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Enantiospecific Total Synthesis of Lairdinol A

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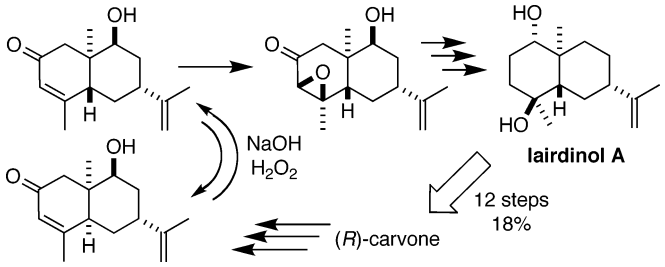

The synthesis of lairdinol A, a component of the host-selective phytotoxin depsilairdin, was achieved in 12 steps (18% overall yield) without the use of protecting groups starting with the Diels−Alder reaction of (*R*)-carvone with 3-trimethylsilyloxy-1,3-pentadiene. The key step established the trans ring fusion by preferential epoxidation of a trans-fused enone in an equilibrating mixture of the cis-fused and trans-fused diastereomers (i.e., equivalent to a dynamic kinetic resolution of these isomers). The synthesis confirms the absolute configurations of lairdinol A and its enantiomer, cyperusol C.

Introduction

Host-selective toxins (HSTs) are biosynthesized by microbial pathogens to facilitate infection of plants.[1] By definition, these compounds are toxic to host plants but relatively harmless to nonhosts. HSTs are essential probes to study the complex metabolic pathways involved in the interaction of plants with their microbial pathogens.[1] Recently, Pedras et al. reported[2] that depsilairdin (**1**) is a highly selective toxin produced by the "blackleg" fungus [*Leptosphaeria maculans* (Desm.) Ces. et de Not., asexual stage *Phoma Lingam* (Tode ex Fr.) Desm.], a particularly devastating pathogen of the oilseeds rapeseed and canola (*Brassica napus*, *B. rapa*). Depsilairdin (**1**) is a structurally interesting depsipeptide that contains a previously unknown amino acid residue [(2*S*,3*S*,4*S*)-3,4-dihydroxy-3-methylproline] and a sesquiterpene fragment possibly originating from lairdinol A (**2**), also isolated from the same fungal cultures (Figure 1).[3] Selective phytotoxicity was also apparent with **2**; however, this activity was not fully studied due to limited availability of material. We became interested in the synthesis of lairdinol A (**2**) in the context of a program to provide sufficient quantities of **1** and derivatives for biological evaluation.

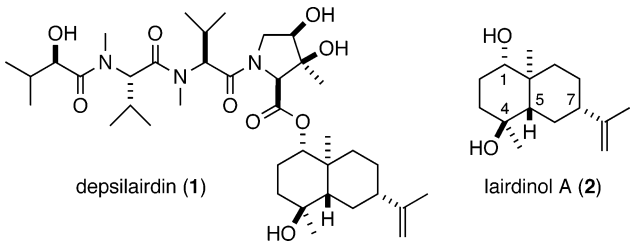

FIGURE 1. Structures for depsilairdin (**1**) and lairdinol A (**2**).

Lairdinol A (**2**) belongs to the eudesmane family of sesquiterpenes.[4] This class of natural products has attracted considerable attention from synthetic chemists.[5] The vast majority of syntheses construct the decalin core by Robinson annulation, often starting with dihydrocarvone.[5−7] Although numerous

(1) Review: Wolpert, T. J.; Dunkle, L. D.; Ciuffetti, L. M. *Annu. Rev. Phytopathol.* **2002**, *40*, 251−285.

(2) Pedras, M. S. C.; Chumala, P. B.; Quail, J. W. *Org. Lett.* **2004**, *6*, 4615−4617.

(3) Pedras, M. S. C.; Chumala, P. B.; Venkatesham, U. *Bioorg. Med. Chem.* **2005**, *13*, 2469−2475.

(4) (a) Wu, Q.-X.; Shi, Y.-P.; Jia, Z.-J. *Nat. Prod. Rep.* **2006**, *23*, 699−734. (b) Fraga, B. M. *Nat. Prod. Rep.* **2006**, *23*, 943−972.

(5) (a) Heathcock, C. H. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1973; Vol. 2, pp 197−558. (b) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1983; Vol. 5, pp 1−541.

(6) Ho, T.-L. *Enantioselective synthesis: natural products from chiral terpenes.*; Wiley: New York, 1992.

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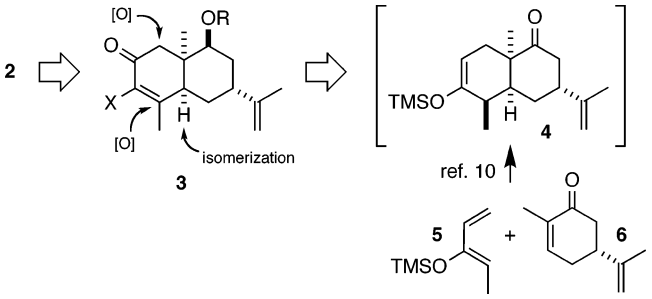
SCHEME 1. Retrosynthetic Analysis for 2



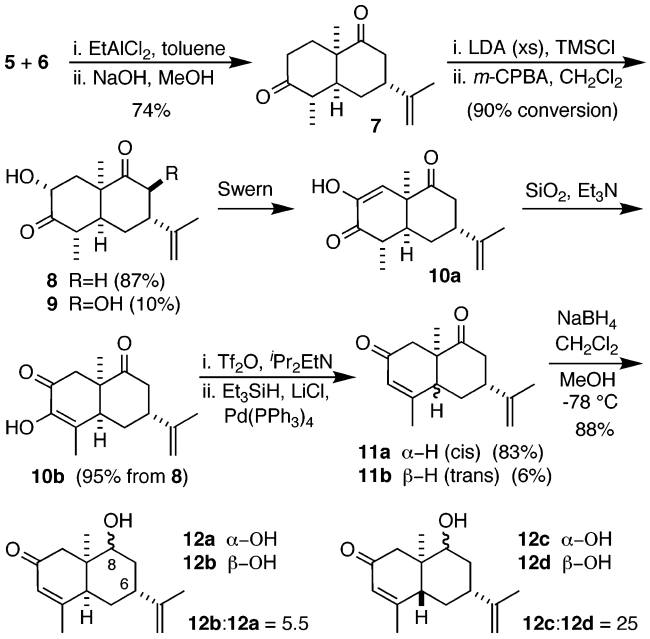
eudesmanoids have been synthesized, the oxidation pattern and relative configuration of **2** are somewhat unusual and synthetic efforts relevant to this structure are scarce.[8] Our approach to lairdinol A (**2**) is outlined in Scheme 1.

We were attracted to the Diels−Alder reaction of (*R*)-carvone (**6**) with diene **5**,[9] previously reported by de Groot et al.,[10] as a means to assemble the complete carbon skeleton of **2** in enantiopure form in a single operation. Surprisingly, this approach has not been applied to eudesmane syntheses presumably because of real or perceived difficulties in introducing desired functionality.[11] Our plan was to take advantage of the enol ether in the initially formed Diels−Alder adduct **4** to effect a regioselective oxidation en route to an enone derivative represented in general terms by structure **3**. The enone functionality in **3** was expected to (i) allow isomerization of the cis ring fusion using the steric bulk of the −OR substituent to favor the desired trans isomer[12] and (ii) facilitate stereoselective introduction of the required hydroxyl groups at C-1 and C-4 (eudesmane numbering). Of course, reductive removal of the oxygen-based functional groups present in **3** would also be required for its conversion to lairdinol A (**2**). Herein we report an efficient synthesis of lairdinol A (**2**) that proceeds without the use of protecting groups.

Results and Discussion

The Diels−Alder reaction of **5** with **6** under the reported conditions gave a mixture of diastereomers including **7** (Scheme 2).[10,13] Unfortunately, our attempts to isolate the enol ether **4** resulted in substantial hydrolysis.[14] Alternatively, in a modification of the de Groot procedure,[10] the Diels−Alder reaction was quenched by addition of methanolic NaOH, which served to hydrolyze the TMS enol ethers in the adducts and to isomerize the product derived from the major adduct **4**[13] to give **7** in 74% yield (87% conversion) after chromatography. The desired regioselective oxidation of **7** was achieved by treatment of the derived bis(TMS enol ether) with *m*-CPBA (1.2 equiv) to give recovered **7** (10%), diol **9**, and **8** (78%; 87% based on 90% conversion).[15] Swern oxidation of **8** gave the corresponding trione that was primarily in the undesired enol form **10a** (**10a**:**10b** ca. 10:1 by ^{1}H NMR); however, simply passing this material through a column of basic silica gel resulted in complete isomerization to **10b** (95% from **8**). Deoxygenation of the enol in **10b** was smoothly achieved by Pd-catalyzed reduction of the corresponding triflate to give a separable 13:1 mixture of **11a** and **11b**, respectively.[16] Chemoselective reduction[17] of the saturated ketone in **11a** using $NaBH_4$ in CH_2Cl_2/MeOH at low temperature gave a 5.5:1 mixture of **12b** and **12a**, respectively, in excellent yield. Similar reduction of **11b** gave **12c** with high diastereoselectivity.

SCHEME 2. Synthesis of Enone 12



Attempted isomerization of **11a** to **11b** under basic conditions led only to decomposition.[18] Isomerization of **12b** or **12d** in degassed methanolic NaOH under inert atmosphere led to a 2.0:1 equilibrium mixture of the two diastereomers favoring the desired **12d**. This equilibrium constant was much smaller than we had initially anticipated based on molecular mechanics calculations assuming only conformers of **12b** and **12d** with the isopropenyl group in an equatorial orientation.[19] However, the ^{1}H NMR spectrum of **12b** clearly indicated that the major conformer had the −OH group in an equatorial orientation (HC-8: br d, J = 9 Hz) and the isopropenyl group in an axial

(7) This approach generally gives products with the isoprop(en)yl group trans to the angular methyl; however, methods to obtain the cis diastereomer are known. (a) Caine, D.; Gupton, J. T., III *J. Org. Chem.* **1974**, *39*, 2654−2656. (b) Agami, C.; Kadouri-Puchot, C.; Le Guen, V. *Tetrahedron*: *Asymmetry* **1993**, *4*, 641−644. (c) Zhabinskii, V. N.; Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1996**, *61*, 4022−4027.

(8) For the synthesis of a racemic diastereomer of **2** from the Wieland−Miescher ketone, see: Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; Brunekreef, G. A.; de Groot, A. *J. Org. Chem.* **1990**, *55*, 941−948.

(9) Danishefsky, S.; Yan, C. F. *Synth. Commun.* **1978**, *8*, 211−218.

(10) Haaksma, A. A.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1992**, *48*, 3121−3130.

(11) This method was used to prepare (+)-α-cyperone in 40% yield over 7 steps from (*S*)-carvone (ref 10). Although various eudesmanes have been prepared from α-cyperone, this route is longer and less efficient than others (ref 7).

(12) For an example of this strategy, see: Ward, D. E. *Can. J. Chem.* **1987**, *65*, 2380−2384.

(13) A mixture of adducts are formed resulting from endo and exo additions of **5** anti (85−90%) and syn (10−15%) to the isopropenyl group in **6**; the major adduct is the endo/anti **4** (ref 10).

(14) For an example of isolation of the TMS enol ether Diels−Alder adduct in a related reaction, see: Angeles, A. R.; Dorn, D. C.; Kou, C. A.; Moore, M. A. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1451−1454.

(15) For a review of α-hydroxylation of ketone enolates and silyl enol ethers, see: Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. *Org. React.* **2003**, *62*, 1−356.

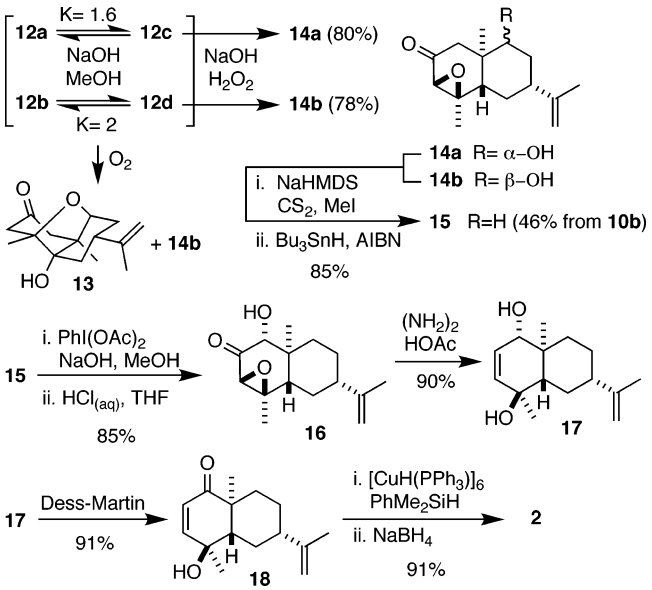
(16) Review: Ritter, K. *Synthesis* **1993**, 735−762.

(17) Ward, D. E.; Rhee, C. K. *Can. J. Chem.* **1989**, *67*, 1206−1211.

(18) This result is likely due to autoxidation (vide infra).

(19) Molecular mechanics calculations (CaChe, version 3.9) on the conformers with equatorial isopropenyl groups predicted that **12b** was ca. 1.2 kcal/mol less stable than **12d** (i.e., predicted K_{eq} ca. 7.4 at 25 °C).

SCHEME 3. Synthesis of 2 from 12



orientation (HC-6: br s, $w_{1/2}$ = 15 Hz) and the observed equilibrium constant can be rationalized by considering this conformer.[20] Similar isomerization of **12a** gave a 1.6:1 mixture of **12c** and **12a**, respectively.

The modest equilibrium constants in favor of the desired trans-fused diastereomers (**12c** and **12d**) represented a serious obstacle to the feasibility of the planned synthetic route. Fortuitously, we observed that similar base-catalyzed isomerization of **12b** conducted in air slowly produced **13** and **14b** in addition to **12b** and **12d** (Scheme 3). The stereoselective formation of the trans epoxide **14b** was particularly of interest as this product incorporates the stereogenic centers at C-4 and C-5 in **2** (eudesmane numbering) with the correct configurations. Base-catalyzed autoxidation of enones is well-known.[21] Under the basic reaction conditions, **12b** and **12d** are equilibrated via their common dienolate. In analogy to the proposal of Frimer et al.,[21b] this dienolate can react with molecular oxygen at the γ-position to provide a hydroperoxide intermediate that can epoxidize **12d** to give **14b** and **13** (after cyclization of the hydroxyenone). Regardless of the actual mechanism, this result suggested that epoxidation of **12d** was much more facile than that of **12b**. We reasoned that epoxidation of cis **12b** under conditions where its oxidation was slower than isomerization to trans **12d** would lead to the desired trans **14b**. Consequently, treatment of **12b** with H_2O_2 and excess NaOH in methanol solution gave **14b** in 78% yield after optimization of the reaction conditions. The use of excess base was necessary to maintain a useful rate of isomerization of **12b**. The resulting facile epoxidation of **12d** under conditions where **12b** and **12d** are equilibrating is equivalent to a dynamic kinetic resolution[22] of these diastereomers. Similar epoxidation of **12a** gave **14a** in 80% yield. Barton−McCombie deoxygenations[23] of **14a** and **14b** gave **15** in excellent yields. Because all of the diastereomers of **11**, **12**, and **14** were ultimately converted into **15** using the same protocols, we were able to convert diosphenol **10b** into **15** in 46% overall yield without separation of the stereoisomers formed in the intermediate stages.

Stereoselective hydroxylation of epoxyketone **15** was effected by treatment with $PhI(OAc)_2$ in basic methanol followed by acid hydrolysis of the intermediate methoxyepoxide to give ketol **16** as the only detectable isomer (Scheme 3).[15,24] Wharton reaction[25] of **16** readily gave the allylic diol **17**. We hoped to directly convert **17** into **2** by exploiting hydroxyl-directed[26] hydrogenation to achieve chemoselective saturation of the allylic alcohol in the presence of the isolated alkene.[27] Unfortunately, all attempts using $[Ir(cod)(PCy)_3(py)]PF_6$,[28] $RhCl(PPh_3)_3$,[29] or Pd−C[30] catalysts failed; in each case, reduction of the isopropenyl group was faster than that of the allylic alcohol.[31] The desired transformation of **17** was efficiently achieved by Dess−Martin oxidation to enone **18** followed by catalytic Cu(I)-mediated conjugate reduction[32,33] with a $NaBH_4$ workup to give **2** in 83% overall yield. Spectroscopic and chiroptical properties of synthetic **2** were essentially identical with those reported for the natural product.

The absolute configuration for lairdinol A (**2**) was assigned based on its relationship with **1** and that both were isolated from the same fungal cultures.[3] The absolute configuration for **1** was assigned indirectly via a 2,5-morpholinedione degradation product.[2] The enantiomer of **2** (i.e., *ent*-**2**), cyperusol C, has been isolated from the plants *Cyperous longus*[34] and *Erigeron*

(20) Molecular mechanics calculations (CaChe, version 3.9) predicted the conformer of **12b** with an axial isopropenyl group was only ca. 0.3 kcal/mol less stable than **12d**. Thus, considering conformers of **12b** with both axial and equatorial isopropenyl groups, the predicted K_{eq} is ca. 1.3 in favor of **12d**.

(21) Review: (a) Frimer, A. A. In *The Chemistry of Enones*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1989; Part 2, Chapter 17, pp 781−921. (b) Frimer, A. A.; Gilinsky-Sharon, P.; Aljadeff, G.; Gottlieb, H. E.; Hameiri-Buch, J.; Marks, V.; Philosof, R.; Rosental, Z. *J. Org. Chem.* **1989**, *54*, 4853−4866.

(22) Review: Pellissier, H. *Tetrahedron* **2003**, *59*, 8291−8327.

(23) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574−1585.

(24) (a) Kamernitskii, A. V.; Turuta, A. M.; Fadeeva, T. M.; Istomina, Z. I. *Synthesis* **1985**, 326−328. (b) Moriarty, R. M.; Gupta, S. C.; Hu, H.; Berenschot, D. R.; White, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 686−688.

(25) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615−3616.

(26) Reviews: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370. (b) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190−203.

(27) For some successful examples of this type of transformation, see: (a) Paterson, I.; Hulme, A. N. *J. Org. Chem.* **1995**, *60*, 3288−3300. (b) Kim, B. M.; Guare, J. P. *Heterocycles* **1995**, *41*, 403−408. (c) Sicinski, R. R.; Rotkiewicz, P.; Kolinski, A.; Sicinska, W.; Prahl, J. M.; Smith, C. M.; DeLuca, H. F. *J. Med. Chem.* **2002**, *45*, 3366−3380. (d) Clissold, D. W. British Patent WO 2003037857, 2003; *Chem. Abstr.* **2003**, *138*, 368671.

(28) (a) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072−1073. (b) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655−2661.

(29) Thompson, H. W.; McPherson, E. *J. Am. Chem. Soc.* **1974**, *96*, 6232−6233.

(30) Thompson, H. W. *J. Org. Chem.* **1971**, *36*, 2577−2581.

(31) With the Crabtree catalyst (reactivity and protocol validated using 3,5,5-trimethylcyclohex-2-en-1-one; ref 28b) ca. equal amounts of dihydrolairdinol A and the corresponding ketone (from rearrangement rather than reduction of the allylic alcohol) were obtained. Using Wilkinson's catalyst, no reaction was observed with the KH-derived alkoxide of **17** (ref 29). Under neutral conditions, **2** (obtained in <20% yield at 80% conversion) was the minor product even at low conversion; however, the obtention of **2** confirms the stereochemical configuration assigned to **17**. Formation of **2** (<7% at 83% conversion) was even less favored with Pd-C as the catalyst; howeve, dihydolairdinol A could be obtained in high yield (see the Supporting Information).

(32) Review: (a) Lipshutz, B. H. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley: Weinheim, Germany, 2002; Chapter 5, pp 167−187. (b) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291−293. (c) Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779−2788.

(33) Formation of the expected (ref 32c) silyl enol ether was not observed under these conditions.

(34) Xu, F.; Morikawa, T.; Matsuda, H.; Ninomiya, K.; Yoshikawa, M. *J. Nat. Prod.* **2004**, *67*, 569−576.

annus.[35] The absolute configuration for *ent*-**2** was determined[34] using the advanced Mosher's method;[36] however, the $\Delta\delta$ values reported are small[37] and it is known[36] that sterically hindered alcohols can give anomalous results. Unfortunately, the specific rotations reported for naturally occurring **2** and *ent*-**2** were obtained in different solvents. Taken together, the above facts raise some uncertainty about the proposed absolute configurations of the natural products. The absolute configuration of synthetic **2** is firmly established by its relationship with (*R*)-carvone (**6**). We obtained specific rotations for synthetic **2** under each of the reported conditions and these results fully confirm the assigned absolute configurations for **2** and *ent*-**2**.[38]

Conclusion

In summary, the synthesis of lairdinol A (**2**) was achieved in 18% overall yield from (*R*)-carvone (**6**) over 12 steps. Novel features of the synthesis include (i) the construction of the skeleton via a Diels−Alder reaction and (ii) establishment of the trans ring junction by preferential epoxidation of a trans enone in an equilibrating mixture of the cis and trans diastereomers. It is also noteworthy that the entire synthesis proceeds without the use of protecting groups, a feature that has attracted interest recently.[39] Syntheses of various other eudesmanoids[40] from the intermediates provided by this route can be easily envisaged. With lairdinol A (**2**) in hand, we can now proceed with the synthesis of depsilairdin (**1**) and our efforts toward this objective will be reported in due course.

Experimental Section[41]

(3*R*,4a*S*,5*S*,8a*R*)-Hexahydro-5,8a-dimethyl-3-(1-methylethenyl)naphthalene-1,6(2*H*,5*H*)-dione (7). The procedure was adapted from that reported by de Groot et al.[10] $EtAlCl_2$ (1 M in hexane; 10 mL, 10 mmol) was added to a stirred solution of (*R*)-(−)-carvone (**6**; 3.0 g, 20 mmol) in dry toluene (70 mL) at room temperature under argon. After 15 min of stirring, the diene **5** (4.7 g, 30 mmol) was added. The reaction mixture was stirred at room temperature for 4 h and then NaOH (1 M in MeOH; 100 mL, 0.1 mol) was added (note: this step hydrolyzes the TMS enol ethers in the adducts and isomerizes the product from the major Diels−Alder adduct (**4**) (i.e., the 5*R* diastereomer of **7**) into the thermodynamically more stable titled diastereomer). After 24 h, the reaction mixture was neutralized by adding aq HCl and extracted with CH_2Cl_2. The combined organic layers were washed sequentially with saturated aq $NaHCO_3$ and water, dried over Na_2SO_4, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to afford recovered carvone (0.40 g, 13%), a mixture of diastereomers of **7** (0.72 g, 18%), and the titled compound (3.0 g, 64%; 74% based on recovered **6**): $[\alpha]_D$ +30 (*c* 0.3, $CHCl_3$) [lit.[10] for *ent*-**7**, −36.7 (*c* 0.3, $CHCl_3$)].

(3*R*,4a*S*,5*S*,7*R*,8a*R*)-Hexahydro-7-hydroxy-5,8a-dimethyl-3-(1-methylethenyl)naphthalene-1,6(2*H*,5*H*)-dione (8). A solution of diketone **7** (2.50 g, 10.7 mmol) and TMSCl (6.80 mL, 5.79 g, 53.3 mmol) in THF (10 mL) was added dropwise via syringe to a stirred solution of LDA [prepared from BuLi (32 mmol) and DIPA (42 mmol)] in dry THF (90 mL) at −78 °C. After 20 min, Et_3N (1.50 mL, 1.07 g, 10.7 mmol) was added. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the bis(TMS enol ether) (4.23 g, 100%). *m*-CPBA (2.33 g, 13.4 mmol) was added to a vigorously stirred solution of the above bis-(TMS enol ether) (4.23 g) in dry CH_2Cl_2 (110 mL) at −30 °C under argon. After 1 h, the reaction was quenched by addition of $P(OMe)_3$ (0.66 mL, 0.69 g, 5.6 mmol). The mixture was allowed to warm to ambient temperature and a 9:1 mixture of THF and 10% aq HF (v/v; 100 mL) was added. After 12 h, the mixture was diluted with aq K_2CO_3 and extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over Na_2SO_4, concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to afford the recovered diketone **7** (0.25 g, 10%), diol **9** (0.20 g, 9%), and the titled compound (2.09 g, 78%; 87% based on recovered **7**): $[\alpha]_D$ +60 (*c* 0.95, C_6H_6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.85 (1H, br s), 4.81 (1H, br s), 4.41 (1H, dd, J = 7, 12 Hz), 3.45 (1H, br s), 2.95 (1H, dd, J = 7, 13 Hz), 2.67 (1H, dd, J = 13, 14 Hz), 2.56 (1H, dddd, J = 3, 3, 13, 13 Hz), 2.44 (1H, dd, J = 3, 14 Hz), 2.33 (1H, dq, J = 11.5, 6.5 Hz), 2.10 (1H, ddd, J = 3.5, 13, 14 Hz), 1.95−1.89 (2H, m), 1.79 (3H, s), 1.33 (3H, s), 1.19 (1H, dd, J = 12, 13 Hz), 1.10 (3H, d, J = 6.5 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 213.1, 212.9, 146.7, 110.6, 71.8, 52.8, 49.2, 44.6, 42.6, 42.5, 40.0, 28.1, 26.5, 20.6, 11.2; HRMS *m*/*z* calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1568 (EI).

(3*R*,4a*S*,8a*R*)-3,4,4a,8a-Tetrahydro-6-hydroxy-5,8a-dimethyl-3-(1-methylethenyl)-1,7(2*H*,8*H*)-naphthalenedione (10b). Dry DMSO (1.4 mL, 1.6 g, 20 mmol) was added dropwise via syringe to a solution of oxalyl chloride (0.87 mL, 1.3 g, 10 mmol) in dry CH_2Cl_2 (80 mL) at −78 °C under argon. After 30 min, a solution of ketol **8** (2.09 g, 8.35 mmol) in CH_2Cl_2 (5 mL) was added dropwise via syringe. After 1 h, DIPEA (4.4 mL, 3.2 g, 25 mmol) was added and the reaction mixture was allowed to warm to ambient temperature over 30 min. The mixture was diluted with CH_2Cl_2, washed sequentially with 10% aq HCl and saturated $NaHCO_3$, and concentrated to afford the crude 1,2-diketone (2.2 g) that was primarily in the undesired enol form **10a** (ca. 10:1). The crude mixture of enols was applied onto a silica gel column [prepared from a slurry of silica gel (50 g) in 5% (v/v) Et_3N in hexane] and eluted with 20% ethyl acetate in hexane to obtain the titled compound as a white sticky solid (1.99 g, 95%): $[\alpha]_D$ +78 (*c* 2.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12 (1H, br s), 4.88 (1H, br s), 4.79 (1H, br s), 3.05 (1H, d, J = 16.5 Hz), 2.85 (1H, br s), 2.59 (1H, br dd, J = 13.5, 14 Hz), 2.47−2.38 (2H, m), 2.23−2.10 (3H, m), 1.89 (3H, s), 1.81 (3H, s), 1.36 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 211.4, 191.5, 146.9, 145.5, 126.9, 110.9, 49.7, 47.1, 43.5, 42.5, 41.3, 29.3, 24.4, 20.8, 13.9; HRMS *m*/*z* calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1411.

(3*R*,4a*S*,8a*R*)-3,4,4a,8a-Hexahydro-5,8a-dimethyl-3-(1-methylethenyl)-1,7(2*H*,8*H*)-naphthalenedione (11a). DIPEA (2.50 mL, 1.86 g, 14.4 mmol) and Tf_2O (1.75 mL, 2.93 g, 10.4 mmol) were added sequentially to a stirred solution of disophenol **10b** (1.99 g, 8.01 mmol) in dry CH_2Cl_2 (80 mL) at 0 °C under argon. After 10 min, the reaction mixture was diluted with ethyl acetate, washed sequentially with 10% aq HCl, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated to give the triflate (3.07 g, 100%)[41] that was essentially homogeneous by ^{1}H NMR. The above crude triflate (3.07 g, ca. 8.07 mmol) and Et_3SiH (3.90 mL, 2.81 g, 24.2 mmol) were added sequentially to a stirred solution of $Pd(PPh_3)_4$

(35) Li, X.; Yang, M.; Han, Y.-F.; Gao, K. *Planta Med.* **2005**, *71*, 268−272.

(36) Review: Seco, J. M.; Quinoa, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17−117.

(37) The $\Delta\delta$ values computed from the NMR data reported in ref 34 are different from those summarized in Figure 3 of that paper. In particular, the computed $\Delta\delta$ values for the four protons at C-2 and C-3 of *ent*-**2** (eudesmane numbering) are <0.01 ppm.

(38) $[\alpha]_D$ +18 (*c* 0.4, CH_2Cl_2), +34 (*c* 1.1, MeOH), +28 (*c* 1.3, $CHCl_3$) [lit. +18 (*c* 0.4 CH_2Cl_2) (ref 2); lit. for *ent*-**2** (cyperusol C) −42.3 (*c* 1.10, MeOH) (ref 34), −25 (*c* 0.13, $CHCl_3$) (ref 35)].

(39) (a) Baran, P. S.; Maimore, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404−408. (b) Porco, J. A., Jr. *Nature* **2007**, *446*, 383,385. (c) Gadermann, K.; Bonazzi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5656−5658.

(40) For selected examples, see: (a) Liu, Y. B.; Jia, W.; Gao, W. Y.; Zhao, A. H.; Zhang, Y. W.; Takaishi, Y.; Duan, H. Q. *J. Asian Nat. Prod. Res.* **2006**, *8*, 303−307. (b) Maatooq, G. T.; Hoffmann, J. J. *Pharmazie* **2002**, *57*, 59−61. (c) Demole, E.; Enggist, P. *Helv. Chim. Acta* **1983**, *66*, 1381−1391. (d) Kumar, N.; Ravindranath, B.; Seshadri, T. R. *Phytochemistry* **1974**, *13*, 633−636.

(41) See the Supporting Information for general methods and procedures.

(0.47 g, 0.40 mmol) and LiCl (0.167 g, 24.2 mmol) in dry DMF (81 mL) at room temperature under argon. The reaction mixture was heated to 60 °C for 2 h after which time the mixture had turned black indicating the reaction was complete. The mixture was allowed to cool to ambient temperature and then was diluted with ethyl acetate (300 mL), washed sequentially with water and brine, dried over Na_2SO_4, and concentrated. The residue was taken up in CH_2Cl_2 and passed through a short pad of silica gel eluting with 25% ethyl acetate in hexane to afford a 13:1 mixture of **11a** and **11b**, respectively (1.90 g, ca. 95% pure by ^{1}H NMR). The crude products from similar reactions (10−13:1 mixtures of **11a** and **11b**, respectively) could be fractionated by FCC (25% ethyl acetate in hexane) to afford **11a** (80−85%) and **11b** (5−8%). Spectroscopic data for **11a**: $[\alpha]_D$ −44 (*c* 0.83, C_6H_6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (1H, br s), 4.89 (1H, br s), 4.75 (1H, br s), 2.84 (1H, d, J = 16 Hz), 2.64 (1H, dd, J = 4, 5.5 Hz), 2.63 (1H, dd, J = 9.5, 15 Hz), 2.52 (1H, dd, J = 5, 15 Hz), 2.45 (1H, dddd, J = 4.5, 5, 9, 9.5 Hz), 2.20 (1H, ddd, J = 4, 9, 14.5 Hz), 2.09 (1H, ddd, J = 4.5, 5.5, 14.5 Hz), 2.08 (1H, d, J = 16 Hz), 1.96 (3H, s), 1.79 (3H, s), 1.31 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 211.8, 196.4, 160.2, 146.3, 128.8, 111.8, 50.1, 46.8, 44.6, 42.1, 41.1, 28.7, 23.7, 22.6, 21.2; HRMS *m*/*z* calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1464 (EI).

(4a*S*,6*R*,8*S*,8a*R*)-4a,5,6,7,8,8a-Hexahydro-8-hydroxy-4,8a-dimethyl-6-(1-methylethenyl)naphthalen-2(1*H*)-one (12b). $NaBH_4$ (1.82 g, 48.0 mmol) was added to a stirred solution of the above 13:1 mixture of crude diketones **11a** and **11b** (1.90 g) in a 1:1 (v/v) mixture of CH_2Cl_2 and MeOH (2.5 mL) at −78 °C under argon. After 16 h, the reaction was quenched by dropwise addition of acetone (10 mL). The mixture was allowed to warm to ambient temperature and then was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated to give the crude product (2.3 g) that was a 72:14:6:8 mixture (by ^{1}H NMR) of **12b**, **12a**, **12c**, and **11a**, respectively (1.82 g). Fractionation of the crude by FCC (20% ethyl acetate in hexane) afforded recovered **11a** (0.17 g, 9%) and a 12:2:1 mixture (by ^{1}H NMR) of **12b**, **12a**, and **12c**, respectively (1.50 g, 80% from diosphenol **10b**). Under the same reaction conditions, reduction of cis **11a** gave a separable 5.5:1 mixture (by ^{1}H NMR of the crude product) of **12b** (80%) and **12a** (10%)[41] after fractionation of the crude by FCC (25% ethyl acetate in hexane). Similarly, reduction of trans **11b** gave a separable 25:1 mixture (by ^{1}H NMR of the crude product) of **12c** (84%)[41] and **12d** (not isolated but obtained by isomerization of **12b**)[41] after fractionation of the crude by FCC (25% ethyl acetate in hexane). In these cases as well as in smaller scale reductions of the **11a**/**11b** mixture, **11** was completely consumed. Spectroscopic data for **12b**: $[\alpha]_D$ −23 (*c* 1.6, C_6H_6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (1H, br s), 4.93 (1H, br s), 4.84 (1H, br s), 3.61 (1H, br d, J = 9 Hz), 2.52 (1H, d, J = 17 Hz), 2.45 (1H, br s), 2.20 (1H, d, J = 17 Hz), 2.17−1.98 (4H, m), 1.96 (3H, s), 1.78 (3H, s), 1.74 (1H, ddd, J = 5, 11, 13 Hz), 1.64−1.57 (1H, m), 1.09 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 199.6, 163.5, 146.2, 126.5, 111.1, 73.3, 44.5, 41.0, 37.5 (br), 32.9 (br), 29.9, 24.9 (br), 23.4, 22.4;[42] HRMS *m*/*z* calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1621 (EI).

(1a*R*,3a*R*,4*S*,6*R*,7a*S*,7b*R*)-Octahydro-4-hydroxy-3a,7b-dimethyl-6-(1-methylethenyl)naphth[1,2-*b*]oxiren-2(1a*H*)-one (14b). An aqueous solution of H_2O_2 (30% in H_2O; 2.6 mL, 26 mmol) was added dropwise over 5 min to a solution of the above crude mixture of alcohols **12** (1.50 g, 6.40 mmol) in methanolic NaOH (0.4 M, 128 mL, 0.05 mol) at room temperature. After 24 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and passed through a short pad of silica gel eluting with 25% ethyl acetate in hexane to obtain a 4:1 mixture of alcohols **14b** and **14a**, respectively (1.21 g, 75%). Under the same reaction conditions, oxidation of **12b** gave **14b** (78%) after fractionation of the crude by FCC (20% ethyl acetate in hexane). Similarly, oxidations of **12a** or **12c** gave **14a** in 78−80% yields after fractionation of the crude products by FCC (20% ethyl acetate in hexane). Spectroscopic data for **14b**: $[\alpha]_D$ −18 (c 2.3, C_6H_6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 (1H, br s), 4.78 (1H, br s), 3.51 (1H, br s), 3.01 (1H, s), 2.99 (1H, d, J = 14 Hz), 2.63 (1H, dd, J = 3, 13.5 Hz), 2.48 (1H, dddd, J = 3, 4, 12.5, 13 Hz), 1.91 (1H, ddd, J = 4, 4, 13 Hz), 1.84 (1H, d, J = 14 Hz), 1.80 (1H, ddd, J = 3, 13, 13 Hz), 1.77 (3H, br s), 1.69 (1H, ddd, J = 3, 4, 13 Hz), 1.47 (1H, br s), 1.37 (3H, s), 1.35 (1H, ddd, J = 12.5, 13, 13.5 Hz), 0.87 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.5, 149.0, 109.7, 74.5, 66.2, 62.9, 47.6, 44.4, 40.6, 39.4, 33.9, 29.2, 21.1, 20.7, 18.4; HRMS *m*/*z* calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1565.

(1a*R*,3a*R*,6*S*,7a*S*,7b*R*)-Octahydro-3a,7b-dimethyl-6-(1-methylethenyl)naphtho[2,1-*b*]oxiren-2(1a*H*)-one (15). $NaN(SiMe_3)_2$ (1.0 M in THF; 5.3 mL, 5.3 mmol), CS_2 (0.87 mL, 1.1 g, 15 mmol), and MeI (1.50 mL, 3.43 g, 24.2 mmol) were sequentially added to a stirred solution of the above 4:1 mixture of **14b** and **14a** (1.21 g, 4.83 mmol), respectively, in THF (48 mL) at 0 °C under argon. The reaction mixture was stirred at room temperature for 16 h and then was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated, and the residue was passed over a short pad of silica gel eluting with 20% ethyl acetate in hexane to afford a 4:1 mixture (by ^{1}H NMR) of xanthates (1.39 g, 85%).[41] Bu_3SnH (1.65 mL, 1.78 g, 6.12 mmol) was added to a stirred solution of the above mixture of xanthates **S2a** and **S2b** (1.39 g, 4.08 mmol) in toluene (41 mL). The reaction mixture was heated under reflux and after 10 min, AIBN (0.100 g) was added. After 10 min, the reaction mixture was concentrated and the residue fractionated by FCC (hexane followed by 10% ethyl acetate in hexane) to afford the titled compound (0.87 g, 91%): $[\alpha]_D$ −45 (*c* 1.0, C_6H_6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 (2H, br s), 3.01 (1H, s), 2.45 (1H, d, J = 14 Hz), 2.06 (1H, dd, J = 3.5, 13 Hz), 2.01 (1H, dddd, J = 4, 4, 13, 13 Hz), 1.96 (1H, d, J = 14 Hz), 1.90 (1H, ddd, J = 3.5, 4, 13 Hz), 1.77 (3H, s), 1.65−1.59 (1H, m), 1.52−1.36 (3H, m), 1.35 (3H, s), 1.32 (1H, ddd, J = 13, 13, 13 Hz), 0.85 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 149.6, 109.3, 66.3, 62.9, 52.1, 48.5, 46.2, 40.0, 39.4, 29.3, 26.5, 21.1, 20.4, 17.8; HRMS *m*/*z* calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1619 (EI).

(1a*R*,3*R*,3a*S*,6*S*,7a*S*,7b*R*)-Octahydro-3-hydroxy-3a,7b-dimethyl-6-(1-methylethenyl)naphtho[2,1-*b*]oxiren-2(1a*H*)-one (16). NaOH (2.5 M in MeOH; 5.0 mL, 13 mmol) and $PhI(OAc)_2$ (0.690 g, 2.14 mmol) were sequentially added to a stirred solution of epoxide **15** (0.250 g, 1.07 mmol) in MeOH (8 mL) at 0 °C. The cooling bath was removed and after 1 h, the reaction was quenched by addition of saturated aq $Na_2S_2O_3$. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and concentrated to get crude methoxydiepoxide (0.320 g).[41] Aq HCl (1.2 N; 2.5 mL, 3 mmol) was added to a stirred solution of the crude methoxydiepoxide (0.320 g) in THF (10 mL) at room temperature. After 10 min, the reaction mixture was quenched by addition of saturated aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to afford the titled compound (0.230 g, 85%): $[\alpha]_D$ −45 (*c* 1.2, C_6H_6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (2H, br s), 4.15 (1H, d, J = 4 Hz), 3.38 (1H, d, J = 4 Hz), 3.29 (1H, s), 2.17 (1H, dd, J = 3, 13 Hz), 2.07−1.99 (1H, m), 1.94−185 (2H, m), 1.79 (3H, s), 1.71−1.65 (1H, m), 1.40 (3H, s), 1.46−1.34 (3H, m), 0.71 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7, 149.6, 109.4, 80.2, 67.8, 62.7, 47.5, 46.5, 45.8, 35.3, 29.1, 26.1, 21.1, 20.5, 11.7; HRMS *m*/*z* calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1567 (EI).

(1*S*,4*S*,4a*S*,7*S*,8a*S*)-1,4,4a,5,6,7,8,8a-Octahydro-1,4a-dimethyl-7-(1-methylethenyl)naphthalene-1,4-diol (17). $H_2NNH_2 \cdot H_2O$ (0.077 mL, 0.080 g, 1.6 mmol) was added to a stirred solution of **16** (0.200 g, 0.799 mmol) in MeOH (8 mL) at 0 °C. After 15 min, acetic acid (0.092 mL, 0.088 g, 1.6 mmol) was added and the cooling bath was removed. After 1 h, the reaction was quenched by addition

(42) Several signals are broad (br) and one carbon is "missing" due to slow conformational exchange.

of saturated aq $NaHCO_3$. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (50% ethyl acetate in hexane) to afford the titled compound (0.170 g, 90%): $[\alpha]_D$ +19 (*c* 0.34, C_6H_6); ^1H NMR (500 MHz, $CDCl_3$) δ 5.57 (2H, ap s), 4.74 (2H, ap s), 3.99 (1H, br s), 2.00−1.91 (3H, m), 1.77 (3H, s), 1.68−1.63 (1H, m), 1.61 (1H, dd, J = 3, 12.5 Hz), 1.41−1.25 (3H, m), 1.18 (3H, s), 0.90 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 135.2, 130.5, 108.6, 78.2, 71.3, 51.3, 45.7, 40.1, 39.5, 27.3, 26.9, 21.3, 21.3, 13.0; HRMS *m*/*z* calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1764 (EI).

(4*S*,4a*S*,6*S*,8a*S*)-4a,5,6,7,8,8a-Hexahydro-4-hydroxy-4,8a-dimethyl-6-(1-methylethenyl)naphthalen-1(4*H*)-one (18). Dess−Martin periodinane (0.457 g, 1.08 mmol) was added to a stirred solution of **17** (0.170 g, 0.720 mmol) in dry CH_2Cl_2 (8 mL) at room temperature. After 20 min, the reaction was quenched by addition of a 1:1 mixture (v/v) of saturated aq $Na_2S_3O_4$ and saturated aq $NaHCO_3$. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (50% ethyl acetate in hexane) to afford the titled compound (0.154 g, 91%): $[\alpha]_D$ +16, (*c* 0.59, C_6H_6); ^1H NMR (500 MHz, $CDCl_3$) δ 6.64 (1H, d, J = 10 Hz), 5.85 (1H, d, J = 10 Hz), 4.75 (2H, br s), 2.03−1.88 (4H, m), 1.77 (3H, s), 1.76−1.70 (1H, m), 1.50−1.36 (3H, m), 1.33 (3H, s), 1.13 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 153.8, 149.9, 125.8, 109.0, 70.8, 52.3, 45.2, 44.9, 35.0, 26.6, 26.5, 22.5, 21.3, 18.3; HRMS *m*/*z* calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1621 (EI).

(1*S*,4*S*,4a*S*,7*S*,8a*S*)-Decahydro-1,4a-dimethyl-7-(1-methylethenyl)naphthalene-1,4-diol (2; lairdinol A). $PhMe_2SiH$ (0.049 mL, 44 mg, 0.32 mmol) was added to a stirred solution of $[CuH(PPh_3)]_6$ (21 mg, 0.011 mmol, weighed in glove box) in toluene (1.5 mL) at room temperature under argon. After 5 min, a solution of **18** (50 mg, 0.21 mmol) in toluene (0.5 mL) was added to the reaction mixture. After 48 h, the reaction mixture was concentrated to give the crude ketone [note: this ketone can be isolated at this juncture by fractionation by FCC (50% ethyl acetate in hexane)]. The residue was taken up in MeOH (3 mL) and $NaBH_4$ (25 mg, 0.63 mmol) was added with stirring at 0 °C. After 10 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (40% ethyl acetate in hexane) to afford **2** (46 mg, 91%). Spectroscopic and chiroptical data for synthetic **2** were essentially identical with those reported previously.[3,34,35]

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Supporting Information Available: Experimental procedures and full spectroscopic data for all synthetic intermediates; ^1H and ^{13}C NMR spectra for all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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