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Synthesis of a Core Carbon Framework of Cyanosporasides A and B

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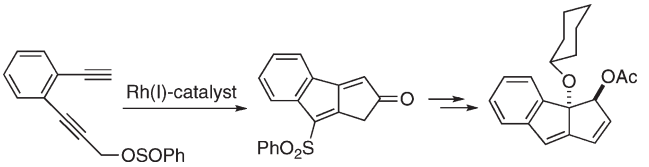
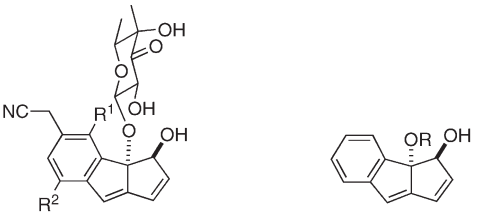


Treatment of 3-(2-ethynylphenyl)prop-2-ynyl benzenesulfinate with 2.5 mol % of $[RhCl(CO)_2]_2$ at 40 °C under an atmosphere of CO effected the successive 2,3-sigmatropic rearrangement and carbonylative [2 + 2 + 1] ring-closing reaction to afford the 8-(phenylsulfonyl)-1*H*-cyclopent[*a*]-inden-2-one in a high yield. Chemical modification of the ring-closed product via lipase-mediated optical resolution produced the optically active 3-acetoxy-3a-cyclohexyloxy-3,3a-dihydrocyclopent-[*a*]indene skeleton, the core carbon framework of cyanosporasides A and B.

Introduction

In 2006, Fenical and co-workers[1] reported the isolation of two structurally novel cyclopent[*a*]indene glycosides, cyanosporasides A (**1**) and B (**2**), from *Salinispora pacifica* collected at a depth of 500 m in Palau. Cyanosporides A (**1**) and B (**2**) have an intriguing novel common structural feature with the 3,3a-dihydrocyclopent[*a*]indene carbon framework as the aglycon moiety as well as a novel 3′-oxo-4′-methyl-β-fucopyranose as the sugar part. Their biological activity is still uncertain except for the weak cytotoxicity of **1** against human colon carcinoma HCT-116.

We have recently been involved in the investigation of the $[RhCl(CO)_2]_2$- or $[RhCl(CO)dppp]_2$-catalyzed intramolecular carbonylative [2 + 2 + 1] ring-closing reaction (Pauson−Khand-type reaction) of phenylsulfonylallenynes,[2] phenylsulfonylallenenes,[3] and bis(phenylsulfonylallene) derivatives[4] leading to the efficient formation of bicyclo[*m*.3.0] skeletons (*m* = 4−6) (Scheme 1). As an extension of our work in this field, we have focused on the synthesis of the carbon framework **3** of cyanosporasides A (**1**) and B (**2**) by taking advantage of the Rh(I)-catalyzed carbonylative [2 + 2 + 1] ring-closing reaction of phenylsulfonylallenynes.



cyanosporaside A: R^1=Cl, R^2=H (**1**)
cyanosporaside B: R^1=H, R^2=Cl (**2**)

carbon framework **3**

FIGURE 1. Structure of cyanosporasides.

Results and Discussion

A year before the isolation of **1** and **2**, Liu and Datta[5] developed the efficient synthesis (82%) of 1*H*-cyclopent[*a*]-inden-2-one (**5**) from 1-ethynyl-2-(1,2-propadienyl)benzene (**4**) through the $Mo(CO)_3(MeCN)_3$-mediated carbonylative [2+2+1] ring-closing reaction at 25 °C in a stoichiometric manner. They also reported the catalytic version of that transformation in the presence of 5 mol % of $[RhCl(CO)_2]_2$

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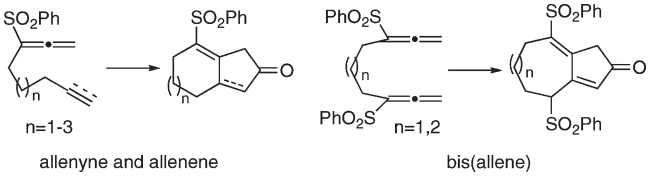
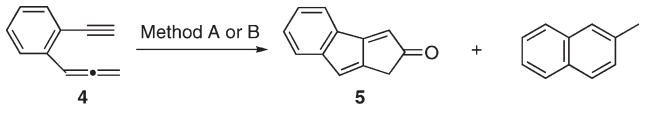
SCHEME 1. Rh(I)-Catalyzed Pauson−Khand-Type Reaction of Allenes



SCHEME 2. Carbonylative Ring-Closing Reaction of Allenyne 4



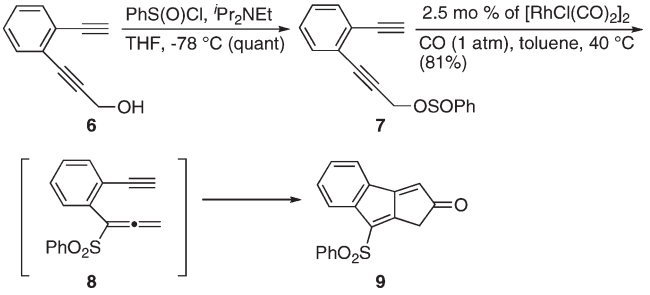
Method A: 1 equiv of $Mo(CO)_3(MeCN)_3$, MeCN, 25 °C, 8 h, **5** (82%)
Method B: 5 mol % of $[RhCl(CO)_2]_2$, toluene, 90 °C, 8h, CO (1 atm), **5** (62%), 2-methylnaphthalene (8%)

at 90 °C to furnish **5** in 62% yield along with the byproduction of 2-methylnaphthalene (8%), the latter of which should arise from the Myers−Saito cycloaromatization[6] of **4**. They claimed that a low reaction temperature is required to avoid the formation of the undesired 2-methylnaphthalene (Scheme 2).

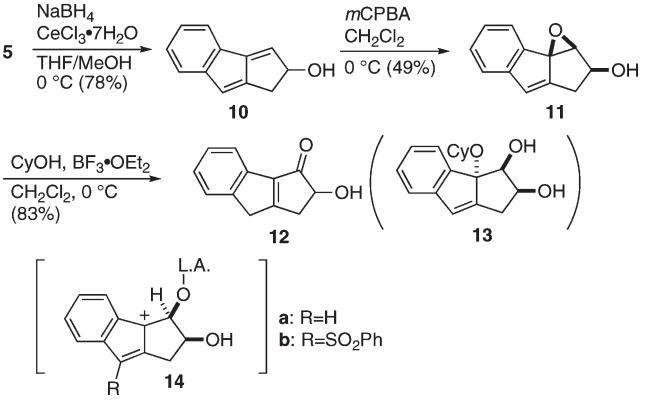
Thus, this investigation began in order to develop the catalytic procedure for the preparation of the 1*H*-cyclopent[*a*]inden-2-one derivatives without production of 2-methylnaphthalene. According to the previously established met hod,[2e] the propargyl alcohol derivative **6** was treated with benzenesulfinyl chloride at −78 °C to afford the corresponding sulfinate **7** in a quantitative yield, subsequent exposure of which to 2.5 mol % of $[RhCl(CO)_2]_2$ in toluene at 40 °C under an atmosphere of CO for 10 h effected the successive 2,3-sigmatropic rearrangement and carbonylative [2 + 2 + 1] ring-closing reaction of the resulting allenyne species **8** to provide 8-(phenylsulfonyl)-1*H*-cyclopent[*a*]inden-2-one (**9**) in 81% yield. The formation of 2-methylnaphthalene could not be detected in the reaction mixture (Scheme 3).

The catalytic preparation of the 1*H*-cyclopent[*a*]inden-2-one skeleton was realized, but the phenylsulfonyl group of **9** might not be essential for the synthesis of the target compound **3**. The simpler 1*H*-cyclopent[*a*]inden-2-one (**5**)[5] seemed to be the better substrate for conversion into the **3**. Therefore, the chemical modification of compound **5** was first examined. Reduction of **5** with $NaBH_4$ in the presence of $CeCl_3$ afforded the allyl alcohol **10** in 78% yield, which was then oxidized with *m*-CPBA to produce the epoxy derivative **11** in 49% yield. The two trisubstituted olefin moieties of **10** with a similar reactivity might contribute to the moderate chemical yield of **11**. The Lewis acid-catalyzed ring-opening of an epoxy group[7] of **11** in the presence of cyclohexanol unexpectedly furnished 2-hydroxy-1,2,3,8-tetrahydrocyclopent[*a*]inden-3-one (**12**) in 83% yield. Although various

SCHEME 3. Preparation of 9



SCHEME 4. Attempt at Conversion of 5 into 13



conditions were screened, the desired *cis*-diol derivative **13** could not be obtained. The formation of **12** can tentatively be rationalized in terms of the intermediacy of the benzylic cation species **14a** (R = H) followed by hydride transfer[8] as shown in Scheme 4.

We assumed that the two olefin parts of 8-(phenylsulfonyl)-1*H*-cyclopent[*a*]inden-2-one (**9**) might be differentiated during epoxidation reaction, because one of them has an electron-withdrawing group, whereas the other does not. In addition, the phenylsulfonyl group of **9** would be expected to indirectly suppress the generation of the benzylic cation species (e.g., **14b**). As a result, the stereoselective S_N2-type ring-opening of the epoxy group at the benzylic position may dominate over the hydride transfer reaction via the benzylic cation species **14b**. Based on these expectations, we tried to convert **9** into the *cis*-diol derivatives **17** (Scheme 5). Treatment of **9** with $NaBH_4$ provided the allyl alcohol derivative **15**, which was exposed to *m*-CPBA to give the desired **16** in 83% yield in a highly stereoselctive manner. The highly stereo- and regioselective ring-opening of the epoxy group[7] of **16** was realized by the reaction of cyclohexanol in the presence of $BF_3 \cdot OEt_2$ in methylene chloride at 0 °C to furnish **17a** in 70% yield. Other alcohols such as allyl alcohol, propargyl alcohol, and methanol also served as good nucleophiles to produce the corresponding diol derivatives **17b−d** in satisfactory yields, the RO groups of which

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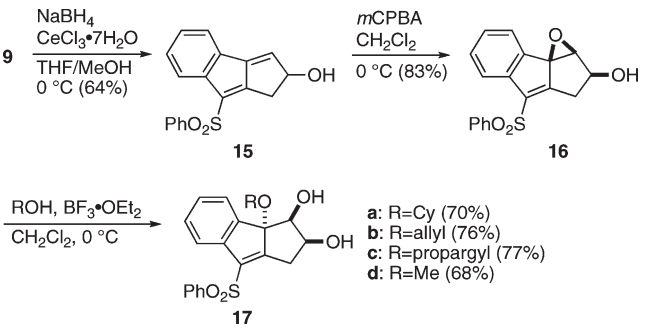
SCHEME 5. Synthesis of Diol Derivatives 17 from 9

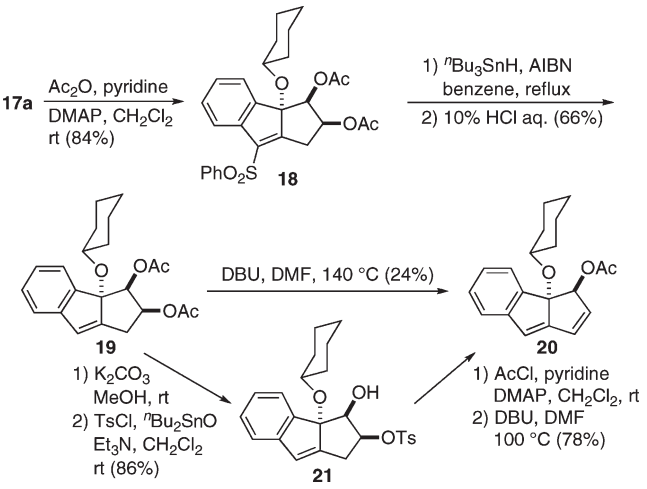


would be converted to a hydroxyl functionality in a later manipulation.

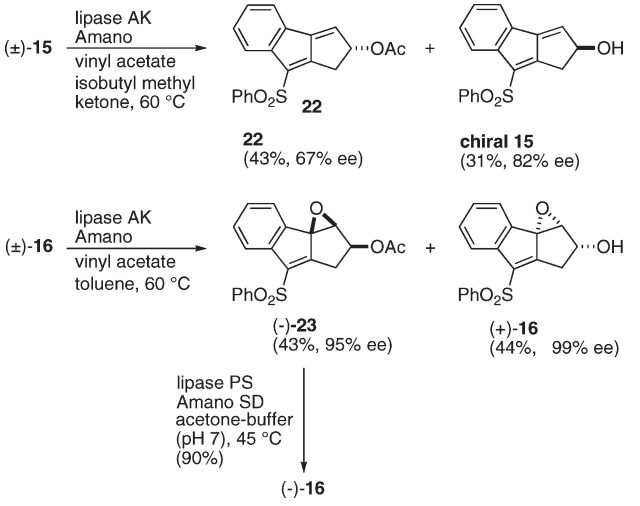
With the required diol derivatives **17** in hand, a further elaboration was carried out using the cyclohexyloxy derivative **17a** (Scheme 6). Acetylation of the diol group under the standard conditions afforded the diacetoxy derivative **18** in 84% yield. The phenylsulfonyl group of **18** was removed by exposure to radical conditions[9] with $^{n}Bu_3SnH$ in the presence of AIBN, followed by acid treatment to provide **19** in 66% yield. The introduction of a double bond between $C_1$and C_2 remains prior to completion of the preparation of the target structure. Upon treatment with DBU in DMF at 140 °C, compound **19** underwent an E2-type elimination to produce the desired **20**, but the chemical yield was rather low (24%). A more powerful leaving group instead of an acetoxy group would improve the chemical yield. Thus, a multistep conversion of **19** into **20** with a higher overall yield was developed. Compound **19** was treated with K_2CO_3, and the resulting diol derivative was subsequently monotosylated with TsCl and $^{n}Bu_2SnO$[10] to provide **21** in 86% yield. DBU treatment of an acetyl derivative, derived from **21**, effected E2-type elimination resulting in the easy formation of **20** in 78% yield.

As the carbon framework **20** of **1** and **2** could be synthesized in a racemic form, the next objective was the preparation of the optically active **20** (Scheme 7). Although the asymmetric reduction of **9** was examined under several conditions such as CBS reduction,[11] Noyori's asymmetric hydrogen transfer reaction,[12] BINAL reduction,[13] and Baker's yeast reduction,[14] and so on, all efforts led to fruitless results. We next attempted the lipase-mediated optical resolution of the alcohol derivative **15**. After screening various conditions, treatment of the racemic **15** with lipase AK Amano (*Pseudomonas fluorescens*)[15] in isobutyl methyl ketone in the presence

SCHEME 6. Synthesis of 3,3a-Dihydrocyclopent[*a*]indene 20 from 17a



SCHEME 7. Synthesis of (−)-16



of vinyl acetate as an acetyl donor at 60 °C provided the best result by producing the chiral acetoxy derivative **22**[16] in 43% yield (67% ee) together with recovery of the chiral **15**[16] in 31% yield (82% ee). In addition to the unsatisfied ee values of both compounds **15** and **22**, a fairly easy racemization of the chiral **15** (83% ee to 50% ee) was observed during its storage for a short time, although the mechanism for the racemization is still uncertain (Scheme 7).

Finally the epoxy alcohol derivative **16** was found to be a suitable substrate for the optical resolution method (Scheme 7). Indeed, the racemic **16** was exposed to lipase AK Amano (*P. fluorescens*)[15] in toluene at 60 °C in the presence of vinyl acetate to afford (−)-**23** in 43% yield (95% ee) together with (+)-**16** in 44% yield (≥99% ee). The absolute stereochemistry of (+)-**16** was determined by application of the modified Mosher method.[17] Calculation of

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(16) The absolute stereochemistry was not determined. The stereochemistry described in Scheme 7 was deduced on the basis of the precedents.[15]

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the value [$\Delta\delta = \delta(S) - \delta(R)$] of the (*S*)- and (*R*)-MTPA esters,[18] derived from (+)-**16**, in their ^{1}H NMR spectra, confirmed its absolute stereochemistry as shown in Scheme 7. Thus, compound (−)-**23** possessing the required absolute stereochemistry was then hydrolyzed with lipase PS Amano SD (*Burkholderia cepacia*)[19] in a mixed solution of acetone and pH 7.0 buffer at 45 °C to furnish (−)-**16** in 90% yield. According to the procedures described in Schemes 5 and 6, the optically active alcohol (−)-**16** was converted into (+)-**17a**, which was subsequently transformed into the final target molecule (+)-**20** through (+)-**18**, (+)-**19**, and (+)-**21**, in turn.

In summary, we have synthesized a 3,3a-dioxygenated-3,3a-dihydrocyclopent[*a*]indene skeleton, the core carbon framework of cyanosporasides A and B, in an optically active form. The most significant feature of this synthesis involves the previously developed Rh(I)-catalyzed carbonylative ring-closing reaction of an allenyne as the key step. Further studies regarding the total synthesis of cyanosporasides A and B are now in progress.

Experimental Section

3-(2-Ethynylphenyl)prop-2-ynyl Benzenesulfinate (7). To a solution of **6** (500 mg, 3.20 mmol) and ^{i}Pr$_2$NEt (1.67 mL, 9.90 mmol) in THF (25 mL) was added PhS(O)Cl (566 mg, 3.52 mmol) in THF (5 mL) at −78 °C. The reaction mixture was stirred for 1 h, quenched by addition of water, and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (5:1) to afford **7** (905 mg, quant) as a pale yellow oil: IR 3308, 1479, 1445 cm^{-1}; ^{1}H NMR δ 7.81−7.79 (m, 2H), 7.56−7.48 (m, 4H), 7.40 (dt, 1H, J = 9.4, 3.8 Hz), 7.31−7.27 (m, 2H), 4.91 (d, 1H, J = 15.8 Hz), 4.64 (d, 1H, J = 15.8 Hz), 3.28 (s, 1H); ^{13}C NMR δ 144.3, 132.6, 132.4, 132.2, 129.1, 128.5, 128.4, 125.4, 124.9, 124.8, 86.8, 86.1, 81.7, 81.3, 52.8; MS m/z 280 (M$^+$, 48.5); HRMS calcd for $C_{17}H_{12}O_2S$ 280.0558, found 280.0557.

8-(Phenylsulfonyl)-1*H*-cyclopent[*a*]inden-2-one (9). To a solution of **7** (905 mg, 3.23 mmol) in toluene (30 mL) was added [RhCl(CO)$_2$]$_2$ (31.4 mg, 8.08×10^{-3} mmol) at room temperature. The reaction mixture was stirred at room temperature under CO atmosphere for 4 h. The reaction mixture was concentrated and chromatographed with hexane−AcOEt (8:1) to afford **9** (810 mg, 81%) as yellow needles: mp 186−187 °C (AcOEt); IR 1720, 1607, 1323 cm^{-1}; ^{1}H NMR δ 8.04 (d, 2H, J = 8.3 Hz), 7.68−7.55 (m, 5H), 7.43 (t, 1H, J = 7.7 Hz), 7.26−7.25 (m, 1H), 6.76 (s, 1H), 3.45 (s, 2H); ^{13}C NMR δ 203.9, 167.4, 150.1, 141.9, 140.6, 134.0. 133.6, 132.8, 129.6, 129.5, 129.3, 127.5, 126.9, 126.0, 121.9, 35.8; MS m/z 308 (M$^+$, 57.9). Anal. Calcd for $C_{18}H_{12}O_3S$: C, 70.11; H, 3.92. Found: C, 69.99, H, 3.97.

8-(Phenylsulfonyl)-1,2-dihydrocyclopent[*a*]inden-2-ol (15). To a solution of **9** (120 mg, 0.390 mmol) in THF (4 mL) was added a mixture of $NaBH_4$ (37.1 mg, 0.975 mmol) and $CeCl_3\cdot7H_2O$ (400 mg, 1.05 mmol) in MeOH (2 mL) at 0 °C. The reaction mixture was stirred for 3 h, quenched by addition of water, and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−Et$_2$O (1:2) to afford **15** (77.7 mg, 64%) as yellow plates: mp 190−191 °C (CH_2Cl_2); IR 3587, 1317, 1151 cm^{-1}; ^{1}H NMR δ 8.03−8.01 (m, 2H), 7.65 (d, 1H, J = 7.8 Hz), 7.60−7.56 (m, 2H), 7.53−7.50 (m, 2H), 7.34−7.31 (m, 1H), 7.21−7.18 (m, 1H), 6.97 (d, 1H, J = 2.4 Hz), 5.48−5.45 (m, 1H), 3.66 (dd, 1H, J = 19.9, 5.7 Hz), 2.87 (dd, 1H, J = 19.9, 1.3 Hz), 2.14 (d, 1H, J = 7.8 Hz); ^{13}C NMR δ 159.5, 148.3, 143.8, 141.7, 140.8, 133.4, 129.6, 129.3, 128.9, 128.8, 127.1, 125.5, 123.4, 120.8, 81.4, 36.1; MS m/z 310 (M$^+$, 29.3); HRMS calcd for $C_{18}H_{14}O_3S$ 310.0664, found 310.0666.

(2*R,3*R**,3a*S**)-3,3a-Epoxy-8-(phenylsulfonyl)-1,2,3,3a-tetrahydorocyclopent[*a*]inden-2-ol (16).** To a solution of **15** (220 mg, 0.710 mmol) in CH_2Cl_2 (7 mL) was added *m*-CPBA (244 mg, 1.42 mmol) at 0 °C. After being stirred for 3 h at the same temperature, the reaction mixture was warmed to room temperature and then stirred for 10 h. The mixture was quenched by addition of saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−Et$_2$O (2:1) to afford **16** (192 mg, 83%) as a pale yellow foam: IR 3587, 1321, 1151 cm^{-1}; ^{1}H NMR δ 8.02−8.00 (m, 2H), 7.72 (d, 1H, J = 7.8 Hz), 7.64−7.60 (m, 1H), 7.56−7.53 (m, 2H), 7.40−7.36 (m, 1H) 7.27−7.26 (m, 1H), 7.24−7.21 (m, 1H), 4.60−4.54 (m, 1H), 4.34 (d, 1H, J = 1.7 Hz), 3.65 (dd, 1H, J = 17.2, 7.4 Hz), 2.49 (dd, 1H, J = 17.2, 6.8 Hz), 2.43 (d, 1H, J = 9.8 Hz); ^{13}C NMR δ 157.4, 140.7, 140.3, 134.7, 134.0, 133.8, 130.0, 129.4, 127.4, 126.5, 122.7, 122.2, 75.6, 73.1, 64.8, 30.4; MS m/z 326 (M$^+$, 16.6); HRMS calcd for $C_{18}H_{14}O_4S$ 326.0613, found 326.0615.

General Procedure for Ring-Opening of Epoxide with Alcohols. To a solution of epoxide **16** (16.3 mg, 0.0500 mmol) and alcohol (0.50 mmol) in CH_2Cl_2 (0.5 mL) was added $BF_3\cdot OEt_2$ (0.019 mL, 0.15 mmol) at 0 °C. The reaction mixture was stirred at room temperature until the complete disappearance of the starting material (monitored by TLC), quenched by addition of saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt to afford diol **17**. Chemical yields of **17** are summarized in Scheme 5.

(2*R,3*R**,3a*R**)-3a-Cyclohexyloxy-8-(phenylsulfonyl)-1,2,3,3a-tetrahydrocyclopent[*a*]indene-2,3-diol (17a):** pale yellow foam; IR 3568, 3367, 1319, 1150 cm^{-1}; ^{1}H NMR δ 7.98−7.96 (m, 2H), 7.58−7.54 (m, 2H), 7.50−7.47 (m, 2H), 7.40 (d, 1H, J = 7.3 Hz), 7.31−7.28 (m, 1H), 7.23−7.19 (m, 1H), 5.13−5.08 (m, 1H), 4.21 (d, 1H, J = 2.9 Hz), 3.34 (dd, 1H, J = 19.0, 9.8 Hz), 2.91 (dd, 1H, J = 19.0, 5.6 Hz), 2.83−2.77 (m, 1H), 2.74 (d, 1H, J = 8.5 Hz), 1.87 (s, 1H), 1.60−1.53 (m, 3H), 1.33−0.90 (m, 7H); ^{13}C NMR δ 164.4, 141.1, 140.8, 139.8, 136.3, 133.6, 129.8, 129.2, 127.0, 126.8, 124.5, 121.6, 96.8, 77.2, 75.3, 73.8, 34.2, 34.1, 33.2, 25.2, 24.0, 23.9; MS m/z 426 (M$^+$, 2.7); HRMS calcd for $C_{24}H_{26}O_5S$ 426.1501, found 426.1504. (+)-(2*S*,3*S*,3a*S*)-**17a**: $[\alpha]^{22}_D$ +24.2 (c = 0.47, $CHCl_3$).

(2*R,3*R**,3a*R**)-3a-Cyclohexyloxy-8-(phenysulfonyl)-1,2,3,3a-tetrahydrocyclopent[*a*]indene-2,3-diyl Diacetate (18).** To a solution of **17a** (44.0 mg, 0.103 mmol), pyridine (0.1 mL), and DMAP (1.3 mg, 0.010 mmol) in CH_2Cl_2 (1 mL) was added Ac_2O (0.032 mL, 0.31 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature, quenched by addition of 10% aqueous HCl, and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (4:1) to afford **18** (43.9 mg, 84%) as colorless needles: mp 145−145.5 °C (hexane−CH_2Cl_2); IR 1749, 1321, 1147 cm^{-1}; ^{1}H NMR δ 8.03−8.01 (m, 2H), 7.62−7.51 (m, 4H), 7.34−7.27 (m, 2H), 7.17 (t, 1H, J = 7.6 Hz), 6.03−5.99 (m, 1H), 5.63 (d, 1H, J = 4.4 Hz), 3.47 (dd, 1H, J = 19.1, 10.0 Hz), 3.09 (dd, 1H, J = 19.1, 6.5 Hz), 2.81−2.77 (m, 1H), 2.05 (s, 3H), 1.62−1.51 (m, 3H), 1.35 (s, 3H), 1.33−1.22 (m, 4H), 1.15−0.89 (m, 3H); ^{13}C NMR δ 169.6, 169.0, 162.1, 140.8, 140.2, 139.2, 136.9, 133.7, 129.8, 129.2, 127.2, 126.9, 125.5, 121.3, 95.4, 76.8, 74.2, 74.1, 34.2, 33.9, 30.2, 25.1, 23.9, 23.8, 20.6, 19.9; MS m/z 510 (M$^+$, 8.3); HRMS calcd for $C_{28}H_{30}O_7S$ 510.1712, found 510.1708. (+)-(2*S*,3*S*,3a*S*)-**18**: $[\alpha]^{23}_D$ +3.5 (c = 0.68, $CHCl_3$).

(18) See the Supporting Information.

(19) (a) Bonomi, P.; Cairoli, P.; Ubiali, D.; Morelli, C. F.; Filice, M.; Nieto, I.; Pregnolato, M.; Manitto, P.; Terreni, M.; Speranza, G. *Tetrahedron: Asymmetry* **2009**, *20*, 467–472. (b) Brem, J.; Paizs, C.; Toşa, M. I.; Vass, E.; Irimie, F. D. *Tetrahedron: Asymmetry* **2009**, *20*, 489–496.

(2*R,3*R**,3a*S**)-3a-Cyclohexyloxy-1,2,3,3a-tetrahydrocyclopent[*a*]indene-2,3-diyl Diacetate (19).** To a solution of **18** (30.0 mg, 0.0588 mmol) in benzene (1 mL) were successively added $^{n}Bu_3SnH$ (51 mg, 0.18 mmol) and AIBN (2.2 mg, 0.018 mmol) at room temperature. After being refluxed for 10 h, the reaction mixture was allowed to cool to room temperature, and 10% aqueous HCl was added. The reaction mixture was stirred for 14 h, quenched by addition of saturated aqueous $NaHCO_3$, and extracted with AcOEt. The extract was washed with water and brine dried and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (6:1) to afford **19** (14.4 mg, 66%) as a colorless oil: IR 1741 cm^{-1}; ^1H NMR δ 7.31 (d, 1H, J = 7.3 Hz), 7.23−7.20 (m, 1H), 7.11 (d, 1H, J = 7.3 Hz), 7.10−7.06 (m, 1H), 6.46 (s, 1H), 5.94 (ddd, 1H, J = 10.3, 5.7, 4.6 Hz), 5.60 (d, 1H, J = 4.6 Hz), 3.19 (ddd, 1H, J = 17.0, 10.3, 2.4 Hz), 2.95−2.90 (m, 1H), 2.41 (dd, 1H, J = 17.0, 5.7 Hz), 2.02 (s, 3H), 1.64−1.61 (m, 2H), 1.60 (s, 3H), 1.58−1.53 (m, 1H), 1.37−1.29 (m, 3H), 1.17−1.09 (m, 3H), 1.01−0.93 (m, 1H); ^{13}C NMR δ 169.8, 169.7, 150.1, 146.7, 141.0, 128.9, 127.4, 125.1, 124.9, 120.8, 95.7, 77.8, 74.0, 73.0, 34.2, 34.1, 29.4, 25.4, 24.1, 24.0, 20.7, 20.3; MS m/z 370 (M^+, 16.9); HRMS calcd for $C_{22}H_{26}O_5$ 370.1780, found 370.1780. (+)-(2*S*,3*S*,3a*R*)-**19**: $[\alpha]^{23}_D$+43.7 (c = 0.26, $CHCl_3$).

(2*R,3*R**,3a*S**)-3a-Cyclohexyloxy-3-hydroxy-1,2,3,3a-tetrahydrocyclopent[*a*]inden-2-yl Benzenesulfonate (21).** K_2CO_3 (17 mg, 0.12 mmol) was added to a solution of **19** (15.0 mg, 0.0405 mmol) in MeOH (0.5 mL) at room temperature. The reaction mixture was stirred for 10 min, quenched by addition of water, and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to leave the crude diol. To a suspension of crude diol, $^{n}Bu_2SnO$ (3.0 mg, 0.012 mmol), and Et_3N (8.8 μL, 0.061 mmol) in CH_2Cl_2 (0.5 mL) was added TsCl (7.8 mg, 0.041 mmol) at room temperature. The reaction mixture was stirred for 16 h, quenched by addition of water, and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (6:1) to afford **21** (15.5 mg, 86%) as colorless needles: mp 140.5−141.5 °C (hexane); IR 3589, 1369 cm^{-1}; ^1H NMR δ 7.85 (d, 2H, J = 8.3 Hz), 7.37−7.33 (m, 3H), 7.26−7.22 (m, 1H), 7.14−7.11 (m, 2H), 6.45 (s, 1H), 5.62−5.58 (m, 1H), 4.26 (t, 1H, J = 3.5 Hz), 3.00 (dd, 1H, J = 17.3, 9.8 Hz), 2.89−2.84 (m, 1H), 2.50 (dd, 1H, J = 17.3, 6.0 Hz), 2.46 (s, 3H), 1.59−1.58 (m, 3H), 1.51−1.50 (m, 1H), 1.37−1.21 (m, 3H), 1.13−1.07 (m, 3H), 0.96−0.93 (m, 1H); ^{13}C NMR δ 149.1, 146.8, 145.1, 140.9, 133.5, 129.9, 129.2, 128.0, 127.9, 125.4, 124.1, 121.4, 96.4, 85.6, 74.4, 72.9, 34.22, 34.20, 29.0, 25.4, 24.2, 24.0, 21.7; MS m/z 440 (M^+, 33.3); HRMS calcd for $C_{25}H_{28}O_5S$ 440.1657, found 440.1660. Anal. Calcd for $C_{25}H_{28}O_5S$: C, 68.16; H, 6.41. Found: C, 67.79, H, 6.35. (+)-(2*S*,3*S*,3a*R*)-**21**: $[\alpha]^{18}_D$ +48.4 (c = 0.22, $CHCl_3$).

(3*R,3a*R**)-3a-Cyclohexyloxy-3,3a-dihydrocyclopent[*a*]inden-3-yl Acetate (20).** To a solution of **21** (5.5 mg, 0.012 mmol), pyridine (0.05 mL), and DMAP (1.0 mg) in CH_2Cl_2 (0.5 mL) was added AcCl (10 μL, 0.12 mmol) at room temperature. The reaction mixture was stirred for 10 min, quenched by addition of water, and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to leave crude acetate. To a solution of crude acetate in DMF (0.5 mL) was added DBU (10 μL, 0.065 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 10 h, quenched by addition of water, and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (6:1) to afford **20** (2.9 mg, 78%) as colorless needles: mp 95−97 °C (hexane); IR 1736 cm^{-1}; ^1H NMR δ 7.38 (d, 1H, J = 7.3 Hz), 7.28−7.20 (m, 2H), 7.12 (t, 1H, J = 7.3 Hz), 6.79 (d, 1H, J = 5.6 Hz), 6.54 (dd, 1H, J = 5.6, 2.5 Hz), 6.51 (s, 1H), 5.71 (d, 1H, J = 2.5 Hz), 2.88−2.82 (m, 1H), 1.69 (s, 3H), 1.52−1.50 (m, 2H), 1.33−1.26 (m, 3H), 1.12−0.94 (m, 5H); ^{13}C NMR δ 170.4, 154.9, 148.0, 142.0, 140.4, 131.6, 129.1, 125.5, 125.4, 123.2, 121.9, 94.5, 77.2, 72.0, 34.3, 34.2, 25.4, 24.3, 24.2, 20.8; MS m/z 310 (M^+, 25.4); HRMS calcd for $C_{20}H_{22}O_3$ 310.1569, found 310.1569. (+)-(3*S*,3a*S*)-**20**: $[\alpha]^{20}_D$ +431.9 (c = 0.11, $CHCl_3$).

Optical Resolution of (±)-16. To a solution of (±)-**16** (60.0 mg, 0.184 mmol) and vinyl acetate (0.5 mL) in toluene (2.5 mL) was added lipase AK Amano (120 mg) at room temperature. The reaction mixture was stirred at 60 °C for 24 h, passed through a filter paper, and concentrated to dryness. The residue was chromatograhed with hexane−AcOEt (4:1 to 2:1) to afford (+)-**16** (26.5 mg, 44%, 99% ee) and (−)-**23** (33.0 mg, 49%, 95% ee).

(2*R*,3*R*,3a*S*)-3,3a-Epoxy-8-(phenylsulfonyl)-1,2,3,3a-tetrahydorocyclopent[*a*]inden-2-ol ((+)-16): pale yellow foam; $[\alpha]^{23}_D$ +28.1 (c = 0.39, $CHCl_3$) for 99% ee. The enantiomeric excess of (+)-**16** was determined to be 99% by chiral HPLC using Daicel Chiralpak IA; hexane/^{i}PrOH = 4:1 as an eluent; flow rate = 1.0 mL/min; detector ultraviolet absorption at 254 nm; t_R = 12.4 min (major), 15.3 min (minor). The other analytical data for (+)-**16** were found to be identical with those of the racemic **16**.

(2*S*,3*R*,3a*R*)-3,3a-Epoxy-8-(phenylsulfonyl)-1,2,3,3a-tetrahydorocyclopent[*a*]inden-2-yl Acetate ((−)-23): pale yellow foam: $[a]^{23}_D$ −78.3 (c = 0.51, $CHCl_3$) for 95% ee; IR 1742, 1323, 1153 cm^{-1}; ^1H NMR δ 8.02−8.00 (m, 2H), 7.72 (d, 1H, J = 7.8 Hz), 7.64−7.61 (m, 1H), 7.57−7.53 (m, 2H), 7.40−7.37 (m, 1H), 7.25−7.21 (m, 2H), 5.34 (ddd, 1H, J = 7.7, 7.3, 1.7 Hz), 4.47 (d, 1H, J = 1.7 Hz), 3.68 (dd, 1H, J = 17.1, 7.7 Hz), 2.67 (dd, 1H, J = 17.1, 7.3 Hz), 2.17 (s, 3H); ^{13}C NMR δ 170.4, 156.2, 140.6, 140.5, 135.8, 133.9, 133.8, 130.1, 129.5, 127.4, 126.7, 122.8, 122.4, 75.7, 72.6, 62.0, 27.1, 20.7; MS m/z 368 (M^+, 9.3), HRMS calcd for $C_{20}H_{16}O_5S$ 368.0718, found 368.0720.

(2*S*,3*S*,3a*R*)-3,3a-Epoxy-8-(phenylsulfonyl)-1,2,3,3a-tetrahydorocyclopent[*a*]inden-2-ol ((−)-16). To a solution of (−)-**23** (60.0 mg, 0.163 mmol) in pH 7.0 phosphate buffer (0.3 M, 0.5 mL) and acetone (1.0 mL) was added lipase PS Amano SD (60.0 mg) at room temperature. The reaction mixture was stirred at 45 °C for 24 h, quenched by addition of brine, and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatograhed with hexane−AcOEt (2:1) to afford (−)-**16** (48.1 mg, 90%) as a pale yellow foam: $[\alpha]^{22}_D$ −28.2 (c = 1.50, $CHCl_3$).

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **7**, **9**−**12**, **15**, **16**, **17a**−**d**, **18**−**22**, and (−)-**23**; characterization data for compounds **10**−**12**, **17b**−**d**, and (−)-**22**. This material is available free of charge via the Internet at http://pubs.acs.org.