Total Synthesis of (*R*)-Dihydroactinidiolide and (*R*)-Actinidiolide Using Asymmetric Catalytic Hetero-Diels−Alder Methodology

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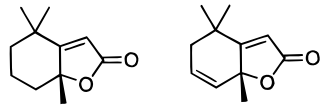
The total synthesis of the naturally occurring bicyclic lactones (*R*)-dihydroactinidiolide and (*R*)-actinidiolide is presented. The key step in the syntheses is the copper(II)−bisoxazoline-catalyzed hetero-Diels−Alder reaction of a cyclic diene with ethyl glyoxylate giving the hetero-Diels−Alder product in high yield and with very high regio-, diastereo-, and enantioselectivity. The total syntheses proceed via an intermediate, which also has the potential for a series of other natural products. The structure of the key intermediate is confirmed by X-ray analysis.

Introduction

(*R*)-Dihydroactinidiolide (**1**) is one of the three components of the pheromone for queen recognition of the workers of the red fire ant, *Soleneopsis invicta*.[1] More

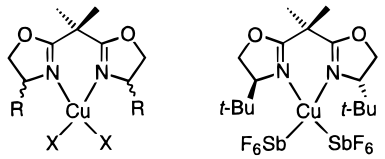


1 **2**

than a dozen different syntheses of racemic dihydroactinidiolide have been reported,[2] whereas only few enantioselective procedures are available.[3] The enantioselective syntheses of (*R*)-dihydroactinidiolide (**1**) are based on the use of chiral starting compounds and multistep reactions, or compounds which, at a certain stage of the reaction path, are separated as the pure enantiomers, often leading to low overall yields of **1**.

A closely related compound to (*R*)-dihydroactinidiolide (**1**) is (*R*)-actinidiolide (**2**). Both **1** and **2** were first isolated as cat attractants from leaves from *Actinidia polygama*[2a] and have since also been identified as flavor components in many plant sources such as tobacco[4] and tea.[5]

This paper describes the first total synthesis of (*R*)-dihydroactinidiolide (**1**) and (*R*)-actinidiolide (**2**) with very high enantiomeric excess (ee) and in high overall yield by asymmetric catalytic hetero-Diels−Alder (HDA) methodology. Furthermore, a common intermediate present in the total synthesis of **1** and **2** may prove useful for the preparation of a series of related compounds. The present total synthesis of **1** and **2** is made possible by our development of highly selective and enantioselective HDA reactions of conjugated dienes with glyoxylates catalyzed by Cu(II)−bisoxazoline complexes **3**.[6,7]



3 (*S*)-**3a**

Results and Discussion

The retrosynthetic approach to the synthesis of (*R*)-dihydroactinidiolide (**1**) and (*R*)-actinidiolide (**2**) using asymmetric catalytic HDA methodology is outlined in Scheme 1.

(*R*)-Dihydroactinidiolide (**1**) and (*R*)-actinidiolide (**2**) can be prepared from **4b** by reduction and elimination, and elimination, respectively. The bicyclic lactone **4b** should be obtainable from **5** by treatment of base followed by acid,[6a,b] while **5** could be obtained by an asymmetric catalytic HDA reaction of 2,6,6-trimethyl-1,3-cyclohexadiene (**6**) with ethyl glyoxylate (**7**). The key step in the total synthesis of **1** and **2** is thus the latter reaction, which has to proceed with high regio- and *endo*-diastereoselectivity, and in high ee. By a screening of several Cu(II)−bisoxazoline complexes **3** it was found that application of 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]Cu(SbF_6)$_2$ ((*S*)-**3a**) as the catalyst in CH_2Cl_2 meets these requirements.

The total synthesis of (*R*)-dihydroactinidiolide (**1**) and (*R*)-actinidiolide (**2**) from 2,6,6-trimethyl-1,3-cyclohexa-

[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1997.

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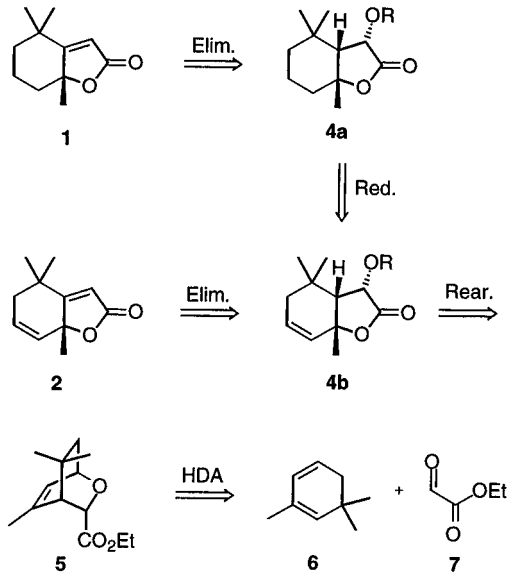
Scheme 1



diene (**6**) and ethyl glyoxylate (**7**) is presented in Scheme 2. The experimental details are in the Experimental Section.

The reaction of 2,6,6-trimethyl-1,3-cyclohexadiene (**6**) with ethyl glyoxylate (**7**) in the presence of the Cu(II)−bisoxazoline catalyst ((*S*)-**3a**) (10 mol %) in CH_2Cl_2 gives the HDA-product **5** in 90% isolated yield, and only the *endo*-diastereomer can be detected by ^1H NMR spectroscopy. The ee of **5** was measured to be 97% by chiral GC (see Scheme 2).

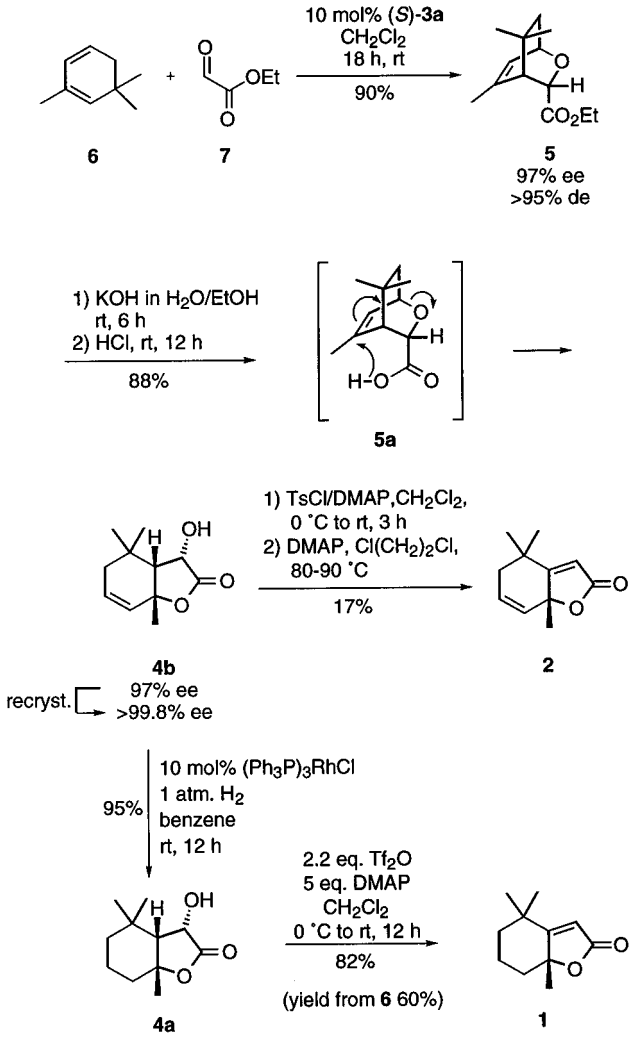
The HDA-product (**5**) was treated with KOH/H_2O−EtOH at rt for 6 h, followed by 3 N HCl overnight giving **4b** in 88% isolated yield and maintaining the high ee obtained in the first step. Compound **4b** can be recrystallized to give enantiomerically pure **4b** (ee > 99.8%). A mechanistic rationale for the formation of **4b** from **5** is outlined in **5a**.

Reduction of **4b** with H_2 and $(Ph_3P)_3RhCl$ (10 mol %) as the catalyst (Wilkinson's catalyst) at rt proceeded smoothly, yielding the desired saturated hydroxy lactone **4a** in 95% yield without affecting the stereogenic centers. An early attempt employing 5% Pd/C as the catalyst in EtOH under the same reaction conditions gave only products formed from ring-opening reactions of the lactone.

The elimination reactions of **4a** and **4b** to give the desired (*R*)-dihydroactinidiolide (**1**) and (*R*)-actinidiolide (**2**), respectively, were expected to proceed readily by first esterification of the hydroxy substituent followed by treatment with a base. However, these reactions turned out to be more difficult than first anticipated, especially the elimination reaction of **4b** leading to **2**. After many unsuccessful attempts, it was finally found that treatment of **4a** with trifluoromethanesulfonic anhydride (Tf_2O) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) at rt furnished directly **1** as the only isolated product in 82% yield and as the only enantiomer detectable by chiral GC. The overall yield of (*R*)-dihydroactinidiolide (**1**) from 2,6,6-trimethyl-1,3-cyclohexadiene (**6**) was 60% (four steps).

Surprisingly, the elimination of H_2O from **4b** under the same reaction conditions as for the synthesis of (*R*)-dihydroactinidiolide (**1**) using Tf_2O gave only an 11% yield of **2** with an ee >99.8% along with a larger amount

Scheme 2



of a chlorine-containing byproduct **4c**. The yield of **2** could be slightly improved (17%) by tosylation of the hydroxy group followed by treatment with DMAP under gentle reflux in $Cl(CH_2)_2Cl$. Again the chlorine-containing compound **4c** was the major product, and the isolated yield of **4c** under these reaction conditions was 77%. Attempts to perform reaction using DBU[8] as the base gave no elimination product, but instead afforded the epimerized lactone **4e**. The difference in the success in the elimination reaction from **4a** and **4b**, respectively, strongly indicates that the carbon−carbon double bond must necessarily interfere with the elimination reaction for the latter compound. The three methyl substituents could also be expected to interfere with the elimination process and in order to establish whether there was any connection between the presence of the three methyl substituents in the substrate and the ease of elimination, the tosylated lactone **4f** was therefore synthesized. Similar to the elimination reaction of **4d**, the epimerized product **4g** was obtained when using DBU as the base. Furthermore, the chloride substitution product **4h** also predominated when tosylate **4f** was refluxed in $Cl(CH_2)_2Cl$, employing DMAP as a base. However, in contrast to the tosyl derivative **4f**, a rapid and clean in situ

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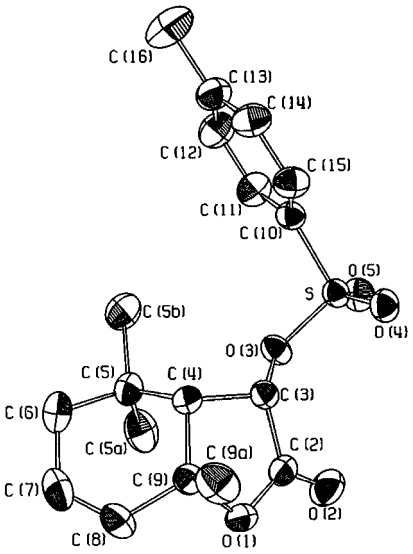
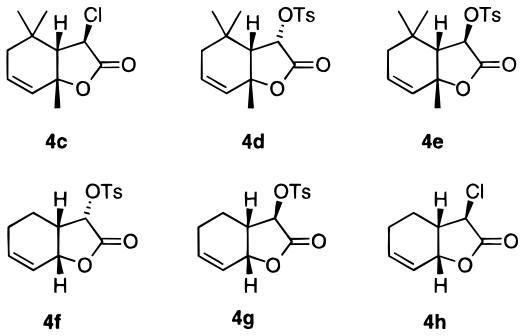


4d

Figure 1. Crystal structure of **4d**.

elimination reaction takes place during the synthesis of the triflate analogue of **4f**. These results indicate that the three methyl substituents are also of importance for the elimination reaction.



To confirm the structure of the bicyclic lactone and to obtain some information about the difficulty in performing the elimination reaction of **4d** leading to (*R*)-actinidiolide (**2**), the crystal structure of **4d** was solved and is presented in Figure 1.

The X-ray structure of the tosylated bicyclic lactone **4d** shows that it has four molecules in the unit cell of space group $P2_12_12_1$. The bond lengths and angles of the bicyclic lactone part of **4d** are similar to the only one of similar type characterized.[9] The tosylate substituent is oriented in the solid state toward the two methyl substituents of the cyclohexene ring. The most important information obtained from the X-ray structure is that the dihedral angle for O(3)−C(3)−C(4)−H(4) is 108° (where the H(4) position is calculated from the X-ray data), which is far from the ideal 180° (antiperiplanar geometry) for an E2-elimination reaction, which might account for the difficulty in elimination under these reaction conditions. It should be mentioned that a *syn*-elimination of selenoxides has provided an efficient entry to the same system,[2b,g,3a] but at least two more steps would be required.

In summary we have shown that the naturally occurring (*R*)-dihydroactinidiolide and (*R*)-actinidiolide can be prepared as enantiomerically pure compounds using asymmetric copper(II)−bisoxazoline-catalyzed hetero-Diels−Alder methodology as the crucial step giving the hetero-Diels−Alder product in high yield and with very high regio, diastereo-, and enantioselectivity. The hetero-Diels−Alder intermediate undergoes an acid-catalyzed rearrangement reaction giving a bicyclic lactone while maintaining the very high enantiomeric excess obtained in the hetero-Diels−Alder reaction. This bicyclic lactone has the potential for also being the key intermediate for the synthesis of a series of other natural products.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using $CDCl_3$ as the solvent and were reported in ppm downfield from tetramethylsilane (TMS). Mass spectra were recorded at 70 eV using a direct inlet. Enantiomeric excess (ee) was determined by GC using a Chrompack Chirasil-DEX CB column. Merck silica gel (230−400 mesh) was used for flash chromatography (FC). Preparative thin-layer chromatography (PTLC) was performed on 200 × 200 × 1.8 mm silica gel (60 $HP_{254+366}$, Merck). TLC was performed on Merck analytical silica gel 60 F_{254} plates and visualized with a basic $KMnO_4$ solution.

Materials. 2,2′-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline], $CuBr_2$, $AgSbF_6$, 2,4,4-trimethyl-2-cyclohexan-1-one, 1.6 M MeLi in Et_2O, *p*-toluenesulfonohydrazide, $(Ph_3P)_3RhCl$, $(CF_3SO_2)_2O$, and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) were purchased from Aldrich Chemical Co. and used as received. Ethyl glyoxylate (**7**) was prepared as described in the literature,[10] stored at −18 °C, and distilled prior to use. Solvents were dried according to standard procedures.

2,6,6-Trimethyl-1,3-cyclohexadiene (6).[11] To a 250 mL flask were added 2,4,4-trimethyl-2-cyclohexan-1-one (5.0 g, 36.2 mmol), *p*-toluenesulfonohydrazide (6.74 g, 36.2 mmol), and MeOH (60 mL). The resulting solution was stirred at rt for 6 h until a lot of white solid was formed. After the solvent was evaporated *in vacuo*, the solid was dried thoroughly under vacuum. Then anhydrous Et_2O (100 mL) was added under N_2, and 1.6 M MeLi in Et_2O (46 mL, 73.6 mmol) was added at −78 °C, dropwise by cannula over 30 min. The solution was stirred at rt overnight. After the Et_2O was evaporated, ice−water (40 mL) was added slowly, and the crude product was extracted using petroleum ether. The combined organic phases were washed using 1 N HCl, saturated $NaHCO_3$, H_2O, and brine (all 10 mL), respectively, dried, filtered, and concentrated. Purification by distilling under water vacuum yielded **6** (3.6 g, yield 81%) as a clear and colorless liquid. ^{1}H NMR δ 5.72−5.75 (m, 2H), 5.20 (d, 1H, J = 1.7 Hz), 2.06 (d, 2H, J = 2.7 Hz), 1.74 (d, 3H, J = 1.7 Hz), 0.98 (s, 6H); ^{13}C NMR δ 132.1, 128.9, 126.8, 125.4, 37.8, 31.0, 28.1, 21.3.

(1*R*,3*S*,4*S*)-Ethyl 5,8,8-Trimethyl-2-oxabicyclo[2.2.2]-oct-5-ene-3-carboxylate (5). To a dry flask was added $CuBr_2$ (22 mg, 0.10 mmol), $AgSbF_6$ (69 mg, 0.20 mmol), and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (31 mg, 0.105 mmol) under N_2. Anhydrous CH_2Cl_2 (2 mL) was added, and the heterogeneous solution was stirred vigorously for 6 h and then filtered through a Pasteur pipet with a plug of cotton and Hyflo to give a clear blue-green solution. To this solution were added freshly distilled ethyl glyoxylate (**7**) (0.102 g, 1.0 mmol) in CH_2Cl_2 (1 mL) and 2,6,6-trimethyl-1,3-cyclohexadiene (170 μL, 1.5 mmol). The solution was stirred at rt for 18 h, the solvent was evaporated in vacuo, and the residue was purified using FC on silica gel (EtOAc:petroleum ether 20:80) to give **5** (198 mg, 90% yield) as a colorless liquid. $[\alpha]_D = +69.5$ (c =

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1.0, $CHCl_3$), 97% ee. ^{1}H NMR δ 6.01−6.04 (m, 1H), 4.57 (d, 1H, J = 2.2 Hz), 4.44−4.48 (m, 1H), 4.15 (q, 2H, J = 7.2 Hz), 2.46 (t, 1H, J = 2.2 Hz), 1.79 (d, 3H, J = 2.2 Hz), 1.74 (dd, 1H, J = 13.2, 2.2 Hz), 1.24 (t, 3H, J = 7.2 Hz), 1.18 (s, 3H), 1.09 (dd, 1H, 12.9, 1.9 Hz), 0.90 (s, 3H); ^{13}C NMR δ 173.2, 141.2, 124.9, 70.3, 68.7, 60.7, 50.1, 42.0, 30.6, 30.0, 28.3, 22.1, 14.4. The reaction can also be performed in a larger molar scale.

(3*S*,3a*R*,7a*R*)-4,4,7a-Trimethyl-3-hydroxy-2-oxo-3a,4,5,7a-tetrahydrobenzofuran (4b). Compound **5** (1.91 g, 8.5 mmol) was added to KOH (1.0 g, 17.8 mmol) dissolved in H_2O (3 mL) and EtOH (5 mL). The solution was stirred at rt for 6 h, partly evaporated in vacuo until total volume was about 4 mL. Then H_2O (3 mL) was added and stirred for 5−10 min, followed by the addition of 3 N HCl until the solution became acidic (pH = 1−2). After being stirred at rt overnight, the solution became bright yellow with a lot of white solid in it. The product was extracted using Et_2O, and the combined ethereal phases were washed using H_2O and brine repeatedly, dried with $MgSO_4$, and evaporated to give **4b** (1.47 g, 88% yield) with 97% ee. The crude product contained only very small amounts of impurities according to NMR spectroscopy. Recrystallization from *i*-Pr_2O gave the enantiopure **4b** (only one enantiomer could be detected by chiral GC). $[\alpha]_D = -94.4$ (c = 0.9, $CHCl_3$). IR (KBr): 3405 (s, OH), 1756 (s, CO), 3040 (w, HC=)cm^{-1}. ^{1}H NMR δ 5.87−5.93 (m, 1H), 5.74−5.79 (m, 1H), 4.90 (d, 1H, J = 8.6 Hz), 3.23 (br s, 1H), 2.31 (d, 1H, J = 8.6 Hz), 1.90 (t, 2H, J = 3.0), 1.44 (s, 3H), 1.19 (s, 3H), 1.02 (s, 3H); ^{13}C NMR δ 177.7, 129.8, 127.3, 81.7, 71.0, 52.7, 39.9, 31.6, 30.3, 27.7, 22.2.

(3*S*,3a*R*,7a*R*)-4,4,7a-Trimethyl-3-hydroxy-2-oxo-3a,4,5,6,7,7a-hexahydrobenzofuran (4a). To a dry flask which had been evacuated and filled with H_2 several times were added $(Ph_3P)_3RhCl$ (100 mg, 0.11 mmol) and freshly distilled benzene (22 mL). The resulting suspension was stirred for several minutes under an atmosphere of H_2. Compound **4b** (196 mg, 1.0 mmol) was added under H_2, and the solution was stirred at rt under H_2 overnight. After evaporation of the solvent, the residue was purified using PTLC (EtOAc:petroleum ether 20:80), giving **4a** (188 mg, 95% yield) with 99.8% ee as established by chiral GC. ^{1}H NMR δ 4.47 (dd, 1H, J = 2.8, 6.6 Hz), 2.81 (d, 1H, J = 2.8 Hz), 1.96 (dt, 1H, J = 12.4, 3.8 Hz), 1.89−1.63 (m, 4H), 1.55−1.43 (m, 1H), 1.50 (s, 3H), 1.25−1.20 (m, 1H), 1.18 (s, 3H), 1.08 (s, 3H); ^{13}C NMR δ 176.7, 87.4, 72.3, 54.8, 36.9, 36.2, 32.9, 30.6, 27.6, 27.3, 19.3.

(*R*)-4,4,7a-Trimethyl-5,6,7,7a-tetrahydrobenzofuran-2-one, (*R*)-Dihydroactinidiolide (1). $(CF_3SO_2)_2O$ (184 μL, 1.1 mmol) was added dropwise to a stirred solution of the bicyclic lactone **4a** (100 mg, 0.5 mmol) and 4-(*N*,*N*-dimethylamino)-pyridine (DMAP) (305 mg, 2.5 mmol) dissolved in anhydrous CH_2Cl_2 (8 mL) at 0 °C. The resulting solution was stirred at 0 °C for 1 h before being warmed to rt and left overnight. Then H_2O (3 mL) was added, the product was extracted using Et_2O, the collected extracts were washed repeatedly using H_2O and brine and dried, and the solvent was evaporated. The crude product was purified using FC (EtOAc:petroleum ether 30:70) to afford (*R*)-dihydroactinidiolide (**1**) (80 mg, 82% yield) with 99.8% ee according to chiral GC. $[\alpha]_D = -105°$ (c = 1.0, in $CHCl_3$), ^{1}H NMR δ 5.64 (s, 1H), 2.23 (dq, 1H, J = 2.5, 12.1 Hz), 1.62−1.77 (m, 3H), 1.53 (s, 3H), 1.46 (m, 1H), 1.33−1.22 (m, 1H), 1.25 (s, 3H), 1.20 (s, 3H); ^{13}C NMR δ 182.5, 171.9, 112.4, 87.2, 41.6, 40.1, 36.5, 29.8, 24.3, 24.2, 19.6. The spectral data were similar with those reported.[3a]

(*R*)-4,4,7a-Trimethyl-5,7a-dihydrobenzofuran-2(4*H*)-one, (*R*)-Actinidiolide (2) *via* Alcohol 4b. $(CF_3SO_2)_2O$ (92 μL, 0.55 mmol) was added dropwise to a stirred solution of **4b** (50 mg, 0.25 mmol) and DMAP (153 mg, 1.25 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was first stirred at 0 °C for 1 h and then at rt overnight. Workup as above gave the crude product, which was purified using FC (EtOAc: petroleum ether 20:80) to give (*R*)-actinidiolide (**2**) (5 mg, 11% yield), 99.8% ee according to chiral GC. $[\alpha]_D = -133°$ (c = 1.0, $CHCl_3$), ^{1}H NMR δ 5.90 (dd, 1H, J = 9.9, 2.2 Hz), 5.73−5.75 (m, 1H), 5.71 (s, 1H), 2.27 (dd, 1H, J = 17.3, 3.8), 2.14 (dt, 1H J = 18, 2.8 Hz), 1.60 (s, 3H), 1.33(s, 3H), 1.29 (s, 3H); ^{13}C NMR δ 180.9, 171.5, 128.9, 128.4, 112.7, 85.5, 44.5, 35.8, 28.2, 26.2, 26.1. The spectral data were identical with those reported.[3a]

(3*S*,3a*R*,7a*R*)-4,4,7a-Trimethyl-3-(tosyloxy_-3a,4,5,7a-tetrahydrobenzofuran-2(3*H*)-one (4d) *via* Alcohol 4b. To a stirred solution of **4b** (196 mg, 1.0 mmol) and DMAP (367 mg, 3.0 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 °C was added dropwise *p*-toluenesulfonyl chloride (393 mg, 2.0 mmol). After stirring at 0 °C for 1 h and at rt for 3 h, H_2O (2 mL) was added, and the solution was stirred for another 5 min. The organic phases were washed successively with 2 N HCl, saturated $NaHCO_3$, H_2O, and brine, dried, and concentrated. The crude product was purified using FC (EtOAc:petroleum ether 20:80) to give **4d** (342 mg, 98% yield). ^{1}H NMR δ 7.89 (d, 2H, J = 8.2 Hz), 7.35 (d, 2H, J = 8.1 Hz), 5.87−5.91 (m, 1H), 5.74 (dt, 1H, J = 10.1, 2.2 Hz), 5.51 (d, 1H, J = 8.2 Hz), 2.47 (d, 1H, J = 8.2 Hz), 2.44 (s, 3H), 1.91−1.94 (m, 2H), 1.45 (s, 3H), 1.21 (s, 3H), 1.02(s, 3H); ^{13}C NMR δ 169.8, 145.3, 133,1, 129.8, 128.2, 126.9, 81.1, 76.0, 52.6, 39.6, 31.6, 30.3, 27.9, 22.3, 21.7.

(*R*)-4,4,7a-Trimethyl-5,7a-dihydrobenzofuran-2(4*H*)-one, (*R*)-Actinidiolide (2) *via* Tosylate 4d. To a dry flask were added **4d** (330 mg, 0.94 mmol), DMAP (488 mg, 4 mmol), and anhydrous $Cl(CH_2)_2Cl$ (10 mL). After gently refluxing for 24 h, the reaction mixture was diluted with Et_2O, washed repeatedly using H_2O and brine, dried with $MgSO_4$, filtered, and concentrated. Purification by FC (EtOAc:petroleum ether 20:80) gave (*R*)-actinidiolide (**2**) (28 mg, 17% yield) with 99.5% ee and **4c** (154 mg, 77% yield). **4c**: ^{1}H NMR δ 5.77−5.82 (m, 1H), 5.66 (d, 1H, J = 11 Hz), 4.30 (br d, 1H, J = 9.9 Hz), 2.37 (br d, 1H, J = 9.3 Hz), 2.09 (d, 1H, J = 18.1 Hz), 1.90 (dd, 1H, J = 4.9, 18.7), 1.63 (s, 3H), 1.17 (s, 3H), 1.09 (s, 3H); 13C NMR δ 171.3, 128.2, 128.1, 83.1, 59.2, 54.2, 34.6, 32.2, 28.9, 28.8, 27.7; MS *m*/*e* (relative intensity) 216 ($(M + 2)^+$, 4), 214 (M^+, 12), 199(100), 135(82), 103(60), 93(99).

Crystallographic Data for 4d. X-ray diffraction analysis on **4d** was carried out on a Siemens SMART CCD diffractometer at 120 K. The structure of **4d** ($C_{18}H_{22}O_5S$, M_W 350.44 amu) was determined from an orthorhombic crystal of dimensions 0.4 × 0.3 × 0.2 mm^3 (space group $P2_12_12_1$), with unit cell a = 8.6904(2) Å, b = 9.7113(2) Å, c = 21.2082(4) Å, V = 1789.87 Å.^{3} It has four molecules per cell, D_x = 1.30 g cm^{-3}, μ = 0.20 mm^{-1}. Mo Kα radiation (λ = 0.71073 Å). 4335 reflections with $I > 3\sigma(I)$, R_w = 0.035.

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Supporting Information Available: Copies of NMR and IR spectra, chiral GC data, and X-ray materials (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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