Synthesis of (−)-Astrogorgiadiol

Douglass F. Taber* and Scott C. Malcolm

Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

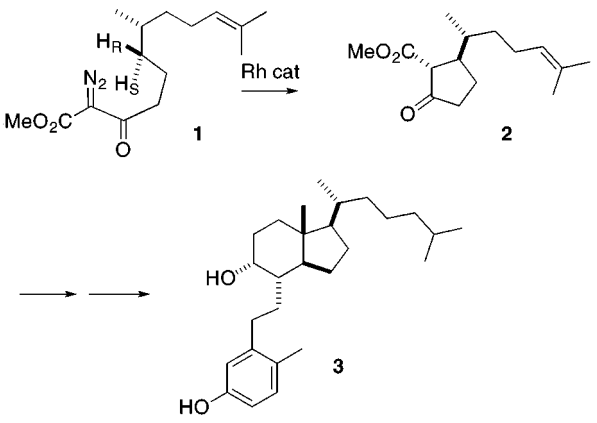
taberdf@udel.edu

Received October 24, 2000

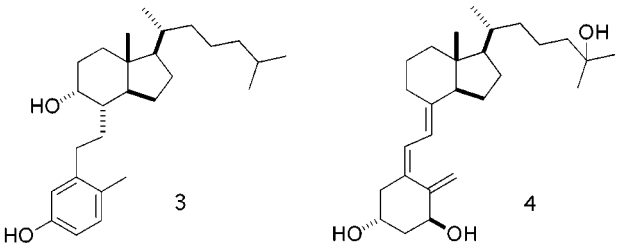
Reaction of Rh_2(*S*)-PTPA$_4$ with the (*R*)-citronellol-derived α-diazo-*β*-ketoester **1** led to the formation of cyclic *β*-ketoester **2** in 95% yield and 48% diastereomeric excess. The purity of **2** was increased to >99% de after one crystallization. To demonstrate its utility in steroid total synthesis, the *β*-ketoester **2** was carried on to secosteroid (−)-astrogorgiadiol (**3**), a naturally occuring vitamin D analogue with antiproliferative properties.

Introduction

The development of general methods for the preparation of polycarbocyclic natural products with control of both relative and absolute configuration has been a longstanding challenge in organic synthesis. The problem of controlling the configuration of a stereogenic center on a pendant side chain relative to the ring to which it is attached has been particularly troublesome. We report that Rh-mediated cyclization of enantiomerically pure **1** can proceed with appreciable selectivity for insertion into H_R, to give the nicely crystalline *β*-ketoester **2**. The utility of **2** as a chiron for the preparation of physiologically active natural products is illustrated by the conversion of **2** to the antiproliferative marine secosteroid (−)-astrogorgiadiol (**3**).[1,2]



Astrogorgiadiol. Vitamin D and its metabolites (for example, 1α,25-dihydroxy vitamin D$_3$ (**4**)) control a variety of processes in the body related to bone calcification and the regulation of serum calcium levels.[3] The observation of vitamin D receptors in roughly 60% of all cancer cell lines has led to the finding that high concentrations of 1,25 will suppress or differentiate many malignant cells.[4] Unfortunately, it is unlikely that 1,25 could be used clinically as an anticancer agent, since large doses also lead to dangerously high levels of calcium in the blood, a condition known as toxic hypercalcemia. Consequently, much research has gone into separating the cell differentiation properties of vitamin D analogues from their effect on calcium homeostasis.[4] Most of the analogues prepared so far (∼80%)[4] have modifications on the upper side chain. A-ring manipulation is rare because of difficulties in synthesis, and aromatic A-ring analogues are almost unheard of. Thus, aromatic A-ring secosteroids constitute a largely unexplored class of vitamin D$_3$ analogues.[5]



Astrogorgiadiol (**3**) was isolated[1] from a Japanese marine sponge of the genus *Astrogorgia* after extracts showed significant biological activity. A purified sample of **3** was subsequently found to inhibit cell division of fertilized starfish eggs at 50 *μ*g/mL. The structural similarity of **3** to vitamin D suggested the possibility of a similar mode of action. Further investigation of this activity, however, depended on this substance being made available by total synthesis. We envisioned that **3** could be prepared from the symchiral *β*-ketoester **2**.

Preparation of the D-Ring Chiron. The starting point for our synthesis was the inexpensive (*R*)-citronellal **5** (Scheme 1). Citronellol **6**, prepared by lithium aluminum hydride reduction of **5**, was converted to its benzenesulfonate, and this was homologated with the dianion of methyl acetoacetate.[6] The resulting *β*-ketoester **8** so obtained had all the required carbons for the D-ring

(1) For the isolation, structure and biological activity of (−)-astrogorgiadiol, see: Fusetani, N.; Nagata, H.; Hirota, H.; Tsuyuki, T. *Tetrahedron Lett.* **1989**, *30*, 7079.

(2) While this work was in progress, a partial synthesis of (−)-astrogorgiadiol from vitamin D was reported: Della Sala, G.; Izzo, I.; De Riccardis, F.; Sodano, G. *Tetrahedron Lett.* **1998**, *39*, 4741.

(3) DeLuca, H. *FASEB Journal* **1988**, *2*, 224.

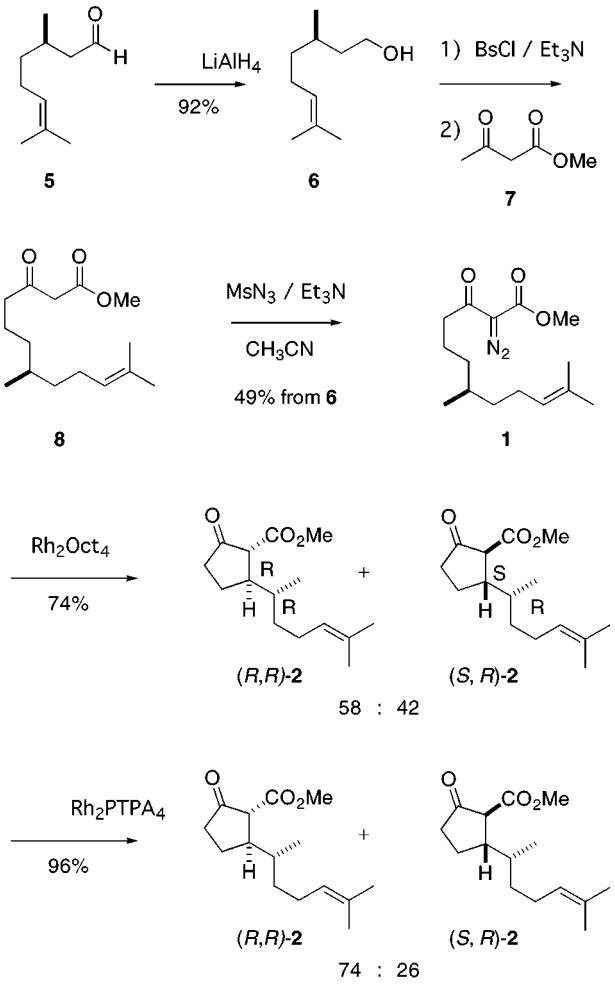
(4) *Vitamin D*; Feldman, D., Glorieux, F. H., Pike, J. W., Eds.; Academic Press: New York, 1997.

(5) Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877 and references cited within.

(6) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082−1087.

10.1021/jo001519g CCC: $20.00
Published on Web 01/12/2001

Scheme 1

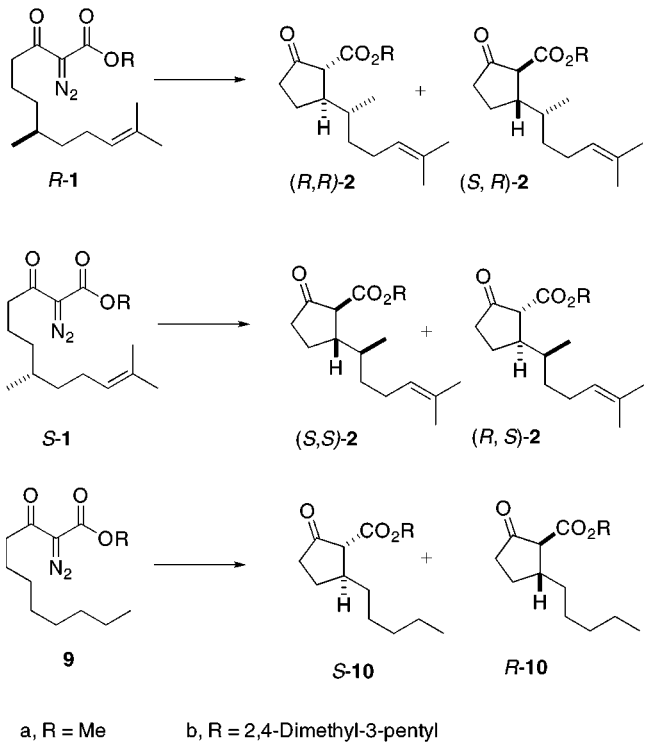


and for the upper side chain. Ketone **8** reacted smoothly with mesyl azide[7] to provide **1**, the substrate for rhodium-mediated cyclization.

The cyclization of the α-diazo-*β*-ketoester **1** with rhodium octanoate resulted in the formation of a moderate excess of (*R*,*R*)-**2**, the desired diastereomer (14% de), presumably as a result of the effect of the stereogenic center in close proximity to the insertion site.[8] This mixture could not be separated by silica gel chromatography, but the desired (*R*,*R*)-**2** could be brought to diastereomeric purity by recrystallization.

Improved Catalysis of the C−H Insertion. If we could improve the ratio of diastereomers from the cyclization of the diazo compound (**1** → **2**), we would increase the final yield of the D-ring *β*-ketoester. To this end, we screened several enantiomerically pure catalysts, the MEPY catalyst of Doyle,[9] the PTPA catalyst of Hashimoto,[10] and the DOSP and BiTISP catalysts of Davies.[11] Through the combination of five catalysts and six substrates (Scheme 2), we briefly explored the optimization of asymmetric induction in the rhodium-mediated cyclization reaction (Table 1). The pentyl side chain substrates **9a** and **9b** (entries 1 and 2) were chosen as controls. With these prochiral substrates it was possible to gauge the effect solely of the catalyst. Similarly, the achiral rhodium acetate catalyst was chosen to allow the determination of the effect of the existing stereogenic center on the dimethylhexenyl side chain.

Scheme 2



In entries 3−6, the substrates were enantiomerically pure. In these cases, we expected, with the enantiomerically pure catalysts, to have a matched and mismatched pair of reacting molecules. Thus, it was important to determine the diastereomeric excess for each pair. In practice, it was easier to secure the enantiomer of the substrates (entries 5 and 6) rather than the enantiomer of each catalyst.

Hashimoto[10] had noted significant improvement in the product ratios when employing the sterically demanding dimethylpentyl ester. It was assumed that the bulk of the ester helped to further discriminate the two modes of cyclization, but this sort of adjustment had not been explored with the other catalysts. Thus, it was important to test those substrates in each case (entries 2, 4, and 6).

The cyclizations were carried out as summarized in Table 1. The pentyl products (**10**) were analyzed as before.[12] The dimethylhexenyl products (**2**) were analyzed by gas chromatography on a chiral column. Entries 3 and 4 are of particular interest since they represent the substrate that leads to the correct absolute configuration of the natural steroids. For these entries, the combination of the (*S*)-BiTISP catalyst and the methyl ester (*R*-**1a**) gave the highest ratio of RR to SR (58% de), but (*R*-**1a**) with (*R*)-PTPA gave a better overall yield of **2**.

The methyl ester cyclization was scaled up. The initial 3:1 mixture of diastereomeric products was recrystallized

(7) Taber, D. F.; Ruckle, R. E., Jr.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077.

(8) For the first report of such an influence of a side chain stereocenter on the diastereoselectivity of Rh-mediated C−H insertion, see: Daniewski, A. R.; Warchol, T. *Polish J. Chem.* **1992**, *66*, 1985.

(9) For the MEPY catalyst, see: (a) Doyle, M. P.; Dyatkin, A. B.; Roos, G. H. P.; Canas, F.; Pierson, D. A.; Vanbasten, A.; Muller, P.; Polleux, P. *J. Am. Chem. Soc.* **1994**, *116*, 4507−4508. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1997.

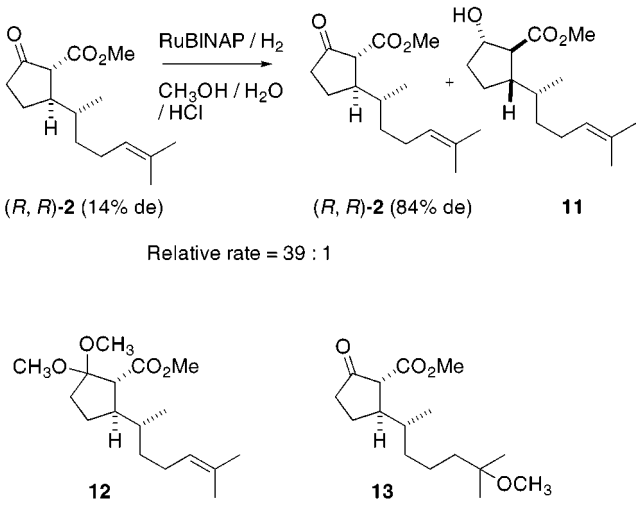
(10) For the PTPA catalyst, see: Hashimoto, S.; Watanabe, N.; Sato, T.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1993**, *34*, 5109−5112.

Table 1. R:S Ratios and Isolated Yields for Rh-Mediated Cyclizations

		acetate	(*R*)-PTPA	(5*S*)-MEPY	(*S*)-DOSP	(*S*)-BiTISP
1	**9a**	50:50 (98%)[a]	60:40 (99%)[a]	51:49 (82%)[d]	51:49 (95%)[a]	
2	**9b**	50:50 (99%)[a]	61:39 (98%)[a]	50:50 (75%)[d]	48:52 (99%)[a]	
3	*R*-**1a**	57:43 (92%)[a]	74:26 (98%)[a] 74:26 (62%)[e]	57:43 (66%)[d]	64:36 (94%)[a]	79:21 (38%)[b]
4	*R*-**1b**	61:39 (99%)[a]	78:22 (89%)[a]	57:43 (48%)[d]	73:27 (95%)[a]	67:33 (12%)[c]
5	*S*-**1a**	45:55 (92%)[a]	31:69 (92%)[a]	42:58 (64%)[d]	46:54 (95%)[a]	75:25 (32%)[b]
6	*S*-**1b**	38:62 (91%)[a]	23:77 (88%)[a]	38:62 (44%)[d]	35:65 (96%)[a]	40:60 (10%)[c]

[a] 2 h; 20 °C. [b] 2 h, 60 °C. [c] 4 h, 60 °C. [d] 16 h, 60 °C. [e] 96 h, −10 °C.

Scheme 3



once to give > 99% pure (*R*,*R*)-**2** in an overall 40% yield for the cyclization.

For all save one run in Table 1, the influence of the side chain stereogenic center was dominant, not the influence of the catalyst. The single exception was uncovered using the combination of the (*S*)-BiTISP catalyst[11] and the methyl esters (entry 3 and entry 5 for BiTISP). With BiTISP, the catalyst was dominant, delivering an excess of pro-*R* insertion even with (*S*)-**1**.

Kinetic Resolution by Ru−BINAP Hydrogenation. It was apparent that even the best of the chiral Rh catalysts would not directly deliver products of high enantiomeric purity. We therefore considered strategies for improving the enantiomeric purity of the cyclopentane products. In particular, kinetic resolution of the mixture seemed possible, by the application of our modification (Scheme 3) of the asymmetric ruthenium-BINAP hydrogenation of *β*-ketoesters.[13]

Complexation of the chiral catalyst to the chiral ketoester can result in either a matched or a mismatched set. The matched set should be lower in energy and therefore lead to a faster rate of reduction. The critical question was, would the ratio of rates be sufficiently high to allow the practical preparation of enantiomerically pure products?

We briefly explored this question using the 1.4:1 ratio of products from Rh_2(octanoate)$_4$ cyclization of **1**. The ruthenium catalyst was prepared by the known method[13b] and was used without further purification. The reduction reaction was performed as we have previously described[13a,14] except the hydrogen pressure was reduced from 50 to 10 psig. This permitted easy analysis of the progress of the reaction by TLC. It was important to carefully optimize the relative amounts of water and HCl in the methanol solvent, to minimize the formation of byproducts **12** and **13**. The reduction was halted after approximately 50% of the starting material had been consumed.

After hydrogenation, the alcohol **11** was easily removed by chromatography, allowing the production of gram-scale batches of diastereomerically enriched **2** (>10:1). The combination of these two procedures, the use of the appropriate enantiomer of the Hashimoto catalyst[10] to give an initial preference for pro-*R* or pro-*S* C−H insertion, followed by selective Ru−BINAP hydrogenation[13,14] to polish the enantiomeric purity of the cyclized *β*-keto ester, will be a powerful method for the preparation of cyclopentane products of high enantiomeric purity.

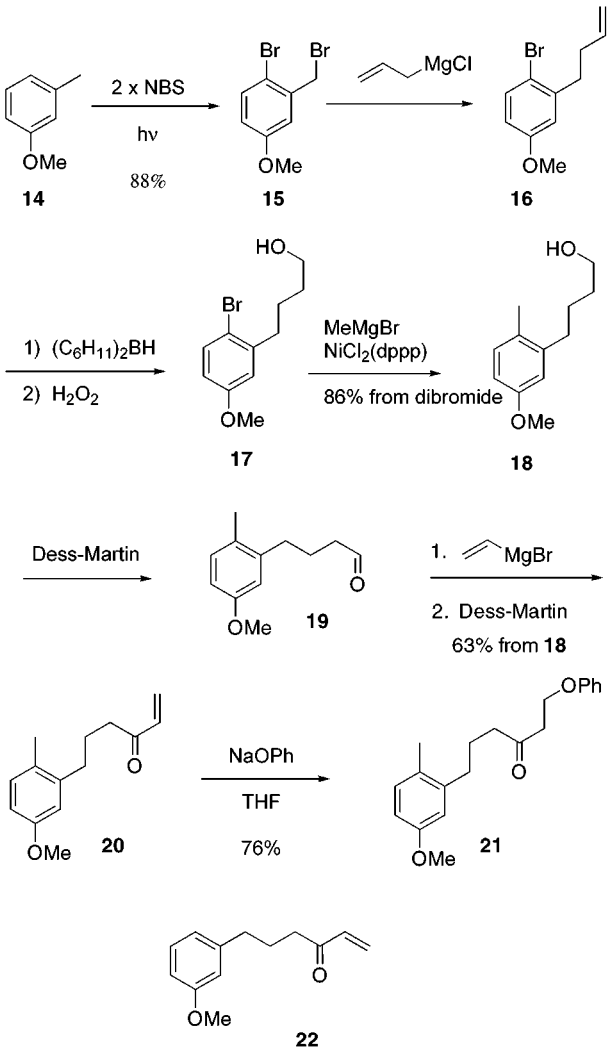
Synthesis of the A-Ring Synthon. Although direct Robinson annulation of α-methyl cyclohexanones usually proceeds with substantial regioselectivity, the regioselectivity has not always been satisfactory with α-methyl cyclopentanones, so alternative strategies have been developed.[15] Nonetheless, the direct Robinson annulation appeared so straightforward that we felt compelled to investigate it. To this end, we prepared (Scheme 4) the A-ring enone **20**.

Our approach was based on the report of the specific dibromination of *m*-methylanisole.[16] The crystalline dibromide **15** was coupled with allylmagnesium chloride,[17] and the resultant alkene was converted to the primary alcohol by hydroboration. The methyl group was then installed by Ni-catalyzed Grignard coupling, following the procedure of Kumada.[18] Oxidation of the alcohol **18** with the Dess−Martin reagent afforded the aldehyde **19**. Addition of vinylmagnesium bromide to the crude aldehyde followed by reoxidation then led to the enone **20**.

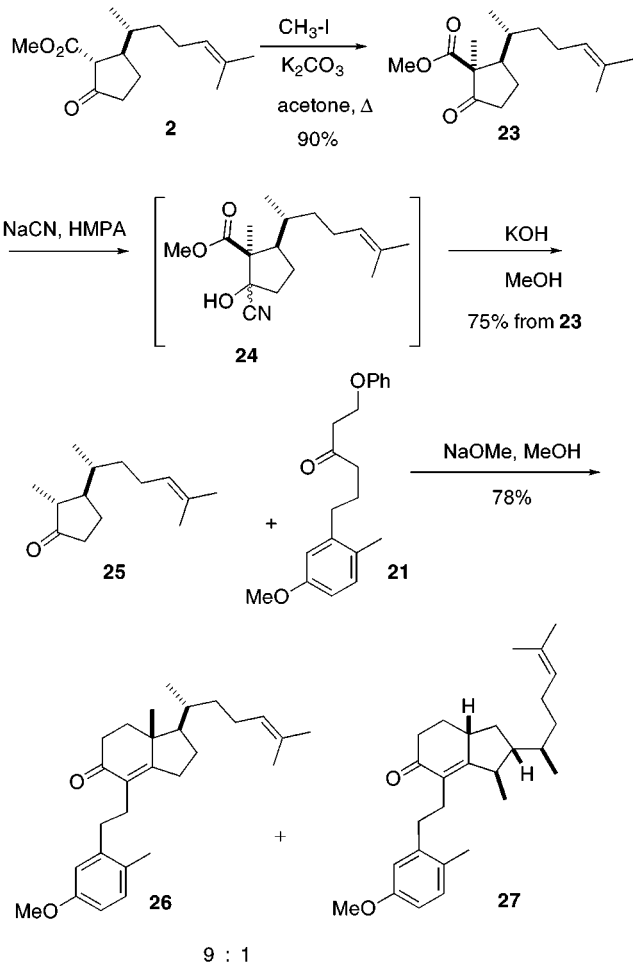
We found that the enone **20** so prepared was contaminated with variable amounts (~5−10%) of the enone **22** lacking the aromatic methyl substituent. This impurity presumably arose from reduction of the aromatic bromide **17** by an adventitious nickel hydride species. Since this impurity could not be removed by chromatography, the enone **20** was purified by preparation of the crystalline phenyl ether **21**.

(11) For the DOSP and BiTISP catalysts, see: Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, *2459*, 9.
(12) Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **1998**, *63*, 3717.
(13) (a) Taber, D. F.; Silverberg, C. J. *Tetrahedron Lett.* **1991**, *32*, 4227. (b) For the original report of the preparation of the Ru−BINAP catalyst, see: Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922.
(14) Taber, D. F.; Wang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 22.
(15) Jankowski, P.; Marczak, S.; Wicha, J. *Tetrahedron* **1998**, *54*, 12071 and references cited within.
(16) Hoye, T. R.; Mi, L. *J. Org. Chem.* **1997**, *62*, 8586.
(17) Taber, D. F.; Green, J. H.; Geremia, J. M. *J. Org. Chem.* **1997**, *62*, 9342.
(18) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.-I.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Soc. Chem. Jpn.* **1976**, *49*, 1958.

Scheme 4



Scheme 5



Robinson Annulation. Methylation of **2** (Scheme 5) followed by decarbomethoxylation gave the α-methyl ketone **25**. The crude product so prepared was found to be contaminated with ∼10% of a 1:1 mixture of the isomeric cyanohydrins (**24**). Exposure of the crude product from the decarbomethoxylation reaction to methanolic KOH reversed the cyanohydrin formation, and the methyl ketone **25**[19] was isolated in 75% yield from **23**.

With **21** and **25** in hand, we were prepared to explore the direct Robinson annulation. We were pleased to observe that NaOMe-mediated condensation of **25** with the phenyl ether **21** in refluxing methanol in fact proceeded smoothly, to give the desired enone **26** as the preponderant product. The major product **25** (^{1}H NMR δ 0.97, 3H, d) contained ∼10% of the regioisomer **27** (^{1}H NMR δ 0.86, 3H, d). This minor regioisomer was conveniently separated at a later stage of the synthesis.

Reduction of the Enone. We next addressed the problem of reducing the CD enone **26** to the *trans*-hydrindane (Scheme 6). Literature results[15] suggested that catalytic hydrogenation would give a preponderance of the trans ring fusion. As expected, reduction (Pd−C, 1 atm H_2) of the side chain alkene proceeded quickly. Reduction of the tetrasubstituted alkene proceeded more slowly (90% conversion after 2 days), to give a mixture of **28**−**31**. It was convenient to equilibrate (KOH/MeOH) this mixture prior to isolation. Under these conditions, **29** (^{13}C δ 215.5) was converted to **28** (^{13}C δ 213.0), while **30** (^{13}C δ 214.9) and **31** (^{13}C δ 215.1) were received as a ∼1:1 mixture. The ratio of **28** to **30** + **31** was 75:25.

Although the side chain alkene of **24** was not needed for (−)-astrogorgiadiol **3**, other related natural products do have more highly substituted side chains. We therefore surveyed several of the methods for the selective reduction of conjugated alkenes that have been developed. Where applicable, mixtures of 1,2 and 1,4 reduction were oxidized and the epimeric product ketones were equilibrated prior to quantitative analysis by ^{13}C NMR. As before, **33** (Scheme 6) was converted under these conditions to **32** (^{13}C δ 213.0; ^{1}H δ 0.98, 3H, s), while **34** (^{13}C δ 214.9; ^{1}H δ 1.11, 3H, s) and **35** (^{13}C δ 215.1; ^{1}H δ 0.88, 3H, s) were received as a ∼1:1 mixture.

The results from the screening of several different reduction procedures[15] are summarized in Table 2. It was apparent that the most promising of these methods was CuH (entry 5),[23] so this procedure was optimized. The CD enone **26** was added to a 10-fold excess of 2:1 DIBAL/

(19) For previous preparations of variations on the symchiral D-ring ketone, see: (a) Desmaele, D.; Ficini, J.; Guingant, A.; Khan, P. *Tetrahedron Lett.* **1983**, *24*, 3079. (b) Hatakeyama, S.; Hirotoshi, N.; Takano, S. *Tetrahedron Lett.* **1984**, *25*, 3617. (c) Pan, L.-R.; Tokoyorama, T. *Tetrahedron Lett.* **1992**, *33*, 1469. (d) He, M.; Tanimori, S.; Ohira, S.; Nakayama, M. *Tetrahedron* **1997**, *53*, 13307.

(20) Keinan, E.; Greenspoon, N. *J. Am. Chem. Soc.* **1986**, *108*, 7314.
(21) Enholm, E. J.; Kinter, K. S. *J. Org. Chem.* **1995**, *60*, 4850.
(22) Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390−1399.

Scheme 6

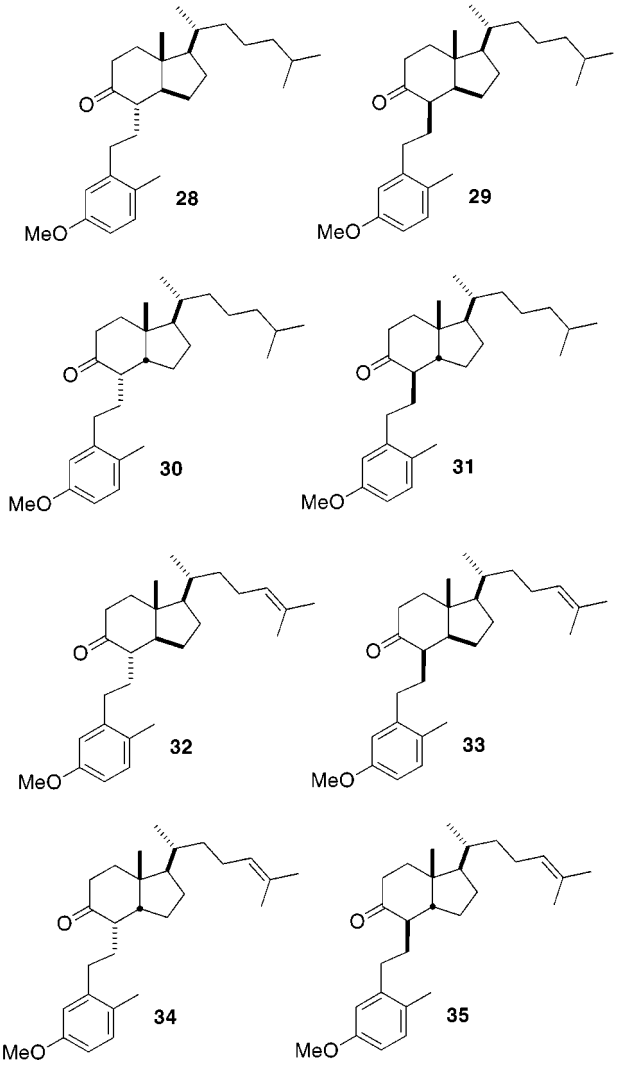


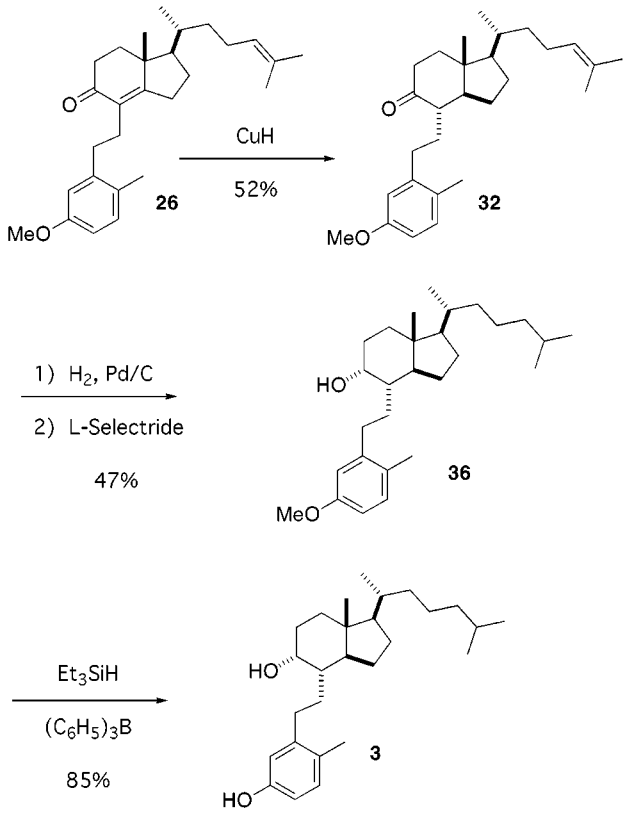
Table 2. Reduction of Enone 24

entry	reagent	conv	yield of **32**	yield of **34** + **35**
1	$(Ph_3P)_4Pd,ZnCl_2$, Ph_2SiH_2[20]	24%	8%	
2	Bu_3SnH, AIBN[21]	68%	25%	31%
3	Li/liq NH_3	100%		23%
4	$(Ph_3P)_3RhCl,Et_3SiH$[22]	80%	25%	13%
5	CuCN/DIBAL/BuLi[23]	49%	53%	

n-BuCu reagent at −50 °C, and the reaction temperature was then raised to −20 °C over 10 min. The starting material was completely consumed to give mixtures of 1,2, 1,4, and complete reduction. For simplicity, the crude product was reoxidized and equilibrated before analysis. The cis-fused ketones **34** and **35** could not be observed in the mixture of products. The reoxidation step was initially found to be problematic as a large amount of a diene was isolated at the expense of the starting enone. This side reaction could be minimized by slow addition of the Dess−Martin reagent to the crude reduction mixture.

Synthesis of (−)-Astrogorgiadiol. Hydrogenation (Scheme 7) of the ketone **32** obtained from the CuH reduction proceeded rapidly to produce material that was identical to the major product (**28**) obtained from catalytic hydrogenation of the enone **26**. Reduction of this ketone

Scheme 7



with L-Selectride gave the expected axial alcohol **36,** which could at this stage be isolated free from the contaminating regioisomer derived from **27**. Deprotection of the aryl methyl ether proceeded[24] uneventfully to provide a compound that was identical to natural (−)-astrogorgiadiol by ^1H and ^{13}C NMR and $[\alpha]_D$ (obs = −7.4°, *c* 0.095, $CHCl_3$; lit.[1] = −16.4°, *c* 0.058, $CHCl_3$; lit.[2] = −4.6°, *c* 0.2, $CHCl_3$). Comparison ^1H NMR spectra were provided by N. Fusetani and G. Sodano.

Conclusion

We expect that the two enantiomers of the crystalline *β*-ketoester **2**, readily prepared in gram quantities from commericially available (*R*)- and (*S*)-citronellol, will be valuable chirons for the construction of terpene-derived natural products. The enantioselective Ru−BINAP hydrogenation of cyclopentanone carboxylates described here should also open a general route to cyclopentane derivatives of high enantiomeric purity.

Experimental Section

^1H NMR and ^{13}C NMR spectra were obtained as solutions in deuteriochloroform ($CDCl_3$). ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" from methylene and quaternary carbons as "u". The infrared (IR) spectra were determined as neat oils. Mass spectra (MS) were

(23) For CuH reduction of *trisubstituted* CD enones, see: (a) Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537. (b) Tsuda, T.; Kawamoto, T.; Kumamoto, Y.; Saegusa, T. *Synth. Commun.* **1986**, *16*, 639. (c) Daniewski, A. R.; Kiegiel, J. *Synth. Commun.* **1988**, *18*, 115. (d) Loughlin, W. A.; Haynes, R. K. *J. Org. Chem.* **1995**, *60*, 807.

(24) Gevorgyan, V.; Liu, J.-X.; Rubin, M.; Benson, S.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 8919.

obtained at an ionizing potential of 15 eV. Substances for which C,H analyses are not reported were purified as specified and gave spectroscopic data consistent with being >95% the assigned structure. Optical rotations were determined as solutions in dichloromethane unless otherwise noted. R_f values indicated refer to thin-layer chromatography (TLC) on 2.5 × 10 cm, 250 μm analytical plates coated with silica gel GF, unless otherwise noted, and developed in the solvent system indicated. All glassware was flame dried under a dry nitrogen stream before use. Tetrahydrofuran (THF), diethyl ether, and 1,2-dimethoxyethane (DME) were distilled from sodium/benzophenone ketyl under dry nitrogen. Dichloromethane (CH_2Cl_2) and toluene were distilled from calcium hydride under dry nitrogen. All reaction mixtures were stirred magnetically, unless otherwise noted.

(R)-Citronellol (6). Powdered $LiAlH_4$ (12.5 g, 329 mmol) was introduced into a 5-L round-bottom flask along with 2 L of THF (dried over 3 Å molecular sieve). The slurry was stirred mechanically under N_2, and the temperature was lowered to 0 °C. (*R*)-Citronellal (**5**, Takasago) (100 g, 648 mmol) was added neat over about 15 min, and the residue was rinsed into the flask with an additional 500 mL of THF. Notwithstanding the fact that TLC indicated complete consumption of citronellal, the mixture was warmed to a gentle reflux and subsequently cooled to 0 °C. The reaction was worked up by sequential dropwise addition of the following to the vigorously stirring mixture: 12.5 mL of water, 12.5 mL of 3 M NaOH, and a solution of 37.5 mL of water in 37.5 mL of THF. After filtration through Celite and thorough washing of the solids with MTBE, the solvent was evaporated to yield 116 g of crude citronellol. This oil was distilled (bulb-to-bulb, 120−140 °C, 0.8 mmHg) to give **6** (93.4 g, 92%) as a clear oil, TLC R_f (10% MTBE/petroleum ether) = 0.09. ^{1}H NMR ($CDCl_3$, δ): 5.10 (m, 1H), 3.66 (m, 2H), 2.1−1.8 (m, 3H), 1.68 (s, 3H), 1.7−1.5 (m, 2H), 1.60 (s, 3H), 1.4−1.3 (m, 2H), 1.17 (m, 1H), 0.90 (d, J = 6.66 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 131.2, 61.0, 39.8, 37.1, 25.4; (d) 124.6, 29.1, 25.6, 19.4, 17.6. IR (cm^{-1}): 3331 (b), 2927, 1454, 1377, 1058. MS (*m*/*z*, %): 55 (64), 69 (100), 82 (44), 95 (33), 109 (14), 123 (18), 138 (6), 156 (6). HRMS calcd for $C_{10}H_{20}O$: 156.1514, found 156.1514. $[\alpha]^{17}_D$ = +3.74 (*c* 1.02, EtOH).

(S)-Methyl 2-Diazo-7,11-dimethyl-3-oxo-10-dodecenoate (1). A solution of citronellol **6** (30.0 g, 192 mmol) in 400 mL of CH_2Cl_2 was allowed to stir at 0 °C under N_2 in a 1-L round-bottom flask. Triethylamine (60 mL, 430 mmol) was added in one portion, followed by DMAP (2.0 g, 1.64 mmol). Finally, benzenesulfonyl chloride (30 mL, 240 mmol) was added dropwise via syringe. After the mixture was stirred for 2 h at 0 °C, it was partitioned between petroleum ether and, sequentially, 3 M aqueous HCl, water, and brine. The organic layer was dried (Na_2SO_4) and the solvent was removed in vacuo at 30 °C. Removal of residual solvent under high vacuum yielded citronellyl benzenesulfonate (62.4 g, 110% of theoretical) as a clear yellow oil, TLC R_f (10% MTBE/petroleum ether) = 0.41. ^{1}H NMR ($CDCl_3$, δ): 7.92 (m, 2H), 7.66 (m, 1H), 7.56 (m, 2H), 5.03 (m, 1H), 4.09 (m, 2H), 1.91 (m, 2H), 1.68 (m, 1H), 1.67 (s, 3H), 1.57 (s, 3H), 1.52 (m, 1H), 1.44 (m, 1H), 1.24 (m, 1H), 1.11 (m, 1H), 0.81 (d, J = 6.49 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 136.1, 131.4, 69.2, 36.6, 35.5, 25.1; (d) 133.6, 129.1, 127.7, 124.2, 28.7, 25.6, 18.9, 17.5. IR (cm^{-1}): 2914, 1449, 1360, 1188, 944.

Sodium hydride (30 g, 60% in mineral oil, 750 mmol) was suspended in 400 mL of THF in a 1-L three-neck round-bottom flask fitted with a mechanical stirrer. The slurry was cooled in an ice−water bath and methyl acetoacetate (46 mL, 426 mmol) was added rapidly dropwise. After the addition was complete, the mixture was stirred for 10 min, then *n*-BuLi (165 mL, 2.33 M in hexanes, 384 mmol) was added rapidly dropwise. The mixture spontaneously warmed to reflux and then cooled over the next 10 min. Finally, a solution of the crude citronellyl benzenesulfonate (192 mmol theoretical) in 100 mL of THF was added via cannula, and the mixture was stirred at room temperature for 1 h. The mixture was quenched cautiously by pouring into saturated aqueous NH_4Cl before being partitioned between MTBE and, sequentially, water and brine. The solvent was removed in vacuo, yielding 67 g of a yellow oil. The residue was distilled (bulb-to-bulb, 140−160 °C, 0.8 mmHg) to yield crude **8** (31.3 g, 64% of theoretical based on citronellol) as a yellow oil, TLC R_f (10% MTBE/petroleum ether) = 0.37. ^{1}H NMR ($CDCl_3$, δ): 5.08 (m, 1H), 3.74 (s, 3H), 3.45 (s, 2H), 2.52 (t, J = 7.34 Hz, 2H), 1.96 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.6−1.2 (m, 6H), 1.13 (m, 1H), 0.87 (d, J = 6.85 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 202.6, 167.5, 130.9, 48.8, 43.2, 36.8, 36.1, 25.3, 20.8; (d) 124.7, 52.1, 32.1, 25.6, 19.2, 17.5. IR (cm^{-1}): 2925, 1748, 1716.

Triethylamine (42 mL, 301 mmol) and mesyl azide (18 g, 149 mmol) were added to a solution of the acetoacetate **8** in CH_3CN (130 mL). Although the reaction is usually complete in 2 h under these conditions, in this case, the mixture was allowed to stir overnight. One-half of the solvent was removed using a rotovap (50 °C) and the remaining liquid was partitioned between petroleum ether and, sequentially, 3 M aqueous NaOH and brine. The solvent was removed in vacuo, leaving 36.8 g of a brown oil. The residue was chromatographed and the purest fraction provided **1** (26.4 g, 49% from citronellol) as a pale yellow oil, TLC R_f (10% MTBE/petroleum ether) = 0.47. ^{1}H NMR ($CDCl_3$, δ): 5.09 (m, 1H), 3.84 (s, 3H), 2.83 (t, J = 7.85 Hz, 2H), 1.96 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.7−1.5 (m, 2H), 1.5−1.3 (m, 3H), 1.15 (m, 2H), 0.88 (d, J = 6.49 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 193.0, 161.8, 131.1, 40.5, 36.9, 36.4, 25.5, 21.9; (d) 124.9, 52.1, 32.2, 25.7, 19.4, 17.6. IR (cm^{-1}): 2914, 2133, 1725, 1659, 1309. This substnace was not stable to analysis by mass spectrometry.

Methyl 5-Dimethylhexenyl-2-oxocyclopentanecarboxylate (2) via Rh_2Oct_4 Catalysis. The CH_2Cl_2 used in the following reaction was distilled from CaH_2 and passed through a column (20 × 150 mm) of anhydrous K_2CO_3 prior to use. The α-diazo-β-ketoester **1** (25.5 g, 101 mmol) was dissolved in 1 L of CH_2Cl_2. A solution of rhodium octanoate (400 mg, 0.56 mol %) in 5 mL of dry CH_2Cl_2 was added in one portion. The solution was allowed to stir for 12 h before being evaporated. The green residue was chromatographed to provide cyclopentanone **2** (17.0 g, 74%) as a light-green oil. Bulb-to-bulb distillation (170 °C at 0.4 mmHg) yielded a clear oil which formed moist crystals on standing. These did not show a sharp melting point. TLC R_f (10% MTBE/petroleum ether) = 0.28. ^{1}H NMR ($CDCl_3$, δ): 5.06 (m, 1H), 3.75 (s, 3H), 2.97 (d, J = 11.6 Hz, 0.43H), 2.95 (d, J = 11.3 Hz, 0.57H), 2.55 (m, 1H), 2.5−2.3 (m, 2H), 2.3−1.9 (m, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.6−1.3 (m, 3H), 1.17 (m, 1h), 0.93 (d, J = 6.83 Hz, 1.3H), 0.91 (d, J = 6.85 Hz, 1.7H). ^{13}C NMR ($CDCl_3$, δ): (Major) (u) 212.4, 170.7, 131.7, 38.7, 33.8, 25.3, 25.1; (d) 124.2, **59.6**, 52.4, **46.7**, 36.8, 25.7, 17.6, 16.9. ^{13}C NMR ($CDCl_3$, δ): (Minor) (u) 212.2, 170.3, 131.6, 38.5, 33.8, 25.3, 25.1; (d) 124.1, **59.7**, 52.4, **46.3**, 35.7, 25.7, 15.5, 16.9. IR (cm^{-1}): 3447 (br), 2966, 1757, 1726.

Integration of the peaks (59.6 versus 59.7) and (46.7 versus 46.3) indicated a 1.4:1.0 mixture of components (14% de). The result was nicely corroborated by GC-FID. Samples were analyzed on a Hewlett-Packard HP6890 gas chromatograph using a Chiraldex γ-cyclodextrin trifluoroacetyl capillary GC column (30 m × 0.25 mm). Signals were obtained from a flame-ionization detector. Upon injection of the sample (5 μL of a 1 mg/mL solution in ethyl acetate), the oven temperature was maintained at 50 °C for 20 min. Then the temperature was increased at 1 °C/min for 100 min. For the methyl ester, the peaks at t = 95.5 (minor) and t = 96.6 (major) integrated at 43:57 (14% de). The dimethylpentyl ester was detected at t = 97.3 (minor) and t = 98.9 (major).

Recrystallization was effected by adding 1 g of the crude **2** to 10 mL of ethanol and 10 mL of water and heating to 50 °C. More ethanol was added to the oily mixture as it was maintained at this temperature until all of the oil was dissolved (up to an additional 10 mL). Seeding can be helpful but, usually, cooling to room temperature produced significantly diastereomerically enriched material (>99% de) as white flakes, mp = 58−59 °C. ^{1}H NMR ($CDCl_3$, δ): 5.07 (m, 1H), 3.75 (s, 3H), 2.95 (d, J = 11.26 Hz, 1H), 2.55 (m, 1H), 2.5−2.3 (m, 2H), 2.20 (m, 1H), 2.06 (m, 1H), 1.94 (m, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.6−1.4 (m, 3H), 1.16 (m, 1h), 0.91 (d, J = 6.85 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 212.4, 170.7, 131.7, 38.7, 33.8, 25.3, 25.1; (d) 124.2, 59.6, 52.4, 46.7, 36.8, 25.7, 17.6,

16.9. IR (cm^{-1}): 2969, 1744, 1724, 1287, 1118. MS (*m*/*z*, %): 55(26), 69 (36), 81 (10), 109 (60), 141 (100), 168 (5), 220 (13), 252 (2). HRMS calcd for $C_{15}H_{24}O_3$: 252.1725; found: 252.1731. $[\alpha]^{17}_D = -51.45$ (*c* 1.14, EtOH).

Rh_2(*S*)-PTPA$_4$. (*R*)-(+)-Phenylalanine (500 mg, 3.03 mmol) and phthalic anhydride (500 mg, 3.38 mmol) were combined in a test tube. Three times the solid was heated until it melted and then was allowed to cool. The solid was recrystallized from 50% ethanol/water (5 mL) to yield (*R*)-*N*-phthaloylphenylalanine (0.65 g, 73%) as a white solid, mp 179−180 °C. The (*R*)-*N*-phthaloylphenylalanine (600 mg, 2.03 mmol) and rhodium trifluoroacetate (164 mg, 0.25 mmol) were combined in a round-bottomed flask. Three times the solid was dissolved in dichloroethane (20 mL) and heated to dryness under a stream of nitrogen. The green oil was chromatographed. The major green fraction was collected and recrystallized from 10% acetone/heptane (5 mL) to give small green needles (114 mg, 33% based on rhodium added). TLC R_f (1:1:3 acetone/CH_2Cl_2/-petroleum ether) = 0.28.

The mother liquor was combined with the other column fractions and evaporated. More rhodium trifluoroacetate was added (100 mg, 0.15 mmol). Two times the sample was dissolved in dichloroethane (20 mL) and heated to dryness under a stream of nitrogen. The green oil was dissolved in hot 2:1 methanol/CH_2Cl_2 (30 mL). Overnight a large mass of green crystals separated. These were collected and dissolved in CH_2Cl_2 (10 mL). Methanol was added (30 mL) and the solution was allowed to sit overnight in an open container. Large green crystals separated and were collected. The crystals (presumably the methanol adduct of the catalyst) were dissolved in ethyl acetate to displace the methanol. Then, all of the solvent was removed by heating in vacuo to yield Rh_2(*S*)-PTPA$_4$ (150 mg, 27% additional yield based on total rhodium added) as a mint green powder.

Methyl 5-Dimethylhexenyl-2-oxocyclopentanecarboxylate (2) via Rh_2(*S*)-PTPA$_4$ Catalysis. The α-diazo-β-ketoester **1** (2.00 g, 7.13 mmol) was dissolved in 100 mL of CH_2Cl_2 (dry, see above) and a solution of Rh_2(*S*)-PTPA$_4$ (47.8 mg, 0.48 mol %) in 5 mL of CH_2Cl_2 was added rapidly dropwise. After 2 h at room temperature, the solvent was evaporated and the green residue was chromatographed to yield **2** (1.73 g, 96%) as a clear oil. The mixture thus obtained was a 74:26 mixture of (*R*,*R*)-**2** and (*S*,*R*)-**2** (48% de). The product was distilled and crystallized as above to yield (*R*,*R*)-**2** (722 mg, 40%) that was diastereomerically pure by ^1H and ^{13}C NMR.

(*S*)-RuBINAP Hydrogenation. A 5 mL reactivial was charged with $[RuCl_2(COD)]_n$ (39 mg, 0.139 mmol), (*S*)-BINAP (100 mg, 0.151 mmol), triethylamine (200 mg, 1.98 mmol), and toluene (4 mL). The vial was sealed and heated in a 140 °C oil bath for 3 h. The solution was allowed to cool slightly and transferred to a round-bottom flask (rinsing with hot THF) under a N_2 stream. The volatile material was removed in vacuo to yield a brown solid. This material was dissolved in THF (10 mL) to provide a 13.9 mM (*S*)-RuBINAP solution.

Cyclopentanone **2** (5.07 g, 20.1 mmol, 14% de) was dissolved in MeOH (100 mL) in a modified Parr bottle. Water (0.5 mL, 28 mmol) and a solution of HCl in MeOH (5.0 mL of a stock solution made from 1 mL of concentrated aqueous HCl and 99 mL of MeOH, 0.60 mmol) were added and the solution was purged with N_2 for 5 min. The 13.9 mM (*S*)-RuBINAP solution (10 mL, 0.69 mol % based on **2**) prepared above was added. Four times the flask was evacuated using a water aspirator and then refilled with H_2 (10 psig) causing the green solution to turn brown. The flask was heated in a 60 °C oil bath with vigorous stirring under an H_2 atmosphere until the starting material was about half consumed (2 h, TLC). The mixture was transferred to a round-bottom flask and the solvent was removed in vacuo. The residue was diluted in CH_2Cl_2 (100 mL). Flash silica gel (10 g) and 3 M aqueous HCl (1 mL) were added and the mixture was allowed to stir for 30 min. The solvent was then evaporated and the resultant solid was chromatographed to yield the recovered cyclopentanone **2** (2.10 g, 84% de, 66% recovery of this diastereomer) as a clear oil. Also isolated was the reduced compound **11** (2.64 g, 90% yield based on **2** not recovered) as a green oil, TLC R_f (50% MTBE/petroleum ether) = 0.51.

An analogous experiment that was not vigorously stirred yielded moderately enriched **2** (3.06 g, 78% de, 47% recovery of this diasteromer). Recrystallization was effected by adding this recovered **2** to 24 mL of ethanol and 12 mL of water and heating to 30 °C. The temperature was reduced to 20 °C and the solution was seeded with a few 97% de crystals. The solution was cooled to −5 °C over 15 min, which produced large crystals. The solution was further cooled to −20 °C and filtered. The crystals were rinsed with a few milliliters of cold 50% aqueous EtOH and dried in vacuo to give significantly diastereomerically enriched **2** (1.46 g, 99% de, 29% overall recovery of this diastereomer) as white flakes, mp 58−59 °C. ^1H NMR ($CDCl_3$, δ): 5.07 (m, 1H), 3.75 (s, 3H), 2.95 (d, *J* = 11.26 Hz, 1H), 2.55 (m, 1H), 2.5−2.3 (m, 2H), 2.20 (m, 1H), 2.06 (m, 1H), 1.94 (m, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.6−1.4 (m, 3H), 1.16 (m, 1h), 0.91 (d, *J* = 6.85 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 212.4, 170.7, 131.7, 38.7, 33.8, 25.3, 25.1; (d) 124.2, 59.6, 52.4, 46.7, 36.8, 25.7, 17.6, 16.9. IR (cm^{-1}): 2969, 1744, 1724, 1287, 1118. MS (*m*/*z*, %): 55(26), 69 (36), 81 (10), 109 (60), 141 (100), 168 (5), 220 (13), 252 (2). HRMS calcd for $C_{15}H_{24}O_3$: 252.1725; found: 252.1731. $[\alpha]^{17}_D = -51.45$ (*c* 1.14, EtOH).

4-Methyl-3-(4-hydroxybutyl)anisole (16). A three-neck round-bottom flask was charged with magnesium (4.2 g, 102.0 mmol), a few crystals of iodine, and 15 mL of THF. The mixture was heated until the iodine color was discharged, then cooled to 0 °C. A solution of allyl chloride (2.8 mL, 34.35 mmol) in 20 mL of THF was added slowly dropwise over about 1.5 h. After the addition was complete, the gray solution was warmed to reflux briefly and then cooled back down to 0 °C. This Grignard solution was added rapidly dropwise via cannula to a solution of dibromide **15** (4.75 g, 16.96 mmol) in 35 mL of THF that was stirring at 0 °C. After 30 min, the solution was quenched cautiously with saturated aqueous NH_4Cl and partitioned between MTBE and, sequentially, water and brine. The combined organic extract was dried (Na_2SO_4) and evaporated to give crude **16** (3.96 g, 97% of expected) as a pale-yellow oil, TLC R_f (10% MTBE/petroleum Ether) = 0.69. The NMR spectrum of **16** indicated that it was 95% pure. ^1H NMR ($CDCl_3$, δ): 7.33 (d, *J* = 8.53 Hz, 1H), 6.69 (d, *J* = 3.07 Hz, 1H), 6.55 (dd, *J* = 8.53, 3.07 Hz, 1H), 5.80 (m, 2H), 5.00 (d, *J* = 17.1 Hz, 1H), 4.93 (d, *J* = 10.2 Hz, 2H), 3.70 (s, 3H), 2.70 (m, 2H), 2.29 (m, 2H). ^{13}C NMR ($CDCl_3$, δ): (u) 158.8, 142.0, 115.2, 114.9, 35.8, 33.8; (d) 137.6, 133.2, 116.1, 112.4, 55.4. IR (cm^{-1}): 2934, 1571, 1472, 1241, 1017. MS (*m*/*z*, %): 63 (21), 77 (44), 91 (38), 105 (15), 120 (32), 147 (10), 161 (100), 171 (16), 199 (84), 201 (82), 240 (41), 242 (40). HRMS calcd for $C_{11}H_{13}BrO$: 240.0149, found 240.0136.

Approximately 5% of the biaryl could be separated as a white solid, TLC R_f (10% MTBE/petroleum ether) = 0.53. ^1H NMR ($CDCl_3$, δ): 7.44 (d, *J* = 8.53 Hz, 2H), 6.72 (d, *J* = 3.07 Hz, 2H), 6.65 (dd, *J* = 8.53, 3.07 Hz, 2H), 3.78 (s, 6H), 3.96 (s, 4H).

A round-bottom flask was charged with a 2 M solution of BH_3·DMS in THF (15 mL, 30 mmol) and cooled to 0 °C. A solution of cyclohexene (6.0 mL, 59.22 mmol) in 15 mL of THF was added dropwise. The cooling bath was removed and the mixture was allowed to stir at ambient temperature for 1 h. A solution of crude alkene **16** (15.42 mmol theoretical) in 15 mL of THF was added in one portion and the resultant mixture was allowed to stir for 2 h. At this time, the mixture was quenched by cautious addition of ethanol (17 mL), 3 M aqueous NaOH (17 mL), and 30% H_2O_2 (51 mL) and allowed to stir overnight. The mixture was partitioned between saturated aqueous NH_4Cl and MTBE, dried over Na_2SO_4, and evaporated. Bulb-to-bulb distillation (60 °C at 0.5 mmHg) of the residue afforded **17** (5.6 g. 140% of expected) as a yellow oil. The material is contaminated with residual cyclohexanol but was used directly in the next step. An analytically pure sample was obtained by chromatography, TLC R_f (50% MTBE/petroleum ether) = 0.27. ^1H NMR ($CDCl_3$, δ): 7.38 (d, *J* = 8.53 Hz, 1H), 6.76, (d, *J* = 3.07 Hz, 1H), 6.61 (dd, *J* = 8.53, 3.07 Hz, 1H), 3.76 (s, 3H), 3.70 (m, 2H), 2.72 (m, 2H), 1.68 (m, 3H).

^{13}C NMR ($CDCl_3$, δ): (u) 158.7, 142.4, 114.7, 62.4, 35.9, 32.1, 25.9; (d) 133.1, 115.9, 112.9, 55.3. IR (cm^{-1}): 3347 (b), 1595, 1572, 1472, 1241. MS (*m*/*z*, %): 77 (24), 91 (25), 105 (11), 121 (47), 146 (9), 161 (100), 178 (8), 199 (28), 201 (26), 212 (35), 214 (30), 258 (36), 260 (31). HRMS calcd for $C_{11}H_{15}BrO_2$: 258.0255, found 258.0255.

The crude **17** (15.42 mmol theoretical) was diluted with 140 mL of dry ether and cooled to 0 °C. $NiCl_2$(dppp) (180 mg, 0.314 mmol) was added to produce a red suspension. A 3 M solution of MeMgBr in ether (11.3 mL, 33.9 mmol) was added dropwise to produce, initially, a milky white precipitate. After about two-thirds of the Grignard had been added, the red particles became sticky and adhered to the walls of the flask. As the solution was warmed to reflux, the red particles were dissolved and the liquid turned yellow. The reaction was monitored over the next 84 h as additional amounts of catalyst and Grignard were added to complete the reaction. The mixture was cooled and quenched with saturated aqueous NH_4Cl solution, extracted with ether, and washed with brine. The organic layer was dried over Na_2SO_4 and the solvent removed in vacuo. Bulb-to-bulb distillation (170−180 °C at 0.5 mmHg) afforded **18** (2.27 g, 76% yield from dibromide) as a clear oil, TLC R_f (50% MTBE/petroleum ether) = 0.34. ^{1}H NMR ($CDCl_3$, δ): 7.03 (d, J = 8.19 Hz, 1H), 6.71 (d, J = 2.73 Hz, 1H), 6.65 (dd, J = 8.19, 2.73 Hz, 1H), 3.77 (s, 3H), 3.67 (d, J = 6.94 Hz, 2H), 2.59 (m, 2H), 2.22 (s, 3H), 1.64 (m, 2H). ^{13}C NMR ($CDCl_3$, δ): (u) 157.7, 141.2, 127.9, 62.2, 33.8, 29.6; (d) 130.8, 114.6, 110.7, 55.1, 18.2. IR (cm^{-1}): 3361 (br), 2936, 1609, 1499, 1252, 1036. MS (*m*/*z*, %): 65 (11), 77 (16), 79 (11), 91 (28), 105 (10), 121 (35), 123 (27), 135 (100), 136 (43), 148 (20), 149 (11), 161 (9), 176 (8), 194 (53). HRMS calcd for $C_{12}H_{18}O_2$: 194.1307, found 194.1301.

The material was contaminated with about 5% of the corresponding desmethyl compound, which could not be efficiently separated by column chromatography. ^{1}H NMR (δ): 7.18 (t, 7.85 Hz, 1H), 6.7−6.8 (m, 2 H), 3.77 (s, 3H). ^{13}C NMR (δ): (u) 159.4, 143.9; (d) 129.1, 120.7, 114.1, 110.8, 55.0.

Enone 20. The Dess−Martin periodinane (6.80 g, 16.03 mmol) was suspended in 40 mL of dry CH_2Cl_2 and a solution of arylbutanol **18** (3.10 g, 15.96 mmol) in 40 mL of CH_2Cl_2 was added to it. The white precipitate was dissolved immediately but reformed slowly. After 30 min at ambient temperature, the reaction was partitioned between ether and, sequentially, 1:1 10% aqueous $Na_2S_2O_3$/saturated aqueous $NaHCO_3$, water, and brine. The aqueous washes were back extracted with ether and washed with water and brine. The combined organic extracts were dried over Na_2SO_4, filtered through silica, and evaporated to give crude **19** (3.64 g, 119% of expected) as a pale-yellow oil, TLC R_f (50% MTBE/petroleum ether) = 0.60. A sample was further purified by chromatography for analysis. ^{1}H NMR ($CDCl_3$, δ): 9.77 (t, J = 1.71 Hz, 1H), 7.05 (d, J = 8.19 Hz, 1H), 6.68 (m, 1H), 6.66 (d, J = 2.73 Hz, 1H), 3.77 (s, 3H), 2.60 (m, 2H), 2.50 (dt, J = 7.17, 1.71 Hz, 2H), 2.23 (s, 3H), 1.91 (m, 2H). ^{13}C NMR ($CDCl_3$, δ): (u) 157.1, 140.6, 127.9, 43.3, 32.6, 22.3; (d) 202.3, 131.0, 114.7, 111.0, 55.1, 18.3. IR (cm^{-1}): 2945, 1723, 1609, 1504, 1252. MS (*m*/*z*, %): 65 (17), 77 (23), 91 (41), 105 (13), 121 (42), 135 (100), 135 (50), 148 (45), 164 (26), 192 (39). HRMS calcd for $C_{12}H_{16}O_2$: 192.1150, found 192.1158.

The crude aldehyde **19** (15.95 mmol theoretical) was dissolved in 25 mL of THF and cooled to 0 °C. A 1 M solution of commercial vinylmagnesium bromide (25 mL, 25.00 mmol) in THF was added dropwise. After 1 h at 0 °C, the mixture was partitioned between saturated aqueous NH_4Cl and MTBE, dried over Na_2SO_4 and evaporated. Silica gel chromatography afforded the vinyl carbinol (2.02 g, 57% yield from alcohol **18**) and alcohol **18** (0.48 g, 15% recovered). For the vinyl carbinol, TLC R_f (50% MTBE/petroleum ether) = 0.56. ^{1}H NMR ($CDCl_3$, δ): 7.04 (d, J = 8.19 Hz, 1H), 6.70 (d, J = 2.73 Hz, 1H), 6.65 (dd, J = 8.19, 2.73 Hz, 1H), 5.87 (ddd, J = 17.07, 10.24, 6.49, 1H), 5.23 (dt, J = 17.07, 1.37 Hz, 1H), 5.11 (dt, J = 10.24, 1.37 Hz, 1H), 4.14 (m, 1H), 3.78 (s, 3H), 2.7−2.5 (m, 2H), 2.23 (s, 3H), 1.7−1.5 (m, 4H). ^{13}C NMR ($CDCl_3$, δ): (u) 157.7, 141.7, 127.9, 114.8, 36.8, 33.3, 25.9; (d) 141.1, 130.8, 114.7, 110.7, 73.2, 55.2, 18.4. IR (cm^{-1}): 3415 (br), 2934, 1609, 1499, 1251.

The crude vinyl carbinol was dissolved in 30 mL of CH_2Cl_2 and Dess−Martin periodinane (3.90 g, 9.20 mmol) was added as a suspension in 20 mL of CH_2Cl_2. The reaction warmed to reflux briefly on its own accord. After 30 min, the mixture was evaporated onto silica gel and chromatographed to afford enone **20** (1.72 g, 86% from the vinyl carbinol) as a clear oil. The three step yield (from alcohol **18**) was 59% based on starting material not recovered. For **20**, TLC R_f (50% MTBE/petroleum ether) = 0.65. ^{1}H NMR ($CDCl_3$, δ): 7.04 (d, J = 8.19 Hz, 1H), 6.69 (d, J = 2.73 Hz, 1H), 6.65 (dd, J = 8.19, 2.73 Hz, 1H), 6.35 (dd, J = 17.4, 10.2 Hz, 1H), 6.19 (dd, J = 17.8, 1.02 Hz, 1H), 5.80 (dd, J = 10.2, 1.02 Hz, 1H), 3.76 (s, 3H), 2.64 (t, J = 7.17 Hz, 2H), 2.59, (m, 2H), 2.23, (s, 3H), 1.90 (m, 2H). ^{13}C NMR ($CDCl_3$, δ): (u) 200.4, 157.7, 140.9, 128.0, 127.8, 38.1, 32.6, 23.9; (d) 136.4, 130.8, 114.6, 110.9, 55.1, 18.2. IR (cm^{-1}): 2945, 1681, 1612, 1500, 1253. MS (*m*/*z*, %): 91 (12), 135 (13), 136 (10), 148 (100), 218 (25). HRMS calcd for $C_{14}H_{18}O_2$: 218.1307, found 218.1303.

The three-step yield for the same procedure using freshly prepared vinylmagnesium bromide (0.5M, 1.5 equiv) was 63%. There was no recovered alcohol **18**.

The enone **20** prepared by the procedure outlined above was contaminated with about 5% of the desmethyl enone **22**. These could be separated by formation of the crystalline phenoxy ketone **21**.

Phenoxy Ketone 21. NaH (25 mg, 1.1 mmol) was added in small portions to a solution of phenol (1 mL) in THF (1 mL). After 30 min, enone **20** (100 mg, 0.458 mmol) was added as a solution in 1 mL of THF. The mixture was allowed to stir at ambient temperature for 3 h before being partitioned between saturated aqueous NH_4Cl and MTBE. The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was chromatographed and recrystallized (10% EtOAc/petroleum ether) to yield **21** (109 mg, 76%) as a white solid, mp 44.0−45.0 °C. TLC R_f (20% MTBE/petroleum ether) = 0.41. ^{1}H NMR ($CDCl_3$, δ): 7.3 (m, 2H), 7.04 (d, J = 8.19 Hz, 1H), 6.94 (t, J = 7.17 Hz, 1H), 6.88 (d, J = 8.53 Hz, 2H), 6.69 (d, J = 2.73 Hz, 1H), 6.66 (dd, J = 8.19, 2.73 Hz, 1H), 4.22 (t, J = 6.14 Hz, 2H), 3.76 (s, 3H), 2.86 (t, J = 6.14 Hz, 2H), 2.6 (m, 4H), 2.23 (s, 3H), 1.9 (m, 2H). ^{13}C NMR ($CDCl_3$, δ): (u) 208.3, 158.5, 157.7, 140.9, 128.0, 62.8, 42.8, 42.1, 32.6, 23.6, 18.3; (d) 130.9, 129.4, 120.9, 114.7, 114.4, 110.9, 55.2, 18.3. IR (cm^{-1}): 2939, 1714, 1600, 1496, 1246. HRMS calcd for $C_{12}H_{24}O_3$: 312.1726, found 312.1720.

Methylated D-Ring Chiron (23). To a solution of cyclopentanone **2** (2.00 g, 7.93 mmol) in 40 mL of acetone was added methyl iodide (1.0 mL, 16.06 mmol) and K_2CO_3 (4.0 g, 28.94 mmol). The mixture was heated to reflux for 5 h before being cooled and partitioned between saturated aqueous NH_4Cl and EtOAc. The organic layer was dried over Na_2SO_4, filtered through silica, and evaporated. The residue was chromatographed to yield the C-methylated compound **23** (1.80 g, 85%) as a clear oil, TLC R_f (10% MTBE/petroleum ether) = 0.40. ^{1}H NMR ($CDCl_3$, δ): 5.08 (m, 1H), 3.67 (s, 3H), 2.57 (m, 1H), 2.24 (m, 1H), 2.15 (m, 1H), 2.04 (m, 1H), 2.0−1.7 (m, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.49 (m, 2H), 1.40 (2, 3H), 1.15 (m, 1H), 1.01 (d, J = 6.83 Hz). ^{13}C NMR ($CDCl_3$, δ): (u) 216.9, 171.4, 131.4, 59.2, 37.5, 34.1, 25.1, 24.5; (d) 124.3, 55.0, 51.8, 35.2, 25.6, 21.3, 18.2, 17.6. IR (cm^{-1}): 2967, 1753, 1732, 1222, 1172. MS (*m*/*z*, %): 67 (35), 82 (26), 97 (41), 109 (100), 123 (38), 137 (31), 160 (28), 188 (56), 219 (10), 233 (42), 248 (89), 266 (2). HRMS calcd for $C_{16}H_{26}O_3$: 266.1882, found 266.1882.

Also isolated was the O-methylated compound (0.22 g, 10% yield) as a clear oil, TLC R_f (10% MTBE/petroleum ether) = 0.07. ^{1}H NMR ($CDCl_3$, δ): 5.04 (m, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 2.97 (m, 1H), 2.58 (m, 2H), 2.02 (m, 1H), 2.0−1.7 (m, 3H), 1.66 (s, 3H), 1.58 (s, 3H), 1.7−1.6 (m, 1H), 1.32 (m, 2H), 0.89 (d, J = 6.83 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 169.4, 165.6, 130.9, 106.3, 30.5, 30.3, 26.1, 20.6; (d) 124.9, 57.5, 50.6, 47.7, 34.6, 25.6, 17.7, 17.5. IR (cm^{-1}): 2951, 1690, 1627, 1376, 1233, 1060. MS (*m*/*z*, %): 95 (12), 155 (100), 182 (10), 195 (13), 266 (16). HRMS calcd for $C_{16}H_{26}O_3$: 266.1882, found 266.1901.

The O-alkylated material (0.22 g, 0.827 mmol), as a solution in 30 mL of THF, could be recycled by brief exposure to concentrated aqueous HCl (1 mL). After 15 min, the mixture

was filtered through silica, evaporated, and chromatographed to give **2** (0.11 g, 53%) as clear oil. The overall yield of **23** then became 90% based on starting material not recovered.

Dimethylhexenyl-methylcyclopentanone (25). To a solution of methylated compound **23** (1.80 g, 6.76 mmol) in 67 mL of HMPA was added NaCN (1.32 g, 26.93 mmol). The mixture was warmed to 75−80 °C for 5 h before being partitioned between MTBE and, sequentially, saturated aqueous $NaHCO_3$ and water. The organic layer was evaporated. When chromatographed at this stage, the mixture was found to contain about 10% of the diastereomeric cyanohydrins **24** in roughly equal amounts, TLC R_f (10% MTBE/petroleum ether) = 0.16. ^{1}H NMR ($CDCl_3$, δ): 5.08 (m, 1H), 2.35 (br s, 1H), 2.2−1.7 (m, 6H), 1.69 (s, 3H), 1.60 (s, 3H), 1.6−1.5 (m, 2H), 1.3−1.2 (m, 2H), 1.10 (d, J = 6.83 Hz, 3H), 0.93 (m, 1H), 0.80 (d, J = 6.83 Hz, 3H). IR (cm^{-1}): 3438 (br), 2239 (w).

TLC R_f (10% MTBE/petroleum ether) = 0.14. ^{1}H NMR ($CDCl_3$, δ): 5.08 (m, 1H), 2.66 (br s, 1H), 2.23 (m, 1H), 2.1−1.8 (m, 4H), 1.8−1.4 (m, 4H), 1.69 (s, 3H)1.61 (s, 3H), 1.4−1.1 (m, 2H), 1.16 (d, J = 6.83 Hz, 3H), 0.83 (d, J = 6.83 Hz, 3H). IR (cm^{-1}): 3432 (br), 2239 (w).

The crude residue from decarbomethoxylation was instead diluted with 20 mL of 10% KOH in MeOH. After 5 min at ambient temperature, the mixture was partitioned between petroleum ether and, sequentially, water and brine. The organic layer was dried over Na_2SO_4 and evaporated. The residue was chromatographed to give ketone **25** (1.06 g, 75%) as a clear oil, TLC R_f (10% MTBE/petroleum ether) = 0.46. ^{1}H NMR ($CDCl_3$, δ): 5.10 (m, 1H), 2.30 (dd, J = 18.43, 8.53 Hz, 1H), 2.10 (m, 2H), 2.0−1.8 (m, 3H), 1.69 (s, 3H), 1.62 (s, 3H), 1.7−1.6 (m, 2H), 1.6−1.4 (m, 2H), 1.15 (m, 1H), 1.08 (d, J = 6.83 Hz, 3H), 1.00 (d, J = 6.49 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 221.6, 131.5, 37.2, 32.3, 25.8, 23.1; (d) 124.4, 50.1, 46.8, 34.0, 25.6, 17.6, 13.8. IR (cm^{-1}): 2963, 1742, 1456, 1378, 1159. MS (*m*/*z*, %): 55 (91), 69 (87), 82 (34), 97 (100), 110 (17), 120 (21), 137 (32), 138 (27), 152 (5), 208 (71). HRMS calcd for $C_{14}H_{24}O$: 208.1827, found 208.1833. Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.83; H, 11.93. $[\alpha]^{17}_D$ = −48.51 (*c* 1.14, EtOH).

CD Enone 26 from the A-Ring Phenyl Ether 21. A solution of 5 M NaOMe in MeOH (0.14 mL, 0.70 mmol) was added to a solution of ketone **25** (79.6 mg, 0.382 mmol) in 2 mL of MeOH at 0 °C. After 10 min, a solution of A-ring phenyl ether **21** (109 mg, 0.349 mmol) in 10 mL of MeOH was added dropwise. The solution was allowed to stir at ambient temperature for 3 h and then warmed to reflux for 26 h. The cooled solution was then partitioned between saturated aqueous NH_4Cl and ether. The organic layer was dried over Na_2SO_4 and evaporated. The residue was chomatographed to yield recovered **25** (23.1 mg, 29%), and after a base wash (3 M aqueous NaOH, to remove phenol), the CD enone **26** (82.7 mg, 78% based on **25** not recovered) as a clear oil, TLC R_f (20% MTBE/petroleum ether) = 0.45. ^{1}H NMR ($CDCl_3$, δ): 7.01 (d, J = 8.19 Hz, 1H), 6.7−6.6 (m, 2H), 5.08 (m, 1H), 3.76 (s, 3H), 2.7−2.5 (m, 3H), 2.5−2.3 (m, 3H), 2.28 (s, 3H), 2.2−2.1 (m, 3H), 2.02 (m, 1H), 2.0−1.8 (m, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.6−1.2 (m, 4H), 1.11 (m, 1H), 1.02 (s, 3H), 0.97 (d, J = 6.83 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 198.3, 174.3, 157.5, 141.4, 131.3, 130.2, 128.0, 45.1, 36.6, 35.6, 33.6, 32.1, 27.4, 27.0, 26.6, 24.5; (d) 130.6, 124.6, 115.4, 110.8, 55.8, 55.1, 33.7, 25.7, 18.7, 18.3, 17.6, 16.4. IR (cm^{-1}): 2961, 1661, 1503, 1455, 1251.

The bicyclic enone **26** was contaminated with ∼10% of its regioisomer **27** that could not be separated by chromatography. This regioisomer was identified by its diagnostic resonance in the ^{1}H NMR (δ 0.86, d).

Copper Hydride Reduction. Copper cyanide (220 mg, 2.46 mmol) was suspended in THF (10 mL) and chilled to −20 °C. A 2.25 M solution of *n*-BuLi in hexanes (1.1 mL, 2.2 mmol) was added dropwise. The brown solution was stirred at −20 °C for 30 min, and then the temperature was lowered to −50 °C. A 1 M solution of DIBAL in hexanes (4.9 mL, 4.9 mmol) was added slowly dropwise. The dark brown solution was allowed to stir at −50 °C for 1 h before the CD enone **26** (99.0 mg, 0.242 mmol) was added as a solution in 1:1 THF/HMPA (3.6 mL). The temperature was raised to −20 °C over the next 10 min and then the mixture was allowed to stir at −20 °C for 1 h. The reaction was quenched with a solution of 1:1 saturated aqueous NH_4Cl and 3 M aqueous HCl (20 mL) at −20 °C and allowed to warm to ambient temperature over 30 min. The mixture was filtered and extracted with MTBE. The organic layer was evaporated and then partitioned between MTBE and, sequentially, 1 M aqueous HCl, water, and brine. The organic layer was dried (Na_2SO_4), filtered through silica gel, and evaporated to yield the crude reduction product (105 mg) as a pale-yellow oil.

A 0.1 M solution of the Dess−Martin periodinane in CH_2Cl_2 (1 mL, 0.1 mmol) was added to a solution of the crude oil from reduction in CH_2Cl_2. After 30 min, and again after 1 h, additional portions (1 mL each) of periodinane were added. After 2 h, the reaction was complete (TLC). A solution of 1:1 10% aqueous $Na_2S_2O_4$/1 M aqueous NaOH (20 mL) was added and the mixture was allowed to stir for 30 min. The mixture was then partitioned between MTBE and, sequentially, water and brine. The organic layer was dried (Na_2SO_4), filtered through silica, and evaporated to yield the crude oxidation product (104 mg) as a yellow oil.

The crude oil from oxidation was dissolved in a 1:1:4 solution of 1% aqueous KOH/MeOH/THF (20 mL) and stirred at ambient temperature for 1 h. The mixture was partitioned between MTBE and saturated aqueous NH_4Cl. The organic layer was evaporated and then partitioned between MTBE and, sequentially, water and brine. The organic layer was evaporated and chromatographed to yield the recovered enone **26** (50.7 mg, 51%) and the *trans*-hydrindanone **32** (26.1 mg, 52% based on **26** not recovered) as a clear oil, TLC R_f (10% MTBE/petroleum ether) = 0.42. ^{1}H NMR ($CDCl_3$, δ): 7.03 (d, J = 8.53 Hz, 1H), 6.72 (d, J = 2.73 Hz, 1H), 6.64 (dd, J = 8.53, 2.73 Hz, 1H), 5.08 (m, 1H), 3.77 (s, 3H), 2.70 (m, 1H), 2.6−2.2 (m, 4H), 2.27 (s, 3H), 2.17 (m, 1H), 2.00 (m, 2H), 1.9−1.5 (m, 6H), 1.69 (s, 3H), 1.61 (s, 3H), 1.5−1.0 (m, 6H), 0.98 (s, 3H), 0.95 (d, J = 6.49 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 213.0, 157.7, 142.3, 131.2, 128.1, 42.8, 38.5, 38.3, 35.7, 31.2, 29.0, 27.7, 25.1, 24.6; (d) 130.8, 124.9, 114.5, 110.8, 55.22, 55.21, 55.0, 50.4, 35.4, 25.7, 18.4, 18.3, 17.6, 11.5. IR (cm^{-1}): 2952, 2869, 1708, 1500, 1251.

Also isolated was a diene (11.0 mg, 11%), presumably formed from elimination of the 1,2 reduction product, as a pale-yellow oil, TLC R_f (10% MTBE/petroleum ether) = 0.73. ^{1}H NMR ($CDCl_3$, δ): 7.04 (d, J = 8.53 Hz, 1H), 6.70 (d, J = 2.73 Hz, 1H), 6.65 (dd, J = 8.53, 2.73 Hz, 1 H), 5.51 (m, 2H), 5.12 (m, 1H), 3.78 (s, 3H), 2.7 (m, 2H), 2.5−1.8 (m, 9H), 2.25 (s, 3H), 1.69 (s, 3H), 1.62 (s, 3H), 1.6 (m, 1H), 1.44 (m, 2H), 1.1 (m, 1H), 0.98 (d, J = 6.14, 3H), 0.88 (s, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 157.8, 148.7, 142.1, 133.0, 131.1, 127.9, 45.8, 36.4, 36.1, 35.6, 33.6, 33.1, 24.6, 23.9; (d) 130.7, 125.1, 124.4, 119.1, 114.7, 110.8, 56.9, 55.2, 33.8, 25.7, 18.8, 18.4, 17.6, 15.5. IR (cm^{-1}): 2926, 1609, 1503, 1250, 1046.

Astrogorgiadiol Methyl Ether (36). A sample of 5% Pd/C (20 mg) was added to a solution of the *trans*-hydrindanone **32** (38.3 mg, 0.0933 mmol) in ethanol (10 mL). Three times in succession, the flask was evacuated and refilled with H_2. After 2 h at ambient temperature and pressure, the mixture was filtered and evaporated. Column chromatography afforded the saturated *trans*-hydrindanone (32.4 mg, 84%) as a clear oil, TLC R_f (10% MTBE/petroleum ether) = 0.42. ^{1}H NMR ($CDCl_3$, δ): 7.03 (d, J = 8.53 Hz, 1H), 6.72 (d, J = 2.73 Hz, 1H), 6.64 (dd, J = 8.53, 2.73 Hz, 1H), 3.77 (s, 3H), 2.7 (m, 1H), 2.6−2.2 (m, 4H), 2.27 (s, 3H), 2.17 (m, 1H), 1.97 (m, 1H), 1.9−0.8 (m, 16H), 0.98 (s, 3H), 0.93 (d, J = 6.49 Hz, 3H), 0.871 (d, J = 6.49, 3H), 0.867 (d, J = 6.49 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 213.0, 157.7, 142.3, 128.1, 42.8, 39.4, 38.5, 38.3, 35.8, 31.2, 29.0, 27.7, 25.1, 23.7; (d) 130.8, 114.5, 110.8, 55.22, 55.20, 55.0, 50.4, 35.6, 28.0, 22.8, 22.5, 18.5, 18.3, 11.5.

A 1.0 M solution of L-Selectride in THF (160 μL, 0.16 mmol) was added dropwise to a solution of the *trans*-hydrindanone (32.4 mg, 0.0785 mmol) in THF (2 mL) at −78 °C. After 2 h, the starting material was 90% consumed (TLC). Additional L-Selectride (80 μL, 0.080 mmol) was added. After an additional 1 h at −78 °C, the mixture was quenched with acetone (400 μL) and allowed to warm to ambient temperature. The

solution was partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed to yield astrogorgiadiol methyl ether **36** (17.8 mg, 47% from **32**) as a clear oil, TLC R_f (20% MTBE/petroleum ether) = 0.47. ^{1}H NMR ($CDCl_3$, δ): 7.04 (d, J = 8.19 Hz, 1H), 6.72 (d, J = 2.73 Hz, 1H), 6.65 (dd, J = 8.19, 2.73 Hz, 1H), 4.04 (bs, 1H), 3.77 (s, 3H), 2.7 (m, 1H), 2.4 (m, 1H), 2.24 (s, 3H), 1.9−0.9 (m, 22H), 0.92 (d, J = 6.49, 3H), 0.863 (d, J = 6.49 Hz, 3H), 0.858 (d, J = 6.49 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 157.8, 142.5, 127.9, 42.9, 39.5, 36.1, 34.1, 31.1, 30.3, 30.1, 27.7, 24.4, 23.7; (d) 130.8, 114.5, 110.7, 67.2, 56.2, 55.2, 47.7, 40.9, 35.7, 28.0, 22.8, 22.5, 18.7, 18.4, 11.0. IR (cm^{-1}): 3453 (br), 2932, 2867, 1499, 1251. HRMS calcd for $C_{28}H_{46}O_2$: 414.3500, found 414.3487.

Astrogorgiadiol (3). The aryl methyl ether **36** (7.7 mg, 18.6 mmol) was dissolved in CH_2Cl_2 (1 mL). Triethylsilane (60 μL, 376 mmol) and a 21 mM solution of tris(pentafluorophenyl) boron (100 μL, 1.95 mmol) in CH_2Cl_2 were added. After 1 h, the reaction was quenched with triethylamine (200 μL). The solution was filtered through silica and evaporated. The residual oil was diluted with 1 M tetrabutylammonium fluoride (1 mL) in THF. After 24 h, the solvent was removed in vacuo and the residual oil was partitioned between water and ether. The organic layer was evaporated and chromatographed to yield **3** (6.3 mg, 85% yield) as a clear oil, TLC R_f (30% MTBE/petroleum ether) = 0.23. $[\alpha]^{18}_D$ = −7.4 (*c* 0.095, $CHCl_3$). ^{1}H NMR (C_6D_6, δ): 6.93 (d, J = 8.19 Hz, 1H), 6.60 (d, J = 2.73 Hz, 1H), 6.45 (dd, J = 8.19, 2.73 Hz, 1H), 4.09 (bs, 1H), 3.8 (m, 1H), 2.7 (m, 1H), 2.3 (m, 1H), 2.22 (s, 3H), 1.9−0.8 (m, 22H), 0.98 (d, J = 6.49 Hz, 3H), 0.925 (d, J = 6.49 Hz, 3H), 0.923 (d, J = 6.49 Hz, 3H), 0.59 (s, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 155.2, 143.3, 43.4, 40.3, 37.0, 34.8, 31.6, 31.3, 31.0, 28.5, 25.1, 24.7; (d) 131.7, 116.4, 113.2, 67.2, 56.8, 48.1, 41.6, 36.5, 28.8, 23.4, 23.1, 19.3, 11.6, 0.4. IR (cm^{-1}): 3387 (br), 2932, 2869, 1463. The ^{1}H NMR spectrum of this substance was superimposable on those provided.[1,2]

Acknowledgment. We thank M. P. Doyle and H. M. L. Davies for providing samples of their enantiomerically pure rhodium catalysts. We thank the Takasago Corporation for a generous gift of (*R*)-citronellal and N. Fusetani and G. Sodano for sharing spectra with us. This work is dedicated to Professor Gilbert Stork on the occasion of his 80th birthday.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001519G