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Synthesis of Loliolide, Actinidiolide, Dihydroactinidiolide, and Aeginetolide via Cerium Enolate Chemistry

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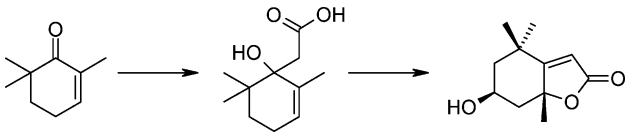
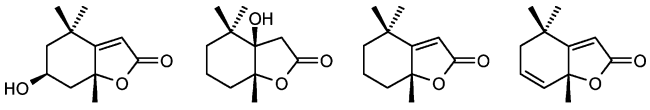


Loliolide, aeginetolide, actinidiolide, and dihydroactinidiolide were synthesized in racemic form from a single common intermediate, prepared through the 1,2 addition of the cerium enolate of ethyl acetate to 2,6,6-trimethylcylohexenone.

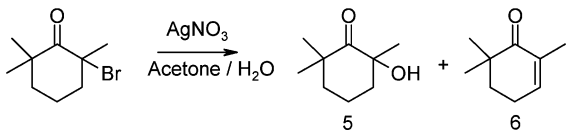
Loliolide (**1**), aeginetolide (**2**), dihydroactinidiolide (**3**), and actinidiolide (**4**) are a series of structurally similar C11-terpene lactones that arise from biological or oxidative degradation of carotenoids. These compounds have been isolated from various plant and insect sources. Loliolide is found in many plants including tobacco and tea.[1] Dihydroactinidiolide (**3**) and actinidiolide (**4**) have also been identified as flavor molecules in tea and tobacco.[2] While **1** is generally found in all varieties of teas, its impact on tea flavor has not been reported. We sought to prepare a pure sample of **1** and evaluate the flavor impact of **1** in teas.

Several elegant preparations of **1** and the other terpene lactones have been published, but all of the syntheses are lacking in some aspect.[3] The issues in the earlier work include inefficient introduction of the lactone ring carbon atoms, difficulty establishing the correct oxidation state or double bond geometry of the α,β-unsaturated lactone ring, and efficient introduction of the 6α hydroxyl group of **1**.



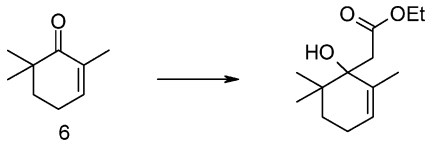
1 2 3 4

While evaluating possible synthetic routes to the loliolide carbon backbone, our earlier experience with the synthesis of 2-hydroxy-2,6,6-trimethylcyclohexanone (**5**) provided useful insights.[4] A previous synthesis of **5** from 2,6,6-trimethylcyclohexanone by bromination and solvolysis resulted in formation of 2,6,6-trimethylcyclohexen-2-one (**6**) as a major byproduct.[5]



5 6

An efficient synthesis of **1**, and the other terpene lactones, could be accomplished by the 1,2 addition of a suitable 2-carbon synthon to a sterically hindered α,β-unsaturated cyclohexenone such as **6**. Ideally, this synthon would have the C1 carbon in an acid oxidation state, such as the enolate of an acetate ester, or another acetate ester enolate equivalent, such as the acetonitrile anion. The problem with this approach is that simple ester enolates would be expected to add to **6** in a 1,4 mode. If an enolate of ethyl acetate could be added to **6** in a 1,2 mode, resulting in compound **7**, this intermediate would contain all of the required carbon atoms in the correct oxidation states for synthesis of **1** and the other terpene lactones.



6 7

While reviewing known chemistry for the addition of enolates to hindered ketones, the work of Lui was identified.[6] In this work, Liu demonstrated the efficient addition of the dichlorocerium enolate of ethyl acetate or acetonitrile to ketones as shown in Scheme 1. When the cerium enolate of ethyl acetate was reacted with unhindered α,β-unsaturated ketones, the addition took place entirely in the 1,2 mode. The dichlorocerium anion of acetonitrile added cleanly with highly hindered ketones such as 2,6,6-trimethylcyclohexanone. These papers contained encouraging results but had no specific examples of 1,2 additions of cerium ester enolates to highly hindered α,β-unsaturated ketones such as **6**.

Compound **7** would be an ideal intermediate for the synthesis of the terpene lactones **1**−**4**. Scheme 2 shows the remaining proposed transformations required to convert compound **7** to the intermediates **8** and **9.** A stereospecific iodolactonization of acid **10** should produce iodolactone **8**. Reduction of the iodide **8** would provide lactone **2**. Dehydration of iodide **8** would produce the α,β-unsaturated lactone **9** which is the key intermediate for the synthesis of the remaining terpene lactones (**1**, **3**, **4)**.

The proposed syntheses of terpene lactones **1** and **4** are described in the Scheme 3.

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(2) (a) Kaneko, H.; Ijichi, K. *Agric. Biol. Chem.* **1968**, *32*, 1337−1340. (b) Bricout, J.; Viani, R.; Muggler-Chavan, F.; Marion, J. P.; Reymond, D.; Egli, R. H. *Helv. Chem. Acta* **1967**, *50*, 1517−1522.

(3) (a) Rubottom, G. H.; Juve, H. D., Jr. *J. Org. Chem.* **1983**, *48*, 422−425. (b) Zamarlik, H.; Gnonlonfoun, N.; Rouessac, F. *Can. J. Chem.* **1984**, *62*, 2326−2329. (c) Rouessac, F.; Zamarlik, H.; Gnonlonfoun, N. *Tetrahedron Lett.* **1983**, *24*, 2247−2250. (d) Kienzle, v. F.; Mayer, H.; Minder, R. E.; Thommen, H. *Helv. Chim. Acta* **1978**, *61*, 2616−2627. (e) Mori, K., Khlebnikov, V. *Liebigs Ann. Chem.* **1993**, 77−82. (f) Hutton, J.; Waters, W. A. *Chem. Commun.* **1966**, 634−635. Recent examples of asymmetric synthesis of terpine lactones: (g) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998,** *63*, 118−121. (h) Kuba, M.; Furuichi, N.; Katsumura, S. *Chem. Lett.* **2002**, 1248−1249. (h) Osamu, I.; Shishido, K. *Chem. Lett* **1995**, 53−54.

(4) Unpublished internal Firmenich result.

(5) (a) Renold, W. EU-0229, 1973. (b) See ref 3a.

(6) (a) Liu, H. J.; Zhu, B.Y. *Can. J. Chem.* **1991**, *69*, 2008−2013. (b) Liu, H. J.; Al-said, N. H. *Tetrahedron Lett.* **1991**, *32*, 5473−5476.

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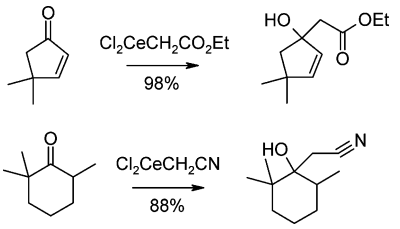
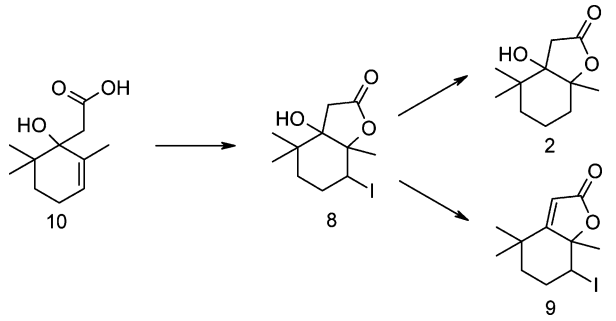
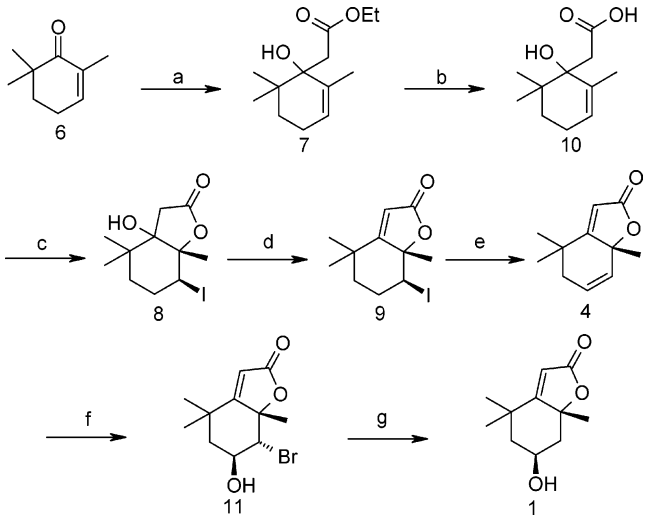
SCHEME 1. Examples of 1,2 Additions of Cerium Enolates to Hindered Ketones and α,β-Unsaturated Ketones



SCHEME 2. Proposed Synthesis of Key Intermediates 8 and 9 for the Synthesis of Terpene Lactones 1−4



SCHEME 3. Synthesis of (±)-Loliolide (1) and (±)-Actinidiolide (4) from 2,6,6-Trimethylcyclohexenone (6)[a]



[a] Conditions: (a) ethyl acetate, $(TMS)_2NLi$, $CeCl_3$, THF; (b) NaOH/H_2O; (c) I_2, K_2CO_3; (d) $SOCl_2$/pyridine; (e) DBU, 150 °C; (f) NBA/H_2O/TFA; (g) Bu_3SnH, AIBCHN, hexane.

The synthesis of racemic **1** was accomplished in seven steps from **6**, in an overall yield of 46.9%. The chemistry for all of the steps is clean. None of the steps required a major isomeric separation or purification by chromatography. All of the new stereocenters were produced with excellent selectivity. In most cases, the crude reaction products were carried to the next synthetic step with out any purification.

The successful conversion of **6** to **7** was the key reaction in our synthesis of **1**. Our main initial concern was that Lui[7] had not published examples of additions of ester enolate to highly hindered α,β-unsaturated ketones such as **6**. We were delighted to find that the 1,2 addition of the dichlorocerium enolate of ethyl acetate to **6** produced hydroxy ester **7** in an 88% crude yield. No products from 1,4 addition could be identified in the reaction mixture. The original published procedure used lithium diisopropylamide to deprotonate ethyl acetate. Commercially available lithium (bistrimethylsilyl)amide was used as a convenient replacement for LDA. The published procedure recommends quenching the reaction mixture with aqueous ammonium chloride while the reaction temperature is cold (−78 °C). If the reaction mixture was allowed to warm to room temperature before quenching, the addition product was found to decompose back to starting material **6**. Quenching while the reaction was still cold prevented this decomposition. The tertiary alcohol of compound **7** was found to readily dehydrate if treated with a strong acid. The cerium salts were insoluble in aqueous ammonium chloride. The use of 10% aqueous acetic acid as the quenching reagent allowed an easy workup by dissolving the cerium salts without the dehydration of **7**.

Hydrolysis of ester **7** proceeded as expected in aqueous sodium hydroxide, but again compound **10** was found to readily dehydrate in the presence of strong acid. Use of aqueous acetic acid to acidify the hydrolysis reaction mixture led to complications during the extraction of acid **10.** Ethyl acetate extracted a significant amount of acetic acid along with **10,** and since both compounds are acids, the acetic acid could not be removed from the product with a simple base wash. Monosodium phosphate served nicely as a weak inorganic acid to acidify the hydrolysis reaction mixture without dehydrating **10**.

Iodolactonization of compound **10** to the iodolactone **8** was accomplished using a procedure similar to previously published work.[8] The cyclization was stereospecific, forming a single diastereomer. Compound **8** is the key intermediate for the synthesis of all the terpene lactones. The key feature of compound **8** is the tertiary alcohol group, which allows the easy synthesis of **2** and allows formation of the α,β-unsaturated lactone. Dehydration of **8** after cyclization controls the geometry of the lactone double bond required for the remaining terpene lactones.

Dehydration of **8** proceeded as expected, however the elimination of hydrogen iodide from compound **9** proved surprisingly difficult. Several typical basic conditions for elimination were tried without success, including potassium *tert*-butoxide in *tert*-butanol or THF, lithium carbonate/lithium bromide in DMF, or DBU in refluxing toluene. Compound **9** was finally converted to **4** by heating to 150 °C in neat DBU in a sealed tube.

Mori and Khlebnikov had previously reported the conversion of **4** to **1**;[9] however, in our hands the published experimental procedure could not be reproduced. The reaction of **4** with NBS in a mixture of acetone and water failed to produce compound **11** as reported. A review of the literature on bromohydration of alkenes suggested several alternatives. *N*-Bromoacetamide in the presence of strong acids had been shown to be a more reactive bromine source than NBS for bromohydration reactions.[10] Treatment of **4** with *N*-bromoacetamide in dioxane/water with trifluoroacetic acid cleanly produced the stereospecific bromohydrate **11** in an 81% crude yield.

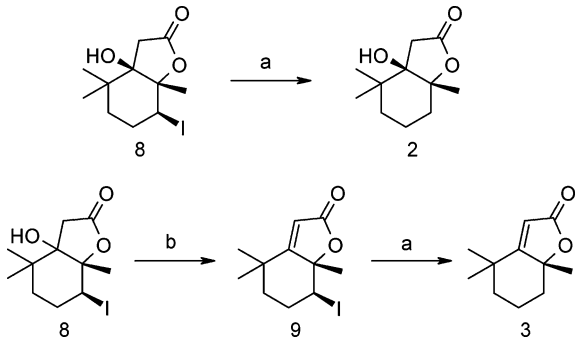
(7) See ref 6a,b.

(8) (a) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819−5825. (b) Furber, M.; Mander, L. N. *J. Am. Chem. Soc.* **1988**, *110*, 4084−4085.

(9) See ref 3e.

(10) (a) Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1953**, *75*, 2273. (b) Winstein, S.; Buckles, R. E. *J. Am. Chem. Soc.* **1942**, *64*, 2780.

SCHEME 4. Synthesis of Aeginetolide (2) and Dihydroactinidiolide (3) from Iodolactone 8[a]



[a] Conditions: (a) Bu_3SnH, AIBCHN; (b) $SOCl_2$/pyridine.

The reduction of **11** with tri-*n*-butyltin hydride in THF at room temperature had also been reported to produce **1**.[9] We attempted to prepare **1** with this procedure with no success. Heating the reaction to reflux also failed, as did running the reaction in hexane at reflux. The treatment of **11** with tri-*n*-butyltin hydride in hexane with catalytic amount of 1,1-azobis-(cyclohexanecarbonitrile) as a free radical initiator at reflux produced **1** in an 86% yield.

The synthesis of **1** for flavor evaluation was the main goal of our project. A particularly elegant aspect of this work is the ready access to additional terpene lactone natural products. Actinidolide (**4**) was produced as a key intermediate during the synthesis of **1**. We demonstrated the versatility of this chemistry with the synthesis of aeginetolide (**2**) and dihydroactinidiolide (**3**). Iodolactone **8** is an ideal intermediate for the synthesis of **2** and **3**. This is due to the presence of synthetically useful functionality on both the lactone and cyclohexane ring. Scheme 4 shows the synthesis of compounds **2** and **3**.

Aeginetolide (**2**) is unique due to the tertiary alcohol on the lactone ring. Compound **8** contains the alcohol with proper stereochemistry. Compound **2** was produced from **8** by free radical dehalogenation with tributyltin hydride. Dihydroactinidiolide (**3**) could have been produced from **2** or intermediate **9**. Again, dehalogenation of **8** with tributyltin hydride followed by dehydration of **9** with thionyl chloride and pyridine produced **3**.

The synthesis of racemic **1** was accomplished in seven steps from **6**, in an overall yield of 46.9%. The key transformation is the 1,2 addition of the cerium enolate of ethyl acetate to **6** to prepare compound **7**. The extension of the cerium enolate additions to highly hindered α,β-unsaturated ketones is a nice route for the synthesis of functionalized tertiary alcohols. Use of a stereospecific iodolactonization for the lactone formation of the C11 terpene esters is a novel approach to this group of natural products and allows easy fucntionalization of the cyclohexane ring compared to previous syntheses. The high degree of functionalzation of compound **8** allows the synthesis of the additional terpene lactone natural products **2**, **3**, and **4**.

The stereospecific iodolactonization of acid **10** to lactone **8** correctly sets the ring stereochemistry. The stereospecific hydobromination of **4** to **11** provides the correct 6α hydroxy stereochemistry. Terpene ester **4** was synthesized as an intermediate during the synthesis **1**. Aeginetolide (**2**) and dihydroactinidiolide (**3**) were prepared from the appropriate loliolide intermediates.

Experimental Section

Synthesis of (±)-Ethyl (1-Hydroxy-2,6,6-trimethyl-2-cyclohexenyl)acetate (7). Cerium chloride heptahydrate (16.16 g, 43.4 mmol) was dried for 12 h under high vacuum at 200 °C. Ethyl acetate (3.82 g, 43.4 mmol) was added to 200 mL of anhydrous THF in a 500 mL flask and cooled to −70 °C with a dry ice bath. Lithium (bistrimethylsilyl)amide (1.0 M in THF, 43.4 mL) was added by syringe, and the resulting solution was stirred for 1 h at −70 °C. The dry cerium chloride powder was added, and the heterogeneous reaction mixture was stirred for an additional 2 h at −70 °C to form the dichlorocerium enolate of ethyl acetate. The reaction mixture was then treated with 2,6,6-trimethylcyclohexenone (3.00 g, 21.7 mmol), and the mixture was stirred at −70 °C for an additional 2 h. The reaction was sampled and prepared for GC analysis by portioning between ethyl acetate and aqueous ammonium chloride. The GC analysis showed the reaction to be at least 90% complete.

The reaction mixture was quenched at −70 °C with the addition of 100 mL of 10% aqueous acetic acid and then extracted with 3 × 200 mL of ethyl acetate. The organic phase was washed with 2 × 100 mL of water, 2 × 100 mL of saturated aqueous sodium bicarbonate, and 1 × 100 mL of saturated sodium chloride and dried over anhydrous sodium sulfate. The product solution was filtered and concentrated under vacuum to give 4.63 g of product as a yellow oil. This is an 88% crude yield. A sample of the crude product was purified by silica chromatography to provide a sample for NMR and mass spectral analysis. The product was quite labile toward dehydration. A suitable elemental analysis could not be obtained for the sample after chromatography. The mass spectrum under EI conditions does not give a sufficient molecular ion for exact mass determination: ^{1}H NMR ($CDCl_3$) 5.39 (1 H bm), 4.56 (1H, s, OH), 4.15 (2 H, d of q), 2.55 (2 H, d of d), 2.1−1.9 (2 H, m), 1.71 (3 H, bd, CH_3), 1.50 (2 H, m), 1.28 (3 H, t), 0.98 (3 H, s), 0.94 (3H, s); ^{13}C NMR ($CDCl_3$) 14.0, 18.8, 22.6, 22.6, 24.3, 33.5, 37.9, 38.8, 61.0, 75.9, 124.0, 137.2, 174.8; MS 262, 170, 82. The crude product was used in the next step without further purification.

Synthesis of (±)-(1-Hydroxy-2,6,6-trimethyl-2-cyclohexenyl)-acetic Acid (10). (±)-Ethyl (1-hydroxy-2,6,6-trimethyl-2-cyclohexenyl)acetate (**7**, 2.19 g, 9.67 mmol) was charged to a 50 mL flask, dissolved in 10 mL of methanol, and diluted with 10 mL of water. Sodium hydroxide (50%, 1.54 g, 21.2 mmol) was added dropwise, and the solution was stirred for 4 h at 25 °C. The methanol was removed at reduced pressure, and the reaction was diluted with 40 mL of water. The basic aqueous product layer was extracted with 20 mL of ethyl acetate and then acidified with monosodium phosphate to pH 4.0. The product layer was extracted with 3 × 20 mL of ethyl acetate and dried with 20 mL of brine and 5 g of anhydrous sodium sulfate. The ethyl acetate solution was filtered and evaporated to yield 2.00 g of crude **10**. This is a 104% mass balance. The product was used without purification for the next step.

A sample was crystallized from hexane and ethyl acetate to provide an analytical sample. The molecule decomposes during GCMS analysis to **6**: ^{1}H NMR ($CDCl_3$) 5.48 (1 H, bs), 2.63 (2 H, d of d), 2.1−1.9 (2 H, bs), 1.71 (3 H, bd), 1.52 (2 H, t), 1.01 (3 H, s), 0.95 (3 H, s); ^{13}C NMR ($CDCl_3$) 18.8, 22.4, 22.7, 23.9, 33.2, 37.8, 38.4, 125.5, 135.8, 178.1; mp 95−96 °C. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.14. Found: C, 66.61; H, 9.21.

Synthesis of (±)-3α-Hydroxy-7α-iodo-4,4,7α-trimethylhexahydro-1-benzofuran-2(3H)-one (8). The reaction was run in a 100 mL flask. The (±)-(1-hydroxy-2,6,6-trimethyl-2-cyclohexenyl)acetic acid (**10**, 1.74 g, 8.77 mmol) was charged to the flask and dissolved in 30 mL of ether. A 30 mL charge of saturated aqueous sodium hydrogen carbonate was added, followed by 6.68 g (26.3 mmol, 3.0 equiv) of iodine. The reaction was stirred overnight at 25 °C and judged to be complete by TLC analysis. The reaction was transferred to a separatory funnel and treated with solid sodium thiosulfate until the excess iodine was decolorized. The aqueous

phase was removed, and the ether phase was washed with 10 mL of brine and dried on sodium sulfate. The ether solution was filtered and concentrated under vacuum to yield 2.39 g of product (84%). The crude product was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) 4.13 (1 H, dd), 3.04 (1 H, d), 2.68 (1 H, s, OH), 2.41 (1 H, d), 2.3−2.1 (2 H, M), 1.71 (3 H, s), 1.52 (1 H, t of d), 1.46 (1 H, d of t), 1.08 (3 H, s), 1.01 (3 H, s); ^{13}C NMR ($CDCl_3$) 21.0, 22.0, 26.5, 32.7, 37.2, 37.3, 39.4, 40.8, 90.7, 174.0, MS 306, 179, 137, 109; mp 102−103 °C. A sample was crystallized from hexane/ethyl acetate for elemental analysis. Anal. Calcd for $C_{11}H_{17}IO_3$: C, 40.76; H, 5.29. Found: C, 40.73; H, 4.87.

Synthesis of (±)-7α-Iodo-4,4,7α-trimethyl-5,6,7,7α-tetrahydro-1-benzofuran-2(4H)-one (9). Compound **8** (2.05 g, 6.32 mmol) was dissolved in 30 mL of pyridine. The reaction mixture was treated with 3.76 g of thionyl chloride (31.6 mmol, 5.0 equiv) and heated in a 60 °C oil bath for 1 h. The reaction was transferred to a 100 mL flask, and the excess pyridine was removed under vacuum. The crude product was dissolved in 50 mL of ethyl acetate and washed with 50 mL of 10% aqueous hydrochloric acid. The ethyl acetate layer was washed with 10 mL of saturated sodium hydrogen carbonate and 10 mL of brine and dried over anhydrous sodium sulfate. The ethyl acetate solution was filtered and concentrated under vacuum to give 1.72 g of product as a solid, an 89.1% yield: ^{1}H NMR ($CDCl_3$) 5.73 (1 H, s), 3.97 (1 H, d of d), 2.37 (1 H, m), 2.28 (3 H, s), 1.65 (1H, t of d), 1.47 (1H, t of d), 1.29 (3 H, s), 1.27 (3 H, s); ^{13}C NMR ($CDCl_3$) 24.2, 24.8, 29.5, 33.5, 35.6, 36.2, 43.3, 87.7, 113.5, 170.2,178.8. MS 307, 179.

A sample was crystallized from hexane/ethyl acetate as fine plates for elemental analysis: mp 167 °C. Anal. Calcd for $C_{11}H_{15}IO_2$: C, 43.16; H, 4.94. Found: C, 43.54; H, 4.84. The crude material was carried to the next step without further purification.

Synthesis of (±)-Actinidiolide (4). Compound **9** (1.13 g, 3.69 mmol) and 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU, 4.49 g, 29.5 mmol) were combined in a glass sealed reactor and heated in a 150 °C oil bath for 24 h. The reaction was cooled, diluted with 50 mL of ethyl acetate, and washed with 3 × 50 mL of 10% aqueous hydrochloric acid. The ethyl acetate solution was washed with 25 mL of saturated sodium bicarbonate solution and 25 mL of saturated sodium chloride solution and dried on anhydrous sodium sulfate. The ethyl acetate solution was filtered and concentrated to give 0.65 g of (±)-actinidiolide in 98% yield. The product was purified by a simple filtration through a silica gel plug to remove color. The spectral data of the product was identical to previously published data for **4**:[9] ^{1}H NMR ($CDCl_3$) 5.90 (1H, bd), 5.7 (1H, d of q), 5.73 (1 H, s), 2.29 (1 H, d of d), 2.15 (1 H, d of t), 1.61 (3 H, s), 1.34 (3 H, s), 1.31 (3 H, s); ^{13}C NMR ($CDCl_3$) 26.1, 26.2, 28.2, 35.8, 44.5, 85.5, 112.7, 128.4, 128.9,171.5, 180.9; MS 180, 178, 163, 150, 135, 107.

Synthesis of (±)-7*β*-Bromo-6α-hydroxy-4,4,7α-trimethyl-5,6,7,7α-tetrahydro-1-benzofuran-2(4H)-one (11). The reaction was run in a 50 mL reactor. Compound **4** (0.459 g, 2.58 mmol) was dissolved in 10 mL of 1,4-dioxane and treated with *N*-bromoacetamide (0.533 g, 3.86 mmol). The resulting solution was treated with 10 mL of 10% aqueous trifluoroacetic acid. The reaction was stirred at 25 °C for 2 h until the reaction was judged to be complete by TLC analysis. The reaction was diluted with 25 mL of ethyl acetate and washed with 50 mL of 10% aqueous sodium thiosulfate to quench the excess *N*-bromoacetamide. The ethyl acetate phase was washed with 50 mL of saturated sodium bicarbonate solution and 50 mL of saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solution was filtered and concentrated under vacuum to give 0.600 g of crude product (81% yield). The crude product was washed with 5 mL of hexane to remove the nonpolar byproducts and excess reagents. The product was dissolved in a minimal amount of acetone, filtered, and crystallized by the addition of 5 volumes of hexane. The crystallized compound was identical by NMR spectroscopy to the previously published reference:[9] ^{1}H NMR ($CDCl_3$) 5.84 (1 H, s), 4.62 (1 H, bs), 4.50 (1 H, bm), 2.8−3.1 (1 H, OH), 2.14 (1H d of d), 1.95 (3 H, s), 1.90 (1 H bd), 1.46 (3 H, s), 1.29 (3 H, s); ^{13}C NMR ($CDCl_3$) 26.0, 26.9, 30.7, 35.5, 40.7, 59.3, 85.9, 115.4, 172.1, 178.3; MS 276, 195, 177, 149, 139.

Synthesis of (±)-Loliolide (1). The reaction was run in a 50 mL reactor with a condenser, stir bar, and a nitrogen inlet. The reactor was charged with 0.43 g of compound **11** (1.55 mmol), tri-*n*-butyltin hydride (0.906 g, 3.12 mmol), 10 mL of hexane, and catalytic 1,1-azobis(cyclohexanecarbonitrile) (0.077 mmol, 5 mol %). The reaction was flushed with nitrogen and then heated to reflux for 4 h. The reaction was monitored by GC analysis and was determined to be complete by absence of **11**. The reaction was cooled to 25 °C, and the white solid was allowed to precipitate. The hexane solution was removed, and the white solid was washed with 10 mL of additional hexanes and dried to give 0.263 g of **1**, an 86% yield. The product was dissolved into 5 mL of ethyl acetate, filtered, and crystallized by the addition 20 mL of hexane. Loliolide (**1**) was recovered as fine prisms and was identical by NMR spectroscopy to previously reported samples;[9] ^{1}H NMR ($CDCl_3$) 5.69 (1 H, s), 4.35 (1 H, bm), 2.50 (1 H, d of t), 2.27 (1 H, OH), 1.78 (3 H, s), 1.77 (1 H, d of d), 1.54 (1 H, d of d), 1.47 (3 H, s), 1.27 (3 H, s); ^{13}C NMR ($CDCl_3$) 26.3, 26.9, 30.6, 36.1, 45.4, 47.1, 66.6, 87.1, 112.6, 172.3, 183.3; MS 196, 178, 140, 111.

Synthesis of (±)-Aeginetolide (2). The reaction was run in a 50 mL reaction flask with a reflux condenser, stir bar, and a nitrogen inlet. The iodo lactone **8** (2.00 g, 6.10 mmol) was suspended in 30 mL of THF and treated with tri-*n*-butyltin hydride (1.97 g, 6.78 mmol) and a catalytic amount of 1,1-azobis(cyclohexanecarbonitrile) (0.075 g, 5 mol %) as a free-radical initiator. The reaction was heated to reflux for 4 h. The reaction was cooled, and the THF was removed under vacuum. The product was suspended in 30 mL of hexane, and the precipitated white solid was filtered and washed with 50 mL of additional hexane. The product was dried and found to weigh 1.21 g, a 99.6% crude yield. The (±)-aeginetolide (**2**) was purified by crystallization from ether and hexane to yield material identical by NMR spectroscopy to previously reported samples:[11] ^{1}H NMR ($CDCl_3$) 2.95 (1 H, d), 2.45 (1 H, OH), 2.38 (1 H, d), 2.10 (1 H, bd), 1.37−1.65 (5 H, bm), 1.50 (3 H, s), 1.05 (3 H, s), 0.98 (3 H, s); ^{13}CNMR ($CDCl_3$) 18.5, 19.8, 22.1, 26.8, 37.3, 37.6, 38.7, 41.3, 81.8, 89.5, 175.3; MS 180, 179, 137, 111, 98.

Synthesis of (±)-Dihydroactinidiolide (3). (±)-Aeginetolide (**2**, 0.238 g, 1.20 mmol) was dissolved in 2.0 mL of pyridine and treated with thionyl chloride (0.283 g, 2.40 mmol). The mixture was heated to 60 °C for 2 h. The reaction was poured into 50 mL of 10% aqueous hydrochloric acid and was extracted with two, 50 mL portions of ethyl acetate. The ethyl acetate layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution and was dried over anhydrous sodium sulfate. The ethyl acetate solution was filtered and concentrated under vacuum to give 0.156 g of crude **3**. The product was purified by bulb-to-bulb distillation to give 0.151 g, a 70% yield. The product is a waxy solid that was identical by NMR spectroscopy to previously reported samples:[9] ^{1}H NMR ($CDCl_3$), 5.63 (1 H, s), 2.24 (1 H, d of q), 1.62−1.82 (3 H, bm), 1.55 (3 H, s), 1.46 (1 H, t of d), 1.28 (1 H, t of d), 1.27 (3 H, s), 1.23 (3 H, s); ^{13}CNMR ($CDCl_3$) 19.6, 24.2, 24.3, 29.8, 36.5, 40.1, 41.6, 87.2, 112.3, 171.9 182.5; MS 180, 137, 111 109.

Supporting Information Available: General experimental conditions, analytical information, and ^{1}H NMR, ^{13}C NMR, and MS data for compounds **1**−**4** and **7**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) See ref 1a. (b) Goyau, B.; Rouessac, F. *Bull. Soc. Chim. Fr.* **1978**, 590−592.