/C in a Parr shaker to afford compound **19** in 93% yield.

The deprotection of the dimethylthexylsilyl group proved to be problematic. The standard procedure, using 3 equivalents of TBAF in dry THF at room temperature, provided only 45% conversion. When the reaction mixture was heated to reflux, the conversion was complete, but the yield after chromatography was only 42%. When the amount of TBAF was decreased to 1.4 equivalents, the yield increased to 72% after 3 hours of reflux in dry THF. Alcohol **15** was then oxidized with pyridinium chlorochromate in CH_2Cl_2 to provide ketone **20** in 91% yield.

Formation of imine **21** was rather complicated. Ketone **20** was treated with tosylamine in the presence of various titanium catalysts, and the use of TiCl_4 or $\text{TiCl}_4/\text{Ti}(\text{O}-i\text{Pr})_4$, in refluxing CH_2Cl_2 , 1,2-DCE, or THF did not lead to any conversion. The use of $\text{Ti}(\text{O}-i\text{Pr})_4$ in refluxing CH_2Cl_2 provided 65% conversion with 35% of the starting material recovered. The best results were obtained using $\text{Ti}(\text{O}-i\text{Pr})_4$ in refluxing THF, which resulted in complete conversion after 5 days. Imine **21** was not stable to silica gel, decomposing to ketone **20**. Purification was accomplished by extraction and rapid filtration through a short plug of silica, and the compound was used immediately in the next step. Imine **21** was oxidized in a biphasic system of toluene and aqueous K_2CO_3 using OxoneTM as an oxidant. The resulting oxaziridine **22** was also not stable to silica gel, decomposing to ketone **20**. Purification of an analytical sample was possible on deactivated silica gel (10% w/w H_2O).

Scheme 3: Hydroxylation with oxaziridine **22**.

Davis hydroxylation attempts. Deoxybenzoin **23** was selected as a model compound for enantioselective hydroxylation. The use of (–)-Davis oxaziridine

led to the production of **24** in 85% yield with 95% ee.⁹ We followed the same procedure using NaHMDS and oxaziridine **22** in dry THF at $-78\text{ }^{\circ}\text{C}$, Scheme 3. Purification of the reaction mixture afforded 85% yield of **24** (*R*)- and **25** (*S*)-benzoin with a disappointing 16% ee in favor of **25**, which was the opposite enantiomer than the one obtained from the reaction with (–)-Davis's oxaziridine. This result may be surprising in view of the similarity of the structure of oxaziridine **22** to that of Davis's oxaziridine. We have not assigned the stereochemistry of **22** but assumed that the oxaziridine had the *endo*- configuration. Modeling of the transition state for the hydroxylation of **23** also assumed the *endo*-**22** and the prediction is clearly in favor of *si*-**23** that would lead to (*S*)-**25**, which is in agreement with the experimental results (see Figure 3 and discussion of calculations below).

Scheme 4: Alkylation with auxiliary **15**.

Alkylation attempts. To test enantioselective alkylation, we prepared phenylacetyl ester **26** from alcohol **15** in 74% yield. Alkylation using lithium diisopropylamide and methyl iodide at $-78\text{ }^{\circ}\text{C}$ provided ester **27** in 84%. Ester **27** was then hydrolyzed using LiOH in aqueous methanol, affording 2-phenylpropanoic acid **28**¹⁰ in 86% yield, Scheme 3. The analysis of the specific rotation revealed an essentially racemic mixture of (*R*)- and (*S*)-enantiomers with 5% ee.

Scheme 5: [4+2] cycloaddition with auxiliary **15**.

[4+2] Cycloaddition attempts. To investigate the asymmetric induction in [4+2] cycloaddition reactions, acryloyl ester **29** was prepared from alcohol **15** in 87% yield by treatment with acryloyl chloride and triethylamine. The subsequent [4+2] cycloaddition was performed in a sealed tube in toluene at 155 °C, Scheme 4. Purification of the reaction mixture by column chromatography provided two compounds, **30a** and **30b** in nearly equal amounts, indicating that almost no asymmetric induction took place.

Initially, these compounds were separated and treated with sodium methoxide to obtain the known methyl esters (**31a**, **31b**).¹¹

¹H-NMR spectrum of **31a** showed a mixture of 95% *endo* and 5% *exo*-isomers. Similarly, **31b** showed a mixture of 90% *endo* and 10% *exo*-isomers. The specific

rotations were also different – **31a** was +1.2 and **31b** was -39.5. The literature value for 99% enantiomerically enriched sample of **31a** is +95.6.¹¹

To determine the composition of the above-mentioned products, and to ensure that no epimerization took place during methanolysis of **30a/30b**, each adduct was separately treated with Red-Al to obtain starting alcohol **15** and alcohols **32a** and **32b**.¹² After chromatographic separation of these alcohols, the specific rotation of both was measured. The specific rotation of starting alcohol **15** remained unchanged, as expected. The values corresponding to the new alcohols **32a** and **32b** however, were different: **32a** was -10.5 and **32b** was +7.7. The literature value for 99% enantiomerically enriched sample of **32a** is +8.7¹² and for **32b** is -10.7.¹³

From these results, we assumed that **32a** and **32b** each represent an individual enantiomer of the *endo*-isomer. To confirm this hypothesis, chiral HPLC analysis of both samples **32a** and **32b** was performed, and a racemic standard was prepared, as shown in Scheme 6.

Scheme 6: Synthesis of **rac-32**.

Chiral HPLC analysis of the racemate (**rac-32**) showed two peaks at 22.3 min and 23.0 min, respectively, and a minor peak corresponding to the *exo*-isomer (likely formed by partial epimerization of the ester) at 23.8 min. The analysis of compound **32a** displayed one major peak at 22.7 min, whereas sample **32b** showed a different peak at 22.0 min, representing the other enantiomer.

Based on these chiral HPLC results, we prepared both *endo*-isomers that were easily separated using standard column chromatography. Unfortunately, the nearly 1:1 ratio of **30a** to **30b** indicates that no significant asymmetric induction

was achieved during the cycloaddition with enantiomeric excess estimated as <5%.

Computational studies.

Disappointed by the outcomes of the three reactions studied, namely alkylation, dihydroxylation, and Diels-Adler cycloaddition, we turned to computational modeling in order to gain insight into the factors contributing to the low levels of asymmetric induction offered by our tricyclic chiral auxiliary. To this end, we focused on understanding the stereoselectivity conferred by oxaziridine **22** in the dihydroxylation reactions affording (S)-benzoin (**25**) in 16% ee, as opposed to the alkylation or the Diels-Alder reactions. The basis for this decision stemmed from the rationale that little, if any, meaningful insight into the origin of stereoselectivity could be gained by studying the latter two cases because of the extremely low stereoselectivity observed (See the SI Section for additional information). Thus, working under the conceptual framework of the Hammond-Leffler postulate with the imposed caveat that oxaziridine oxygen transfer occurred early on the reaction coordinate, Monte Carlo Multiple Minimum (MCMM) searches using the OPLS3 forcefield as implemented in the Schrödinger MacroModel program were used to rationalize the stereoinduction offered by **22**.¹⁵ More specifically, we performed a MCMM simulation initiated from a geometry conforming to a C...O bond forming precomplex for addition of an enolate derived *in situ* from **23** to the oxaziridine ring of **22**. Imposed on this system were a C...O bond distance constraint of 2.8 Å, while the coordinates of the *C, *O, and *N of the oxaziridine ring were frozen, as shown in Figure 2.

Figure 2. Imposed constraints for MCMM search.

This search provided a conformer distribution (5.02 kcal/mol cut-off threshold) that revealed a 0.35 kcal/mol energetic difference between the lowest energy *si*- vs. *re*-stereofacial addition modes (*si*-**23** and *re*-**23**), which favored the formation of (S)-benzoin.¹⁶ Notably, this is in reasonable agreement with the experimental formation of (S)-benzoin in 16% ee (predicted = 29% ee), shown in Figure 3. Perhaps worth noting is the fact that the C-O-N (bond-making/bond-breaking) angle in *si*-**23** and *re*-**23** was displaced from the 180° metric that one might expect based on the theoretical work of Bach, which is not at all surprising given the use of precomplexes vs. transition states for this analysis.¹⁷

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Figure 3. Lowest energy *si*- vs. *re*-stereofacial addition modes (*si*-23 and *re*-23) and superimposition

As for the factors contributing to stereoselectivity a superimposition (maximum atom deviation = 0.5 Å) of these two stereofacial addition modes offered visible clues (see *si/re-23* overlay, Figure 3). Foremost in this regard was the flipped, circa 180°, orientations of the enolates relative to the oxaziridine ring, which resulted in subtle differences in terms of negative van der Waals contacts (i.e., steric interactions). For instance, the displaced edge-to-face C-H/ π aryl arrangement between the tosyl ring and the enolate phenyl group of *re-23* introduced an unfavorable C-H...C contact measuring 2.67 Å, which is markedly below the summed radii of C and H (C = 1.7 Å, H = 1.2 Å).¹⁸ In addition, an unfavourable steric relationship between a hydrogen of the tricyclic core of **22** and the nearby phenyl of the enolate was also present in *re-23* (C-H...C, distance = 2.81 Å). Conversely, the offset π - π alignment in *si-23* did not result in a comparable steric interaction between the tosyl ring and the proximal phenyl of the enolate with the closest interaction being a C-H...C contact (distance = 2.89 Å). Meanwhile no unfavourable van der Waals contacts were found between the tricyclic motif and enolate in *si-23*. At that stage, to provide for a more evolved and in-depth vision of the elements governing stereoselectivity the optimization of structures *si-23* and *re-23* to first-order saddle points at the density functional theory (DFT) level was attempted, which, unfortunately were unsuccessful. Notwithstanding, despite the fact that our chiral auxiliary did not provide good levels of asymmetric induction, it is noteworthy that the conceptual understanding that has emerged from this study offers some promise as a point of departure for designing new chiral auxiliaries. Indeed, the MCMM modelling approach employed herein is fast (processing time on a standard PC desktop computer = 2 min) and simple to execute. Accordingly, its use as springboard for DFT studies and employment as a rapid method for assessing stereoselective trends provided by chiral auxiliary oxaziridine reagents is ongoing and developments on this front will be reported.

Conclusions

The chiral auxiliary group **15**, prepared from the homochiral diene-diol derived chemoenzymatically from toluene (**2**), was investigated for asymmetric induction in several reactions: Davis-type hydroxylations utilizing its oxaziridine derivative, alkylation of appended esters, and [4+2] cycloadditions of an appended acrylate with cyclohexadiene. The very low levels of induction observed in hydroxylation reactions were disappointing. No induction was observed in alkylation or cycloaddition reactions, although enantiomers of bicyclic alcohols **31a** and **31b** were isolated after separation of the diastereomeric adducts. We attribute the lack of any reasonable induction to the freely rotating side chain of appended functionalities. The expected structural similarity of **15** to chiral auxiliary groups derived from camphor and other rigid bicyclic systems was clearly not evident in the results obtained. The computational study confirmed the reasons for the low levels of induction observed especially in the case of hydroxylation.

For additional computational data, and ^1H NMR/ ^{13}C NMR spectra for all key compounds, see Supplementary Information.

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Experimental section

General experimental.

All nonaqueous reactions were conducted under an inert (nitrogen or argon) atmosphere, using standard Schlenk techniques for the exclusion of moisture and air. All solvents were distilled unless otherwise noted. Analytical thin-layer chromatography was performed on silica gel 60 Å 250µm TLC plates with F-254 indicator. Flash column chromatography was performed using silica gel (230–400 mesh). Melting points are uncorrected. Optical rotation was measured in 1 dm cell at 25 °C and 589 nm, concentration in g/100 mL on Perkin-Elmer 341 polarimeter. IR spectra were obtained on Bruker ALPHA FT-IR spectrometer. ^1H and ^{13}C spectra were recorded on Bruker 300 MHz and/or 600 MHz spectrometers. All chemical shifts are referenced to TMS or residual nondeuterated solvent. Data for proton spectra are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m)], coupling constants [Hz], integration). Carbon spectra were recorded with complete proton decoupling and the chemical shifts are reported in ppm (C). Mass spectra and high resolution mass spectra were performed by the analytical division at Brock University. Combustion analyses were performed by Atlantic Microlabs, Atlanta, GA.

(–)-(3a*S*,7*S*)-3a-Methyloctahydro-3,6-methanobenzofuran-7-ol (15)

A solution of compound **19** (17.5 g, 56.3 mmol) in an anhydrous THF (80 mL) was cooled to 0 °C and tetrabutylammonium fluoride [1M solution in THF (78.9 mL, 78.9 mmol)] was added. The reaction mixture was heated to reflux for 3 hours. The reaction mixture was then quenched with H₂O (150 mL), and

extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide a yellow oil which was purified by column chromatography on silica gel eluting with [hexane/EtOAc (3:1)]. The alcohol **15** was obtained as white solid. Yield 6.82 g (72%).

15: R_f = 0.26 [hexane/EtOAc (3:1)]; mp 129-131 °C (hexane); $[\alpha]_D^{22} = -8.8$ (c = 0.5, CHCl_3); IR (neat) ν 2924, 2867, 1069, 1048, 1039, 987, 923, 897, 760 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.16-4.00 (m, 1H), 3.75 (d, J = 6.7 Hz, 1H), 3.66 (t, J = 6.8 Hz, 1H), 3.46 (dd, J = 7.4, 5.2 Hz, 2H), 1.91-1.43 (m, 9H), 0.99 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 80.8, 76.4, 71.5, 40.3, 40.1, 31.3, 30.2, 25.8, 24.3, 23.6; MS (EI) m/z (%) 186 (5), 150 (10), 133 (35), 107 (20), 93 (100), 91 (80), 79 (95), 77 (60), 55 (75); HRMS (EI) calcd for $\text{C}_{10}\text{H}_{16}\text{O}_2$: 168.1154. Found 168.1150; Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_2$: C, 71.39; H, 9.59. Found C, 71.26; H, 9.52.

(1*R*,6*S*)-6-(((2,3-Dimethylbutan-2-yl)dimethylsilyl)oxy)-2-methylcyclohexa-2,4-dienol (16**)²**

Diol **2** (0.9 g, 7.13 mmol) was recrystallized from EtOAc and dissolved in dry DMF (20 mL). Imidazole (0.56 g, 8.28 mmol) was added to the stirring mixture, followed by dimethylhexylchlorosilane (1.65 mL, 8.42 mmol) and the mixture was allowed to react at -20 °C for 23 hours. The reaction mixture was then diluted with Et_2O (50 mL) and washed with brine (3 x 25 mL). The brine was back-extracted with Et_2O (3 x 25 mL) and the combined organic extracts were washed with sat. CuSO_4 (3 x 25 mL), water (30 mL) and brine (30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil, which was purified by column chromatography on silica gel (10% deactivated with H_2O) with [hexane/based washed EtOAc (95:5)]. The

product **16** was obtained as yellow oil. Yield 1.73 g (91%). Spectral data were in agreement with previously published data.

16: R_f = 0.72 [hexane/EtOAc (9:1)]; $[\alpha]_D^{22}$ = 69.5 (c = 0.5, CHCl_3) (lit.² $[\alpha]_D^{22}$ = 86.11 (c = 1.26, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 5.87 (ddd, J = 9.6, 5.3, 1.6 Hz, 1H), 5.74 (d, J = 5.4 Hz, 1H), 5.62 (dd, J = 9.6, 2.6 Hz, 1H), 4.56-4.39 (m, 1H), 3.89 (t, J = 5.3 Hz, 1H), 2.63 (d, J = 4.8 Hz, 1H), 1.94 (s, 3H), 1.75-1.55 (m, 1H), 1.03-0.77 (m, 14H), 0.16 (d, J = 6.2 Hz, 7H).

(((1*S*,6*R*)-6-(Allyloxy)-5-methylcyclohexa-2,4-dien-1-yl)oxy)(2,3-dimethylbutan-2-yl)dimethylsilane (17**)**

A solution of silyl ether **16** (1.07g, 3.99 mmol) in dry THF (30 mL) was added dropwise to a stirring slurry of NaH (0.28 g, 6.98 mmol) in dry THF (10 mL) at 0 °C. The resulting mixture was stirred for 10 minutes at this temperature, which was followed by the rapid addition of allylbromide (0.45 mL, 5.19 mmol). The mixture was allowed to warm to room temperature and after five hours of stirring the reaction mixture was quenched with H_2O (10 mL) and extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with H_2O (30 mL), brine (3 x 25 mL) and dried (Na_2SO_4). Concentration under reduced pressure provided a yellow oil, which was purified by column chromatography on silica gel (10% deactivated with H_2O) eluting with [hexane/EtOAc (15:1)]. The product **17** was obtained as a yellow oil. Yield 0.88 g (65%).

17: ^1H NMR (300 MHz, CDCl_3) δ 6.26 (dd, J = 8.2, 6.9 Hz, 1H), 5.96 (dd, J = 6.1, 4.9 Hz, 1H), 5.69 (dd, J = 8.3, 1.3 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 4.03 (dd, J = 7.6, 4.8 Hz, 1H), 3.62 (s, 1H), 3.48 (dt, J = 6.8, 2.0 Hz, 1H), 3.35 (d, J = 6.8 Hz,

1H), 2.28 (d, $J = 3.9$ Hz, 1H), 1.85-1.46 (m, 9H), 1.41-1.13 (m, 17H), 0.99-0.69 (m, 25H), -0.01–0.26 (m, 11H).

(–)-(2,3-Dimethylbutan-2-yl)dimethyl(((3a*S*,7*S*)-3a-methyl-2,3,3a,6,7,7a-hexahydro-3,6-methanobenzofuran-7-yl)oxy)silane (18**)**

A solution of silyl ether **17** (1.43 g, 4.63 mmol) in dry THF (30 mL) was heated to reflux for 2 hours. After the reaction was deemed to be complete, the solvent was removed under reduced pressure to give a light yellow oil, which was purified by column chromatography on silica gel, eluting with [hexane/EtOAc (15:1)]. The product **18** was obtained as a yellow oil. Yield 1.18g (83%).

18: $R_f = 0.61$ [hexane/EtOAc (9:1)]; $[\alpha]_D^{22} = -61.8$ ($c = 0.5$, CHCl_3); IR (neat) ν 3041, 2949, 2872, 1250, 1127, 1101, 912, 888, 860, 832, 776 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 6.23 (dd, $J = 8.2, 6.9$ Hz, 1H), 5.66 (dd, $J = 8.3, 1.4$ Hz, 1H), 4.00 (dd, $J = 7.5, 4.9$ Hz, 1H), 3.61 (d, $J = 7.6$ Hz, 1H), 3.46 (dt, $J = 6.8, 2.0$ Hz, 1H), 3.33 (d, $J = 6.8$ Hz, 1H), 2.39-2.18 (m, 1H), 1.83-1.39 (m, 4H), 1.22 (s, 3H), 0.97-0.77 (m, 13H), 0.16–0.02 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 134.8, 132.2, 77.6, 74.4, 72.1, 45.9, 40.2, 36.8, 34.4, 34.0, 25.1, 21.2, 20.6, 20.2, 18.7, 18.5, –2.7, –3.4; MS (EI) m/z (%) 223 (100), 205 (39), 193 (52), 131 (55), 91 (32), 75 (62), 73 (29); HRMS (EI) calcd for $\text{C}_{18}\text{H}_{32}\text{O}_2\text{Si}$ (loss of C_6H_{13}): 223.1154. Found 223.1155; Anal. Calcd for $\text{C}_{18}\text{H}_{32}\text{O}_2\text{Si}$: C, 70.07; H, 10.45. Found C, 70.37; H, 10.45.

(–)-(2,3-Dimethylbutan-2-yl)dimethyl(((3a*S*,7*S*)-3a-methyloctahydro-3,6-methanobenzofuran-7-yl)oxy)silane (19**)**

The Diels-Alder adduct **18** (1.93 g, 6.25 mmol) was dissolved in absolute ethanol (100 mL) and 10% Pd/C was added (250 mg, 0.23 mmol). The mixture was hydrogenated in Parr shaker at 20 psi of H₂ for 3 hours. The reaction mixture was then filtered through *Celite*TM and the solvent was removed under reduced pressure to provide 1.84 g of a colorless oil, which was purified by column chromatography on silica gel, eluting with [hexane/EtOAc (15:1)]. The product **19** was obtained as a colorless oil. Yield 1.81 g (93%).

19: R_f = 0.65 [hexane/EtOAc (9:1)]; $[\alpha]_D^{22}$ = -17.7 (c = 0.5, CHCl₃); IR (neat) ν 2926, 2866, 1249, 1130, 1099, 830, 773 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.08-3.95 (m, 1H), 3.69 (d, J = 6.7 Hz, 1H), 3.57 (d, J = 6.7 Hz, 1H), 3.41 (d, J = 7.5 Hz, 1H), 1.85-1.38 (m, 9H), 0.99-0.70 (m, 15H), 0.18-0.01 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 81.8, 75.9, 73.9, 40.7, 40.0, 34.5, 32.2, 31.1, 26.0, 25.1, 24.5, 23.9, 20.6, 20.3, 18.7, 18.5, -2.6 , -3.3 ; MS (EI) m/z (%) 226 (29), 225 (92), 223 (33), 196 (29), 195 (100), 133 (28), 119 (44), 91 (31), 75 (86), 73 (46), 59 (30); HRMS (EI) calcd for C₁₈H₃₄O₂Si (loss of C₆H₁₃): 225.1311. Found 225.1315; Anal. Calcd for C₁₈H₃₄O₂Si: C, 69.62; H, 11.04. Found C, 70.05; H, 10.98.

(–)-(3a*S*,6*R*)-3a-Methylhexahydro-3,6-methanobenzofuran-7(7a*H*)-one (20)

Alcohol **15** (330 mg, 1.96 mmol) was dissolved in dry CH₂Cl₂ (30 mL) and pyridinium chlorochromate (2.11 g, 9.81 mmol) was added. The mixture was

allowed to stir for 20 hours at room temperature. The reaction mixture was then diluted with Et₂O (30 mL) and filtered through a short plug of silica gel. The solvent was removed under reduced pressure, and the title compound was recrystallized from hot hexane (20 mL) affording **20** as a white solid. Yield 298 mg (91%).

20: R_f = 0.43 [hexane/EtOAc (3:1)]; mp 105-106 °C (hexane); $[\alpha]_D^{22} = -25.7$ (c = 0.5, CHCl₃); IR (neat) ν 2955, 2931, 2874, 1715, 1237, 1028, 1000, 884, 486 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.15 (dd, J = 7.9, 4.3 Hz, 1H), 3.60-3.44 (m, 2H), 2.23 (d, J = 2.6 Hz, 1H), 2.15 (dd, J = 9.5, 4.3 Hz, 1H), 2.04 (dd, J = 13.3, 9.5 Hz, 1H), 1.93-1.53 (m, 5H), 1.05 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 212.8, 84.0, 76.2, 43.1, 39.9, 38.7, 31.4, 26.2, 23.2, 22.6; MS (EI) m/z (%) 166 (89), 138 (57), 120 (75), 109 (44), 107 (87), 105 (56), 96 (37), 95 (55), 93 (74), 92 (66), 91 (62), 83 (84), 82 (32), 81 (54), 80 (30), 79 (73), 77 (45), 68 (30), 67 (100), 55 (63), 53 (53); HRMS (EI) calcd for C₁₀H₁₄O₂ : 166.0994. Found 166.0986; Anal. Calcd for C₁₀H₁₄O₂: C, 72.26; H, 8.49. Found C, 72.23; H, 8.49.

(E)-4-Methyl-N-(3a-methylhexahydro-3,6-methanobenzofuran-7(7aH)-ylidene)benzenesulfonamide (21)

To a stirring solution of ketone **20** (20 mg, 0.1203 mmol) in dry THF (3 mL) was added titanium(IV) isopropoxide (102.57 mg, 0.361 mmol) followed by the rapid addition of 4-toluenesulfonamide (22.66 mg, 0.132 mmol). The mixture was heated to reflux for 89 hours. The reaction was then quenched with brine and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried (Na₂SO₄), concentrated under reduced pressure, and the resulting residue was

filtered through a short plug of silica gel eluting with [hexane/EtOAc (3:1)]. The solvent was evaporated under reduced pressure affording **21** as a colorless oil.

(3a*S*)-3a-Methyl-2'-tosylhexahydro-2H-spiro[3,6-methanobenzofuran-7,3'-[1,2]oxaziridine] (22)

Imine **21** (50 mg, 0.156 mmol) was dissolved in toluene (3 mL) and an aqueous solution of K_2CO_3 (83.1 mg, 0.6 mmol) was added. The mixture was stirred vigorously and an aqueous solution of OxoneTM (105.3 mg, 0.342 mmol) was added dropwise. The mixture was stirred for 6 hours at room temperature. The aqueous layer was separated, extracted with toluene (3 x 3 mL) and the combined organic extracts were washed with 10% aqueous solution of Na_2SO_3 , dried over anhydrous $MgSO_4$ and purified by column chromatography on silica gel (10% deactivated with H_2O) eluting with [hexane/EtOAc (4:1)]. Yield 30 mg (57%).

22: R_f = 0.21 [hexane/EtOAc (4:1)]; $[\alpha]_D^{22}$ = -63.6 (c = 1.285, $CHCl_3$); IR (neat) ν 2929, 2874, 1349, 1164, 1115, 892, 814, 709, 671, 659, 566, 529; 1H NMR (300 MHz, $CDCl_3$) δ 5.83 (ddd, J = 9.6, 5.3, 1.6 Hz, 1H), 5.74 – 5.66 (m, 1H), 5.59 (dd, J = 9.6, 2.7 Hz, 1H), 4.48 – 4.35 (m, 1H), 3.86 (t, J = 5.4 Hz, 1H), 2.59 (d, J = 4.9 Hz, 1H), 1.90 (s, 1H), 1.72 – 1.56 (m, 1H), 0.94 – 0.78 (m, 2H), 0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.45, 145.25, 134.92, 129.79, 129.70, 128.82, 128.39, 97.89, 93.73, 84.60, 81.86, 76.12, 76.06, 41.77, 40.96, 39.46, 39.26, 31.71, 31.54, 31.50, 25.70, 24.84, 23.70, 23.20, 22.83, 22.75, 21.70; MS (EI) m/z (%) 679 (44), 662 (39), 661 (100), 360 (25), 358 (48), 342 (25), 320 (28).

Asymmetric hydroxylation

Sodium bis(trimethylsilyl)amide (0.12 mL, 0.05 mmol) was cooled in acetone/dry ice bath to -78°C and a solution of deoxybenzoin **23** (18 mg, 0.092 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at this temperature for 30 minutes, and a solution of oxaziridine **22** (46 mg, 0.138 mmol) in THF (1 mL) was added. The reaction was monitored by TLC for 4 hours, before being quenched with NH_4Cl , and the mixture was allowed to warm to room temperature. The aqueous solution was extracted by Et_2O (3 x 5 mL), and the combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel eluting with [hexane/ EtOAc (5:1)]. Yield 17 mg (85%).

24 + 25: $R_f = 0.46$ [hexane/ EtOAc (5:1)]; $[\alpha]_{\text{D}}^{22} = 18.5$ ($c = 0.83$, CHCl_3); ee = 16 %; ^1H NMR (400 MHz, CDCl_3) δ 7.91 (dd, $J = 5.2, 3.4$ Hz, 2H), 7.66 – 7.09 (m, 8H), 5.96 (s, 1H), 4.56 (s, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 199.0, 139.0, 133.9, 129.7, 128.7, 128.6, 127.8, 76.23.

The same reaction was run with (-) Davis Reagent for comparison. $[\alpha]_{\text{D}}^{22} = -78.5$ ($c = 0.83$, CHCl_3); ee = ~95%(estimated).

(7S,7aR)-3a-Methyloctahydro-3,6-methanobenzofuran-7-yl 2-phenylacetate
(**26**)

Alcohol **15** (0.185 mg, 1.1 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL) and NaH (60% in oil dispersion, 48 mg, 1.2 mmol) was added at 0 °C. The reaction mixture was stirred for one hour before phenylacetyl chloride (0.26 mL, 2.0 mmol) was added, and the reaction mixture was then stirred for 16 h at room temperature. The reaction mixture was then quenched with a saturated solution of NH_4Cl and extracted with EtOAc (3 x 25 mL). The combined organic extracts were concentrated under reduced pressure and the residue was purified by column chromatography on silica gel eluting with [hexane/EtOAc (6:1)] providing **26** as a colorless oil. Yield 233 mg (74%).

26: $R_f = 0.78$ [hexane/EtOAc (3:1)]; $[\alpha]_D^{22} = -55.1$ ($c = 1.0$, CHCl_3); IR (neat) ν 2931, 2870, 1728, 1452, 1356, 1218, 1165, 1025, 702; ^1H NMR (400 MHz, CDCl_3) δ 7.62 – 7.07 (m, 5H), 4.56 (d, $J = 6.2$ Hz, 1H), 3.90 (t, $J = 24.7$ Hz, 2H), 3.77 – 3.52 (m, 2H), 3.15 (d, $J = 7.8$ Hz, 1H), 1.94 – 1.06 (m, 8H), 0.84 (d, $J = 63.4$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.2, 134.5, 129.5, 129.4, 128.6, 128.4, 126.8, 78.7, 76.3, 76.0, 41.4, 40.9, 40.5, 39.8, 32.3, 27.2, 25.7, 24.1, 23.5; MS (EI) m/z (%) 286 (25), 167 (15), 150 (20), 118 (45), 105 (20), 91 (100), 77 (20); HRMS (EI) calcd for $\text{C}_{18}\text{H}_{22}\text{O}_3$: 286.1569. Found 286.1561; Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{O}_3$: C, 75.50; H, 7.74. Found C, 75.36; H, 7.63.

(7S,7aR)-3a-Methyloctahydro-3,6-methanobenzofuran-7-yl 2-phenylpropanoate (27)

A solution of freshly prepared LDA (0.82 mmol) in THF was added dropwise to a solution of phenylacetyl ester **26** (0.21 g, 0.74 mmol) in THF (7 mL) at $-78\text{ }^{\circ}\text{C}$. The reaction mixture was stirred for one hour before the dropwise addition of methyl iodide (0.05 mL, 0.82 mmol). The reaction mixture was then slowly warmed to $-20\text{ }^{\circ}\text{C}$, before being quenched with a saturated solution of NH_4Cl and extracted with EtOAc (3 x 25 mL). The combined organic extracts were concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel eluting with [hexane/EtOAc (6:1)] yielding 187 mg (84%) of **27** as a colorless oil.

27: $R_f = 0.83$ [hexane/EtOAc (3:1)]; IR (neat) ν 2930, 2870, 1729, 1493, 1376, 1205, 1165, 1063, 728; ^1H NMR (400 MHz, CDCl_3) δ 7.41 – 7.29 (m, 4H), 7.29 – 7.22 (m, 1H), 4.61 – 4.44 (m, 1H), 4.06 – 3.89 (m, 1H), 3.89 – 3.69 (m, 2H), 3.26 (d, $J = 7.8\text{ Hz}$, 1H), 2.82 (d, $J = 7.9\text{ Hz}$, 1H), 1.94 – 1.34 (m, 8H), 0.95 (d, $J = 3.8\text{ Hz}$, 3H), 0.91 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 174.2, 173.7, 140.90, 140.86, 129.5, 128.7, 128.4, 128.3, 128.0, 127.8, 126.9, 126.8, 78.83, 78.81, 76.3, 76.1, 75.7, 45.6, 45.5, 40.5, 39.8, 39.6, 32.3, 32.2, 27.2, 27.1, 25.6, 25.5, 24.2, 23.47, 23.45, 18.7, 18.0; MS (EI) m/z (%) 300 (10), 210 (10), 167 (10), 151 (20), 132 (20), 105 (100), 91 (75), 79 (20); HRMS (EI) calcd for $\text{C}_{19}\text{H}_{24}\text{O}_3$: 300.1725. Found 300.1729; Anal. Calcd for $\text{C}_{19}\text{H}_{24}\text{O}_3$: C, 75.97; H, 8.05. Found C, 76.25; H, 8.01.

2-Phenylpropanoic acid (**28**)¹⁰

Ester **27** (0.145 g, 0.48 mmol) was dissolved in 25% aqueous MeOH (4 mL), lithium hydroxide monohydrate (100 mg, 2.4 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. The solvent was then removed

under reduced pressure and the resulting residue was purified by column chromatography on silica gel eluting with [hexane/EtOAc (6:1)] yielding 62 mg (86%) of **28** as a colorless oil. The spectroscopic data correspond to those previously reported in the literature.

28: R_f = 0.10 [hexane/EtOAc (1:1)]; $[\alpha]_D^{22}$ = -3.6 (c = 1.0, CHCl_3) ((S)-(+)-2-phenylpropionic acid - lit.¹⁰ $[\alpha]_D^{22}$ = $+72.6$ (c = 1.6, CHCl_3)); ^1H NMR (300 MHz, CDCl_3) δ 7.39 – 7.25 (m, 5H), 3.76 (q, J = 7.2 Hz, 1H), 1.54 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 180.8, 139.8, 128.7, 127.6, 127.4, 45.4, 18.1.

(7S,7aR)-3a-Methyloctahydro-3,6-methanobenzofuran-7-yl acrylate (29)

Alcohol **15** (60 mg, 0.36 mmol) was dissolved in anhydrous THF (5 mL) before triethylamine (0.08 mL, 0.54 mmol) and acryloyl chloride (0.04 mL, 0.47 mmol) were added, and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was then quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (3 x 25 mL). The combined organic extracts were concentrated under reduced pressure and the resulting residue was purified by column chromatography on silica gel eluting with [hexane/EtOAc (6:1)] providing **29** as a colorless oil. Yield 69 mg (87%).

29: R_f = 0.68 [hexane/EtOAc (3:1)]; $[\alpha]_D^{22}$ = -111.5 (c = 1.0, CHCl_3); IR (neat) ν 2930, 2871, 1719, 1634, 1453, 1269, 1192, 1060, 860; ^1H NMR (300 MHz, CDCl_3) δ 6.41 (dd, J = 17.3, 1.6 Hz, 1H), 6.15 (dd, J = 17.3, 10.3 Hz, 1H), 5.80 (dd, J = 10.3, 1.6 Hz, 1H), 4.64 (dd, J = 6.4, 1.6 Hz, 1H), 4.06 – 3.99 (m, 1H), 3.97 (d, J = 6.5 Hz, 1H), 3.38 (d, J = 7.8 Hz, 1H), 1.93 – 1.46 (m, 7H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 165.9, 130.3, 128.6, 78.9, 76.3, 76.1, 40.5,

39.8, 32.5, 27.3, 25.8, 24.2, 23.5; MS (EI) m/z (%) 222 (5), 150 (40), 135 (10), 121 (25), 109 (35), 93 (55), 79 (40), 55 (100); HRMS (EI) calcd for $C_{13}H_{18}O_3$: 222.1256. Found 222.1254; Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found C, 70.34; H, 8.23.

(1S, 2S, 4S)-(3aS,7S)-3a-Methyloctahydro-3,6-methanobenzofuran-7-yl bicyclo[2.2.2]oct-5-ene-2-carboxylate (30a) and (1R,2R,4R)-(3aS,7S)-3a-Methyloctahydro-3,6-methanobenzofuran-7-yl bicyclo[2.2.2]oct-5-ene-2-carboxylate (30b)

Ester **29** (129 mg, 0.58 mmol) was dissolved in toluene (1 mL) before the addition of 1,3-cyclohexadiene (0.7 mL, 7.2 mmol), and the mixture was heated in sealed tube for 15 hours. The volatiles were then removed under reduced pressure and the resulting residue was purified by column chromatography on silica gel eluting with [hexane/EtOAc (12:1)]. Two isomers **30a** (47.6 mg) and **30b** (53.5 mg) were obtained.

30a: light yellow oil; R_f = 0.37 [hexane/EtOAc (12:1)]; $[\alpha]_D^{22}$ = -45.7 (c = 0.5, $CHCl_3$); IR (neat) ν 2928, 2866, 1730, 1162, 1050, 899, 695 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 6.31 (t, J = 6.9 Hz, 1H), 6.25 – 6.11 (m, 1H), 4.49 (t, J = 7.1 Hz, 1H), 4.01 (ddd, J = 13.4, 8.1, 5.3 Hz, 1H), 3.91 (t, J = 7.8 Hz, 1H), 3.47 – 3.31 (m, 1H), 2.94 (d, J = 3.7 Hz, 1H), 2.67 (ddd, J = 11.3, 6.8, 3.8 Hz, 1H), 2.59 (dd, J = 10.0, 7.1 Hz, 1H), 1.91 – 1.81 (m, 2H), 1.74 – 1.67 (m, 2H), 1.67 – 1.39 (m, 14H), 1.00 – 0.90 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 134.9, 131.7, 79.0, 76.2, 75.6, 42.7, 40.5, 39.9, 32.5, 32.4, 30.0, 29.5, 27.4, 25.8, 25.5, 24.4, 24.2, 23.5; MS (EI) m/z (%) 167 (76), 151 (67), 150 (26), 107 (61), 93 (28), 91

(25), 79 (100), 77 (28); HRMS (EI) calcd for $C_{19}H_{23}O_3$: 302.1882. Found 302.1879; Anal. Calcd for $C_{19}H_{23}O_3$: C, 75.46; H, 8.67. Found C, 75.21; H, 8.47.

30b: white solid; R_f = 0.46 [hexane/EtOAc (12:1)]; mp 97-99 °C (hexane/EtOAc); $[\alpha]_D^{22}$ = -95.97 (c = 1.0, $CHCl_3$); IR (neat) ν 3048, 2935, 2870, 1727, 1187, 1168, 1048, 913, 690 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 6.38 – 6.24 (m, 1H), 6.18 (dd, J = 10.8, 3.7 Hz, 1H), 4.46 (d, J = 6.5 Hz, 1H), 4.09 – 3.96 (m, 1H), 3.93 (d, J = 6.5 Hz, 1H), 3.38 (d, J = 7.7 Hz, 1H), 2.96 (d, J = 3.4 Hz, 1H), 2.71 – 2.52 (m, 2H), 1.90 – 1.75 (m, 3H), 1.92 – 1.74 (m, 3H), 1.70 (ddd, J = 11.3, 6.0, 3.9 Hz, 2H), 1.67 – 1.56 (m, 4H), 1.55 – 1.38 (m, 4H), 0.92 (d, J = 5.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 134.6, 131.9, 79.0, 76.1, 75.7, 42.5, 40.5, 39.9, 32.7, 32.6, 29.7, 29.3, 27.4, 25.8, 25.7, 24.4, 24.2, 23.5; MS (EI) m/z (%) 167 (75), 151 (74), 121 (25), 107 (64), 93 (29), 81 (25), 79 (100), 77 (26); HRMS (EI) calcd for $C_{19}H_{23}O_3$: 302.1882. Found 302.1877; Anal. Calcd for $C_{19}H_{23}O_3$: C, 75.46; H, 8.67. Found C, 75.17; H, 8.67.

(1S,4S)-Methyl bicyclo[2.2.2]oct-5-ene-2-carboxylate (31a)

(1R,4R)-Methyl bicyclo[2.2.2]oct-5-ene-2-carboxylate (31b)¹¹

Diels-alder adduct **30a** (53.5 mg, 0.18 mmol) was dissolved in MeOH (2 mL) under an argon atmosphere. After the addition of sodium methoxide (0.7 mL 25% v/v in MeOH) was the resulting mixture stirred for the next 4 h at room temperature. After the completion, acidic Dowex exchange resin was added to neutralize the pH. The resin was filtered out and solvent was removed under the reduced pressure. The residue was purified using column chromatography on silica gel eluting with [hexane/EtOAc (4:1)]. Ester **31a** was obtained as light yellow oil (14.7 mg) yield 59.12%. NMR analysis confirmed that the ester is

mixture of *exo*- and *endo*- (1:10). Identical procedure was applied to produce **31b** from **30b**.

31a: $R_f = 0.86$ [hexane/EtOAc (4:1)]; $[\alpha]_D^{20} = +1.2$ ($c = 0.5$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 6.33 (dd, $J = 19.7, 12.2$ Hz, 1H), 6.15 (t, $J = 7.3$ Hz, 1H), 3.69 (s, 1H), 3.63 (s, 3H), 2.92 (d, $J = 3.4$ Hz, 1H), 2.68 – 2.53 (m, 2H), 1.80 – 1.61 (m, 2H), 1.56 (ddd, $J = 21.0, 9.6, 6.8$ Hz, 2H), 1.51 – 1.41 (m, 1H), 1.39 – 1.12 (m, 5H), 0.92 – 0.76 (m, 1H).

31b: $R_f = 0.86$ [hexane/EtOAc (4:1)]; $[\alpha]_D^{20} = -39.5$ ($c = 0.5$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 6.33 (dd, $J = 19.7, 12.2$ Hz, 1H), 6.15 (t, $J = 7.3$ Hz, 1H), 3.69 (s, 1H), 3.63 (s, 3H), 2.92 (d, $J = 3.4$ Hz, 1H), 2.68 – 2.53 (m, 2H), 1.80 – 1.61 (m, 2H), 1.56 (ddd, $J = 21.0, 9.6, 6.8$ Hz, 2H), 1.51 – 1.41 (m, 1H), 1.39 – 1.12 (m, 5H), 0.92 – 0.76 (m, 1H). This compound was a mixture of 5% *exo*- and 95% *endo*-isomers.

(1S,2S,4S)-Bicyclo[2.2.2]oct-5-en-2-ylmethanol (32a)^{12,14}

Diels-alder adduct **30a** (104 mg, 0.34 mmol) was dissolved in anhydrous THF (5 mL). After the addition of Red-Al (0.43 g, 1.38 mmol), the resulting mixture was stirred for 3 h at room temperature. After the reaction was deemed to be complete, a saturated aqueous solution of Rochelle's salt was added and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic extracts were concentrated under reduced pressure and the residue was purified by column chromatography on silica gel eluting with [hexane/EtOAc (4:1)] yielding 40 mg (84%) of **32a** as a colorless oil. The spectroscopic data correspond to those previously reported in the literature.^{12,14}

32a: $R_f = 0.20$ [hexane/EtOAc (4:1)]; $[\alpha]_D^{20} = -10.2$ ($c = 0.9$, EtOH); ^1H NMR (400 MHz, CDCl_3) δ 6.27 (t, $J = 7.4$ Hz, 1H), 6.13 (t, $J = 7.3$ Hz, 1H), 3.37 – 3.16 (m,

2H), 2.61 (d, $J = 3.9$ Hz, 1H), 2.56 – 2.43 (m, 1H), 2.01 – 1.79 (m, 1H), 1.67 (ddd, $J = 12.4, 9.7, 2.8$ Hz, 1H), 1.62 – 1.40 (m, 3H), 1.40 – 1.16 (m, 2H), 0.75 (ddt, $J = 12.4, 5.4, 2.8$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 135.0, 131.7, 67.5, 40.5, 31.4, 30.2, 29.7, 25.9, 24.7; t_{R} (HPLC, chiral column IA, 98:2 Hept/iPrOH, 15 °C, 0.5 mL/min) 22.72 min.

(1*R*,2*R*,4*R*)-Bicyclo[2.2.2]oct-5-en-2-ylmethanol (32b**)**^{13,14}

Diels-alder adduct **30b** (103 mg, 0.34 mmol) was dissolved in anhydrous THF (5 mL). After the addition of Red-Al (0.43 g, 1.38 mmol), the resulting mixture was stirred for 3 h at room temperature. After the reaction was deemed to be complete, a saturated aqueous solution of Rochelle's salt was added and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic extracts were concentrated under reduced pressure and the residue was purified by column chromatography on silica gel eluting with [hexane/EtOAc (4:1)] yielding 38 mg (80%) of **32b** as a colorless oil. The spectroscopic data correspond to those previously reported in the literature.^{13,14}

32b: $R_f = 0.20$ [hexane/EtOAc (4:1)]; $[\alpha]_{\text{D}}^{20} = +7.7$ ($c = 0.9$, EtOH); ^1H NMR (400 MHz, CDCl_3) δ 6.28 (t, $J = 7.3$ Hz, 1H), 6.14 (t, $J = 7.2$ Hz, 1H), 3.36 – 3.14 (m, 2H), 2.58 (d, $J = 18.7$ Hz, 1H), 2.51 (d, $J = 2.7$ Hz, 1H), 1.98 – 1.78 (m, 1H), 1.68 (ddd, $J = 12.3, 9.7, 2.6$ Hz, 1H), 1.62 – 1.39 (m, 3H), 1.39 – 1.14 (m, 2H), 0.84 – 1.14 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 135.1, 131.7, 67.5, 40.5, 31.3, 30.2, 29.7, 25.9, 24.7; t_{R} (HPLC, chiral column IA, 98:2 Hept/iPrOH, 15 °C, 0.5 mL/min) 22.0 min.

Bicyclo[2.2.2]oct-5-en-2-ylmethanol (*rac*-32)¹⁴

Methyl acrylate (2.0 mL, 22 mmol) was dissolved in toluene (5 mL) before the addition of 1,3-cyclohexadiene (3.5 mL, 31 mmol). The mixture was then heated in a sealed tube for 15 h. Volatiles were then removed under reduced pressure and the resulting residue was directly used in the subsequent step. The resultant methyl ester (0.2 g, 1.2 mmol) was dissolved in anhydrous THF (5 mL). After the addition of Red-Al (1.0 g, 3.20 mmol), the resulting mixture was stirred for 3 h at room temperature. After the reaction was deemed to be complete, a saturated aqueous solution of Rochelle's salt was added and the mixture was extracted with EtOAc (3 x 40 mL). The combined organic extracts were concentrated under reduced pressure and the resulting residue was purified by column chromatography on silica gel eluting with [hexane/EtOAc (4:1)] yielding 130 mg (80%) of **rac-32** as a colorless oil. Spectral data were in agreement with previously published results.¹⁴

rac-32: R_f = 0.20 [hexane/EtOAc (4:1)]; $[\alpha]_D^{22}$ = -0.8 (c = 0.5, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 6.28 (t, J = 7.4 Hz, 1H), 6.13 (t, J = 7.4 Hz, 1H), 3.36 – 3.14 (m, 2H), 2.58 (d, J = 18.7 Hz, 1H), 2.51 (d, J = 2.7 Hz, 1H), 1.98 – 1.78 (m, 1H), 1.68 (ddd, J = 12.3, 9.7, 2.6 Hz, 1H), 1.62 – 1.39 (m, 3H), 1.39 – 1.14 (m, 2H), 0.84 – 1.14 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 135.1, 131.7, 67.5, 40.5, 31.3, 30.2, 29.7, 25.9, 24.7; t_R (HPLC, chiral column IA, 98:2 Hept/iPrOH, 15 °C, 0.5 mL/min) 22.3 and 23.0 min.

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