further purification. Homoallylic alcohol **26** (120 mg, 0.25 mmol) was then dissolved in ethanol (1 mL) and the solution added to a flask containing 10% palladium on activated carbon (68 mg, 0.06 mmol Pd) that had previously been charged with catalyst, evacuated, and flushed with hydrogen via balloon delivery. The hydrogenation continued 36 h under 1 atm hydrogen. The mixture was then filtered, and saturated alcohol **27** was obtained after concentration and purification by SGC to provide a colorless oil: 60 mg (50%); R_f (50% ethyl acetate/hexanes) 0.5; $[\alpha]_D$ = +15° (*c* 3.3, $CHCl_3$); ^1H NMR (300 MHz) δ 7.85 (d, *J* = 7.1 Hz, 2 H, *o*-$PhSO_2$), 7.60 (m, 3 H, *m*-$PhSO_2$), 3.90 (d, *J* = 3.8 Hz, 1 H, C7aH), 3.67 (t, *J* = 7.1 Hz, 2 H C5H), 2.86 (m, 1 H, C7H), 2.0–1.6 (m, 6 H), 1.63 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.45–1.32 (m, 3 H), 1.06 (d, *J* = 6.2 Hz, 3 H, C7CH3), 0.02 (s, 9 H, TMS); ^{13}C NMR (75 MHz) δ 141.1 (e), 133.4 (o), 129.6 (o), 128.7 (o), 106.6 (e), 83.7 (o), 83.1 (e), 66.3 (e), 63.1 (e), 46.6 (o), 32.6 (e), 31.0 (e), 30.4 (e), 29.8 (e), 28.4 (o), 27.2 (o), 26.6 (o), 26.2 (e), 21.0 (o), 18.7 (o), 0.2 (o); mass spectrum, *m/z* (relative intensity) Cl 483 (100), 425 (20), 411 (10), 143 (60); exact mass for $C_{25}H_{42}O_5SSi$ + H (M + H) calcd 483.2601, found 483.2583.

(+)-5-[(3a*R*,4*R*,5*S*,7*S*,7a*S*)-Hexahydro-2,2,3a,7-tetramethyl-5-(phenylsulfonyl)-5-(trimethylsilyl)-1,3-benzodioxol-4-yl]-1-pentyl *p*-Toluenethiosulfonate (30). **30** was prepared by use of procedure C from alcohol **27** (80 mg, 0.17 mmol), yielding the desired *p*-toluenethiosulfonate **30** as a colorless oil: 50 mg (48%, for the three steps); R_f (20% ethyl acetate/hexanes) 0.25; $[\alpha]_D$ = +8.3° (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz) δ 7.90–7.30 (m, 9 H, ArH), 3.79 (d, *J* = 2.4 Hz, C7aH), 3.00 (t, *J* = 7.1 Hz, CH_2S), 2.85 (m, 1 H, C7H), 2.45 (s, 3 H, CH_3ArSO_2), 2.30 (m, 2 H), 1.90–1.60 (m, 5 H), 1.62 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.4–1.2 (m, 3 H), 1.03 (d, *J* = 7.1 Hz, 3 H, C7CH_3), 0.0 (s, 9 H, TMS); ^{13}C NMR (75 MHz) δ 144.6 (e), 142.1 (e), 141.1 (e), 133.4 (o), 129.8 (o), 129.5 (o), 128.7 (o), 127.0 (o), 106.6 (e), 83.7 (o), 82.9 (e), 66.2 (e), 46.6 (o), 36.1 (e), 31.0 (e), 30.2 (e), 29.7 (e), 29.6 (e), 28.6 (e), 28.4 (o), 27.2 (o), 26.1 (o), 21.6 (o), 21.0 (o), 18.7 (o), 0.2 (o).

(+)-(3a*S*,4*S*,5a*R*,11a*R*,11b*R*)-5a-(Phenylsulfonyl)-2,2,4,11b-tetramethyl-6-thiacyclooctano[2,3-*e*]-1,3-benzodioxole *S*,*S*-Dioxide (32). **32** was prepared by use of procedure D.1.2 followed by procedure D.2.2 with *p*-toluenethiosulfonate **30** (18.0 mg 0.028 mmol), yielding bis(sulfone) **32** as a colorless foam: 8.0 mg (65%); R_f (20% ethyl acetate/hexanes) 0.30; $[\alpha]_D$ = +21.0° (*c* 0.40, $CHCl_3$); ^1H NMR (300 MHz) δ 8.02 (d, *J* = 7.4 Hz, 2 H, *o*-$PhSO_2$), 7.67 (t, *J* = 7.4 Hz, 1 H, *p*-$PhSO_2$), 7.53 (t, *J* = 7.4 Hz, 2 H, *m*-$PhSO_2$), 4.83 (ddd, *J* = 4.6, 11.5, 16.2 Hz, 1 H, C7H), 3.86 (br s, 1 H, C3aH), 3.43 (dt, *J* = 2.8, 18.5 Hz, 1 H, C7H), 2.85 (br t, 1 H, C11H), 2.67 (t, *J* = 11.5 Hz, C5H), 2.55 (m, 3 H), 2.20 (m, 1 H), 2.00 (m, 1 H), 1.85 (m, 2 H), 1.68 (s, 3 H, CH_3), 1.55 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 1.3 (m, 4 H), 0.92 (d, *J* = 6.9 Hz, C4CH_3); mass spectrum, *m/z* (relative intensity) Cl 457 (15), 399 (100), 143 (12); exact mass for $C_{22}H_{32}O_6S_2$ + H (M + H) calcd 457.1719, found 457.1716.

(3a*S*,4*S*,10a*S*,10b*R*)-(6*Z*)-Hexahydro-2,2,4,10b-tetramethylcyclohept-6-eno[2,3-*e*]-1,3-benzodioxole (33). **33** was prepared by use of procedure E (and heating the solution to reflux for 15 min) from bis(sulfone) **32** (14.0 mg, 0.032 mmol) to yield a colorless oil olefin: 5.0 mg (65%); R_f (10% ethyl acetate/hexanes) 0.5; ^1H NMR (300 MHz) δ 5.48 (br t, 1 H, C6H), 3.67 (d, *J* = 3.5 Hz, C3aH), 2.42 (m, 2 H), 2.10–1.20 (10 H), 1.55 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.05 (d, *J* = 7.0 Hz, 3 H, C4CH_3); mass spectrum, *m/z* (relative intensity) Cl 251 (19), 193 (100), 175 (20); exact mass for $C_{16}H_{26}O_2$ + H (M + H) calcd 251.2011, found 251.2011.

Acknowledgment. We thank the NIH (GM 32693) for its financial support of this work. Access to high-field NMR was provided through the Purdue University Biological Magnetic Resonance Laboratory (NIH RR0107, NSF BBS8714258, and NSF 8703974). Ms. Arlene Rothwell is also gratefully acknowledged for providing mass spectral services.

Supplementary Material Available: Experimental procedures and the procedure for an alternate synthesis of model substrates **3a** and **3c** (4 pages). Ordering information is given on any current masthead page.

Asymmetric Total Synthesis of Dibenzocyclooctadiene Lignans (-)-Schizandrin and (-)-Isoschizandrin. Structure Revision of (+)-Isoschizandrin

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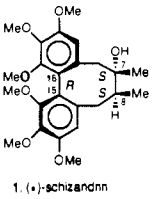
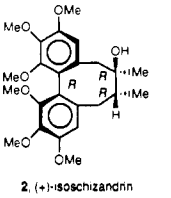
Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. *Received April 16, 1990*

Abstract: The oxazoline-mediated biaryl coupling reaction was applied successfully to the total synthesis of a series of dibenzocyclooctadiene lignans in chiral nonracemic form. The diastereoselectivities achieved in the coupling reaction varied in a predictable manner, primarily as a function of the ortho substituents on the phenyl Grignard reagent. Chiral cyclooctanones **17r** and **17s** were accessible in 23% overall yield (seven isolated intermediates) from the preparatively useful biaryl coupling of phenyl bromide **5c** with phenyloxazoline **6**. For both ketones, nucleophilic attack occurred preferentially trans to the C-8 methyl substituent. Methyllithium addition to **17s** gave a single product (**18**). The epimeric alcohol **21** was prepared selectively (10:1) by an olefination–epoxidation–reduction sequence. Methyllithium addition to **17r** gave an 8:1 mixture of (-)-isoschizandrin (**22**) and (-)-schizandrin (**23**). Chemical and spectroscopic evidence supported the reassignment of the structure for natural (+)-isoschizandrin to the 15,16*R*,7*R*,8*S* configuration.

The fruits of *Schizandra chinesis* Baill. are used medicinally in Asia as an antitussive and a tonic. Extracts from these fruits have yielded more than 36 dibenzocyclooctadiene lignans.[1] The first of these lignans to be isolated was (+)-schizandrin **1**.[2]



1, (+)-schizandrin



2, (+)-isoschizandrin

Twenty-seven years later in 1988, (+)-isoschizandrin was recovered from these extracts and assigned the structure **2**.[3] These novel

(1) Ikeya, Y.; Kanatani, H.; Hakozaki, M.; Taguchi, H.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1988**, *36*, 3974. For a review on lignans and neolignans, see: Whiting, D. A. *Nat. Prod. Rep.* **1987**, 499.

(2) Ikeya, Y.; Taguchi, H.; Yosioka, I.; Kobayashi, H. *Chem. Pharm. Bull.* **1979**, *27*, 1383. Kochetkov, N. K.; Khorlin, A.; Chizhov, O. S.; Scheichenko, V. I. *Tetrahedron Lett.* **1961**, 730.

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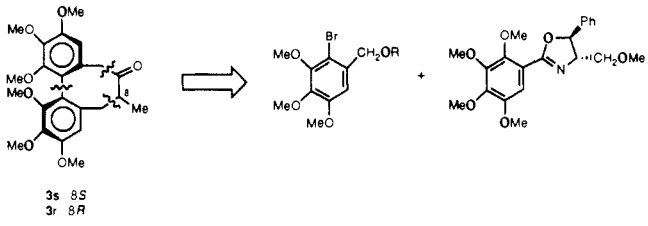
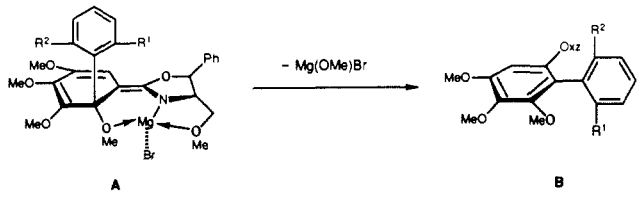
Scheme I



Scheme II



biologically active biaryl lignans offer attractive targets for total synthesis.[4]

The oxazoline-mediated biaryl coupling strategy originating from this laboratory has provided convenient access to a number of chiral biaryl compounds.[5] We felt that a reasonable approach to **1** and **2** could be developed to further demonstrate the efficacy of this methodology. In our synthetic plan, cyclooctanones **3r** and **3s** served as the pivotal precursors to these targets (Scheme I). As depicted in Scheme I, key bond disconnections were envisioned at the biphenyl axis and at both benzylic positions. The biphenyl bond would be formed by the coupling of a phenyl Grignard with an *o*-methoxy-substituted phenyloxazoline. Axial diastereoselectivity would be achieved in this reaction by using a chiral oxazoline. Finally, since ketones **3r** and **3s** are potentially interconvertible by enolization, initial synthetic efforts were not concerned with setting the configuration at C-8.

Results and Discussion

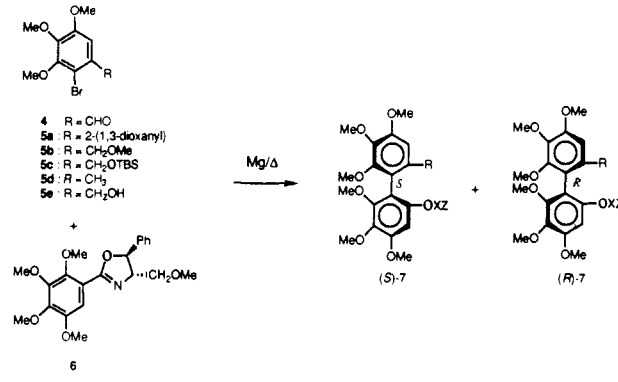
As mentioned previously, the aryl–aryl coupling of a Grignard reagent with an aryloxazoline was to be the key asymmetric process leading to the targets. This efficient and unusually mild coupling reaction[6] is believed to proceed through an addition–elimination mechanism. Thus, the overall stereoselectivity of the coupling would stem from the selectivity achieved in each of these steps. As in the chelate-controlled nucleophilic additions to chiral aryloxazolines,[7] an initial stereoselective addition of the Grignard reagent to the phenyloxazoline leading to azaenolate intermediate A would be expected (Scheme II). Free rotation about the newly formed carbon–carbon bound should be possible, and the orientation of the two ortho substituents of the Grignard reagent prior to loss of the magnesium alkoxy halide would be translated to the axial chirality in the biaryl product B. The preferred orientation of these substituents would depend upon the interactions within A, which could include coordination to the magnesium ion and steric hindrance from the oxazoline substituents, i.e., the phenyl group and the methine hydrogen.

To elucidate the factors inducing asymmetry in this process, a series of differently substituted phenyl Grignard reagents was examined. With the targets of our total synthesis in mind, one ortho substituent was kept as a methoxy group while the other was varied to encompass a range of steric and electronic demands. Thus, starting with 2-bromo-3,4,5-trimethoxybenzaldehyde (**4**)[8] and the corresponding carbinol (**5e**),[9] we prepared a series of derivatives **5a–d**, which in addition to **5e** were transformed into the Grignard reagents and allowed to react with the (tetramethoxyphenyl)oxazoline **6**[5a] (Scheme III, Table I). The coupling reactions were conducted in THF at reflux temperature for 1–2 days. The Grignard reagents derived from bromides **5a–d** were prepared by the entrainment method (Mg/ethylene dibromide),[5a,10] whereas bromide **5e**, having the free hydroxyl group, was treated sequentially with methylmagnesium chloride and *tert*-butyllithium. The diastereomer ratios for the biphenyls **7** were determined by HPLC analysis and when possible were corroborated by ^{1}H NMR. In the case of entry e, the ratio was obtained from the isolated biphenyl products.

Table I. Coupling of **5a–e** and Aryloxazoline **6** To Give Biphenyls **7a–e**

entry	**5**, *R*	(*S*)-**7**	(*R*)-**7**	% yield
a	2-(1,3-dioxanyl)	2.8	1	53
b	CH_2OMe	2.8	1	40
c	CH_2OSiMe_2-*t*-Bu	6.2	1	68
d	CH_3	6.5	1	52
e	CH_2OH	1	5.2	26

Scheme III



The interplay of steric and electronic influences becomes apparent in the results presented in Table I. The (*S*)-biphenyl products were formed by collapse of the azaenolate intermediates (A, R^1 = OMe) having the *o*-methoxy substituent in a position to complex to the magnesium ion. The 2.8:1 ratio of (*S*)- and (*R*)-biphenyls in **7a** reflected a competition of the 1,3-dioxanyl substituent for complexing with the magnesium ion; the 6-membered chelate available to the aryl oxygen of the methoxy substituent was favored over the 7-membered one with the benzylic oxygens of the 1,3-dioxanyl substituent. The ratio with the methoxymethyl substituent (entry b) was the same as with the 1,3-dioxanyl substituent. Apparently, the added steric bulk of the dioxane ring countered the effect of the additional oxygen available for complexation. An interesting effect appeared in the case of the bulky siloxymethyl substituent (entry c). Here, the steric crowding and loss of electron density (coordinating ability) from the benzylic oxygen by the silicon[11] acted in concert to afford a clearly enhanced diastereomer ratio of 6.2:1. A similar enhancement of diastereoselectivity was noted with the methyl substituent (entry d), where competitive complexation was lacking and relative steric requirements were minimal. Finally, the hydroxymethyl substituent (entry e) would be present as the alkoxide in the coupling reaction. The alkoxide competed effectively with the *o*-methoxy group for magnesium ion chelation, and a significant reversal in stereochemistry was observed; the (*R*)-biphenyl

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(4) Synthesis of racemic schizandrin: Ghera, E.; Ben-David, Y. *J. Chem. Soc., Chem. Comm.* **1978**, 480. Synthesis of schizandrin-type lignans: Takeya, T.; Okubo, T.; Nishida, S.; Tobinaga, S. *Chem. Pharm. Bull.* **1985**, *33*, 3599 and references therein.
(5) (a) (–)-Steganone: Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 5446. (b) Biphenyls: Meyers, A. I.; Himmelsbach, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 682. (c) Binaphthyls: Meyers, A. I.; Lutomski, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 879.
(6) Meyers, A. I.; Flanagan, M. E. *Org. Synth.* **1990**, submitted for publication.
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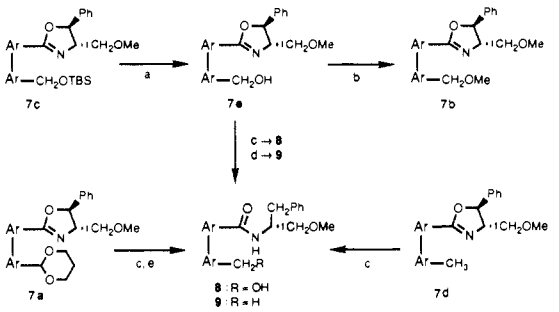
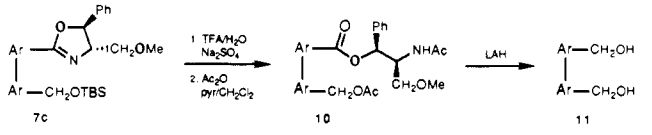
Scheme IV[a]



[a] Key: (a) TBAF; (b) NaH/MeI; (c) H_2/Pd–C/EtOAc; (d) H_2/Pd–C/EtOAc/trace $HClO_4$; (e) (1) H_3O^+, (2) $NaBH_4$.

Scheme V[a]



[a] (*S*)-**7c** → (*S*)-**10** (75%) → (*S*)-**11** (87%); $[\alpha]_D$ +36.3° (*c* 3.30, $CHCl_3$), (*R*)-**7c** → (*R*)-**10** (80%) → (*R*)-**11** (93%); $[\alpha]_D$ −43.2° (*c* 1.98, $CHCl_3$) (lit.[2] ((*R*)-**11**) $[\alpha]_D$ −38.2° (*c* 0.510, $CHCl_3$)).

isomer was favored by a 5.2:1 ratio, albeit in poor yield. Various attempts to increase the yield of this homogeneous reaction were met with little improvement.

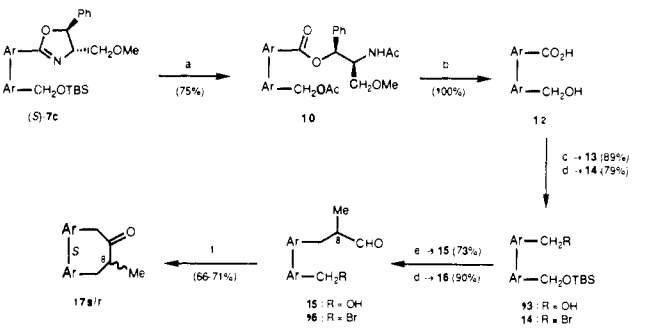
The silyl ether biphenyls **7c** were obtained in 68% yield with a reasonable diastereomer excess (de = 72%) and were separable by radial chromatography. The major isomer ((*S*)-**7c**), which was utilized in the subsequent natural product synthesis, however, led to the antipodes of **1** and **2**. Use of the chiral auxillary of opposite configuration would undoubtedly provide the naturally occurring enantiomers. There were a number of attempts to increase both the yield and diastereomer ratio (6.2:1) of **7c** in Table I, but these were met with little success. Dilution (4-fold) had no effect on the product ratio. The ratio reached approximately 7:1 when the coupling was conducted at room temperature; however, the reaction was prohibitively slow. Heating a pure diastereomer at reflux in THF failed to isomerize the chiral axis, indicating the kinetic nature of the coupled products.

The relative stereochemistry of **7a–e** was interrelated by chemical interconversion (Scheme IV). Thus, subjecting the silyl ether biphenyl **7c** to fluoride ion provided alcohol **7e**, which upon treatment with sodium hydride/iodomethane afforded the corresponding methyl ether **7b**. Hydrogenolysis of hydroxyoxazoline **7e** in the absence of acid gave hydroxy amide **8**.[12] In the presence of acid, hydrogenolysis of the benzylic alcohol led to **9**. This material was shown to be identical with the amide derived from the methyl-substituted biphenyl **7d**. Hydrogenolysis of dioxane **7a**, followed by acetal cleavage and aldehyde reduction, permitted comparison with **8**.

The absolute stereochemistry of the biaryl products was determined by the correlation with a known chiral biphenyl (**11**) obtained via the oxidative degradation of schizandrin (Scheme V).[2] The silyl ether biphenyls **7c** were converted separately to this diol by an efficient three-step sequence:[13] (i) oxazoline ring opening with aqueous trifluoroacetic acid, (ii) acetylation of the unstable ammonium salt with acetic anhydride, and (iii) reduction of the chromatographically stable diester amide **10** with lithium aluminum hydride.

Relying upon the C_2 symmetry in diol **11**, the carbons necessary to construct the cyclooctane ring could be introduced at either benzylic terminus. The monoprotection of **11** was required to differentiate these reactive sites. Under optimum conditions

Scheme VI[a]



[a] Key: (a) (1) TFA/H_2O/Na_2SO_4, (2) Ac_2O/pyr; (b) NaOH; (c) (1) TBSCl, (2) DIBAL; (d) NBS/PPh_3; (e) (1) $(CH_3)CHLiCHNC_6H_{11}$, (2) H_3O^+; (f) (1) SmI_2/THF/HMPA, (2) PCC/Al_2O_3.

(sodium hydride/*tert*-butyldimethylsilyl chloride/THF), the monosilyl ether was isolated in yields of 53–68% along with the diether in 11–12%.[14]

A more straightforward approach to this differentiation problem took advantage of amide **10** containing benzylic carbons in different oxidation states, which was hydrolyzed quantitatively to the corresponding hydroxy acid **12** (Scheme VI). Treatment with excess silyl chloride gave a silyl ester/ether intermediate which, without isolation, was reduced to hydroxy silyl ether **13**. Variable amounts of diol **11** were isolated from the product mixture when the reduction was performed in THF with lithium aluminum hydride. The irreproducibility in the yields was traced to the hydroxide generated in the workup procedure. When the reduction was attempted with diisobutylaluminum hydride in CH_2Cl_2 at 0 °C, diol **11** was detected prior to workup; however, no further cleavage of the silyl ether was noted from the essentially neutral quenched reaction mixture. When the temperature was lowered to −78 °C, silyl ether **13** was obtained exclusively in 89% yield. Treating the latter with triphenylphosphine and freshly recrystallized *N*-bromosuccinimide[5a,15] afforded bromide **14** in 79% yield together with corresponding dibromide **14a** in 8% yield. It was next required to extend the carbon chain by two, and this was performed as follows. Alkylation of the lithium anion derived from *N*-propylidenecyclohexanamine with benzyl bromide **14** provided hydroxy aldehyde **15** as a 1:1 mixture of C-8 methyl epimers in 73% yield after an aqueous acid workup.[16] This material was converted smoothly to bromo aldehyde **17** in 90% yield with *N*-bromosuccinimide/triphenylphosphine.

The requisite intramolecular cyclization of bromo aldehyde **16** was mediated by samarium diiodide in THF in the presence of HMPA.[17] The use of HMPA was necessary to suppress a major side reaction in which ketone **17** was formed at the expense of starting material through a Meerwein–Ponndorf process.[18] Oxidation of the crude cyclization mixture with pyridinium chlorochromate on alumina[19] gave ketone **17** in 71% yield. Despite the presence of an additional stereoisomer, the intermediate cyclooctanols with different C-8 configurations were separable by chromatography more readily than the ketones. Moreover, no epimerization at C-8 was noted during the PCC oxidation. By this protocol, ketones **17r** and **17s** were isolated in 66% combined overall yield.

The equilibration of ketone **17** was examined in both basic (sodium methoxide/methanol) and acidic (*p*-toluenesulfonic

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(19) Cheng, Y.-S.; Liu, W.-L.; Chen, S.-H. *Synthesis* **1980**, 223.

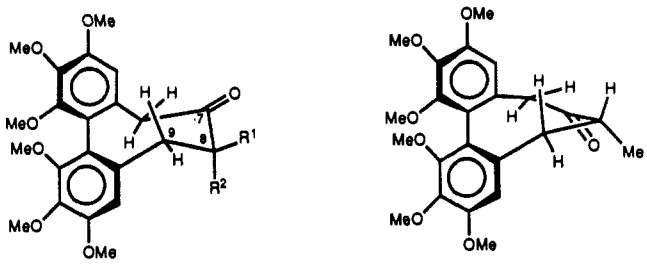
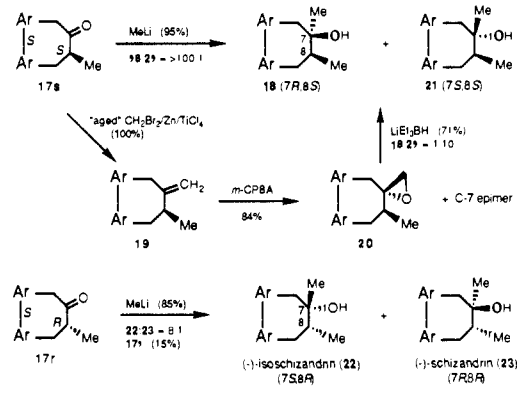


Figure 1. Dibenzocyclooctadiene conformations.

Scheme VII



acid/benzene) conditions. In both cases, a 70:30 mixture of 8*S* and 8*R* ketones (**17s**:**17r**) was obtained from a nearly equimolar starting mixture. This equilibrium preference was consistent with predictions based upon an examination of Dreiding models. The reasonable conformations available to dibenzocyclooctadiene systems are limited mainly to twist-boat–chair (TBC) and twist-boat (TB) conformations (Figure 1).[20] For the 8*S* ketone in the more stable TBC conformation, the C-8 methyl group occupies a pseudoequatorial position, while for the 8*R* ketone, the methyl group occupies a pseudoaxial position. To relieve interactions between the phenyl ring and the methyl group, the 8*R* ketone may adopt the TB conformation; however, unfavorable eclipsing interactions between the C-8 and C-9 substituents are introduced. The net result may permit a substantial ground-state population of this TB conformation.

The completion of the total synthesis required the stereoselective conversion of the these ketones to tertiary alcohols (Scheme VII). From the conformational considerations presented above, we could expect attack at the carbonyl to occur trans to the C-8 methyl group for both ketones. For the 8*S* ketone (**17s**), attack at the β-face of the carbonyl group is obstructed by both the C-8 methyl substituent and the pseudoaxial 9β-hydrogen. For the 8*R* ketone **17r** in the TBC conformation, the influences of the C-8 methyl group and the 9β-hydrogen compete with each other. However, the α-face of the carbonyl would be shielded to a greater extent by the effect of the methyl group. In the TB conformation, this face is effectively blocked by the phenyl ring and the methyl group.

The addition of methyllithium to ketone **17s** provided a single tertiary alcohol (**18**) in 95% yield having the anticipated 7*R* configuration (Scheme VII). To obtain the C-7 epimer **21**, the originally proposed structure of (−)-isoschizandrin, an olefination–epoxidation–reduction sequence was employed. Ketone **17s** was treated with the "aged" methylene dibromide/zinc/titanium tetrachloride reagent to give a quantitative yield of the exocyclic olefin **19**.[21] From the ^{1}H NMR spectrum, the conformation of **19** appeared to be quite close to that of ketone **17s**. The epoxidation, therefore, was expected to proceed with good selectivity from the same face of the molecule as the methyllithium addition. In the event, the reaction of **19** with *m*-CPBA produced epoxide **20** in 84% yield as a single compound by capillary GC analysis. Hydride-induced epoxide ring opening with lithium triethylborohydride gave a 10:1 mixture of the epimeric tertiary alcohols **21** and **18** in 71% yield.[22] Surprisingly, however, **21** differed spectroscopically from isoschizandrin.

The epimeric cyclic ketone **17r** was investigated next in an effort to clarify this discrepency. The reaction of methyllithium and ketone **17r** by inverse addition (ketone to nucleophile) provided a quantitative yield of an 8:1 mixture of (−)-isoschizandrin (**22**) and (−)-schizandrin (**23**) based on recovered starting material (15%). It is important to note that the starting material was recovered without epimerization. By normal methyllithium addition, starting ketone was recovered in 30% yield. These products (**22** and **23**) were spectroscopically identical (^{1}H/^{13}C) with those reported in the literature. In addition, the optical rotations were within experimental error of the literature values and were of opposite signs as expected for the unnatural enantiomers. Since isoschizandrin and schizandrin were reported in the literature to differ in their C-8 configurations, a structure revision was clearly necessary. On the basis of ^{1}H NOE and chemical synthesis experiments (vide infra), (−)-isoschizandrin has the 15,16*S*,7*S*,8*R* configuration as given in **22**. This stereochemical assignment is consistent with the anticipated addition of methyllithium to the carbonyl occurring trans to the C-8 methyl group. Furthermore, for dibenzocyclooctadienes in the TB conformation, the 6β-hydrogen is nearly parallel to the π-system of the carbonyl group; this π-system bisects both C-6 hydrogens in the TBC conformation. The observed enolization with ketone **17r** but not with **17s** illustrates the significance of the TB conformation in the 8*R* ketone.

Data from ^{1}H NOE experiments have been used extensively in the structure characterization of the naturally occurring dibenzocyclooctadiene lignans. Isomeric schizandrin and isoschizandrin each have three chiral elements; therefore, four pairs of enantiomers are theoretically possible. Through the additions of methyllithium to ketones **17r** and **17s**, all four possible diastereomers were available for analysis. It is believed that the comparative ^{1}H NOE data for these four substances would provide a more reliable basis for assignment than that from a single compound.

The ^{1}H NOE data obtained herein for the methyls, C-8 protons, and aryl protons were diagnostic in assigning the stereostructures for dibenzocyclooctadienes **18**, **21**, **22**, and **23** (Figure 2). When the NOE results permitted assignment of the C-9 protons, the coupling constants between them and the C-8 proton were consistent with dihedral angles determined by inspection of Dreiding models.

In the original structure elucidation of isoschizandrin, Ikeya et al.[3] saw no enhancement of the C-11 aryl proton upon irradiation of the C-8 methyl resonance. This finding led to the initial configurational assignment at C-8. In our hands, irradiation of the C-8 methyl signal produced a 3.0% enhancement in the C-11 proton, while none was observed upon irradiation of the C-8 proton.[23]

Our structural assignments were corroborated further by chemical synthesis. A number of methodologies have been developed to formally alkylate carbonyl substrates with predictable absolute stereoselectivities; among others, chiral hydrazones (RAMP/SAMP)[24] and chiral oxazolines[25] have found wide use.

(20) Gottlieb, H. E.; Mervic, M.; Ghera, E. *J. Chem. Soc., Perkin Trans. 1*, **1982**, 2353.
(21) Lombardo, L. *Org. Synth.* **1987**, *65*, 81 and references therein.
(22) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.
(23) In a recent communication from Dr. Ikeya, he has informed us that reinvestigation of the NMR spectrum of isoschizandrin at 500 MHz reveals an appreciable NOE between the aromatic C-11 proton and the C-8 methyl. Thus, our revised assignment has been verified by Dr. Ikeya.
(24) (a) Review: Enders, D. *Asymmetric Synthesis*; Academic Press: New York, 1984; Vol 3, p 275. (b) Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 2933. (c) Davenport, K. G.; Eichenauer, D. E.; Enders, D.; Newcomb, M.; Bergbreiter, D. E. *J. Am. Chem. Soc.* **1979**, *101*, 5654.
(25) (a) Review: Lutomski, K. A.; Meyers, A. I. *Asymmetric Synthesis*; Academic Press: New York, 1984; Vol 3, p 213. (b) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem.* **1976**, *98*, 567.

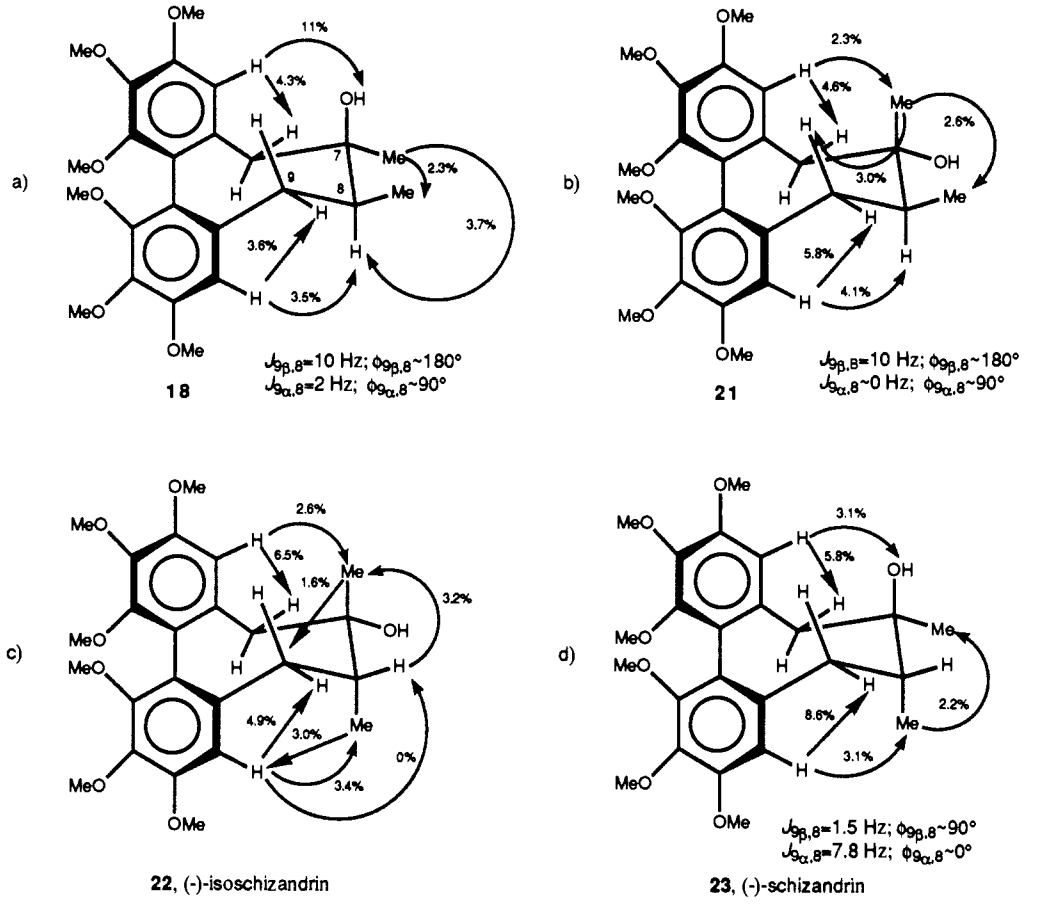
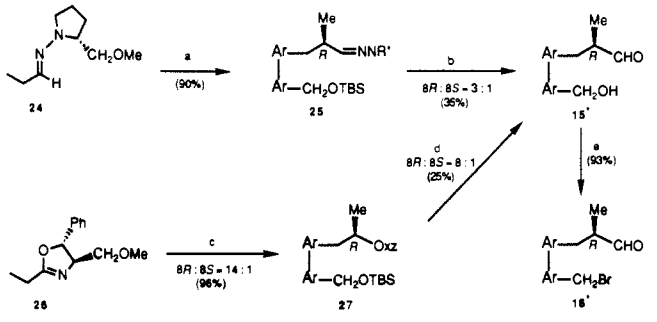


Figure 2. ^{1}H NOE data for synthetic dibenzocyclooctadienes.

Scheme VIII[a]



[a] Key: (a) (1) LDA, (2) **14**; (b) (1) MeI, (2) H_3O^+; (c) (1) LDA, (2) **14**; (d) (1) MeOTf, (2) $NaBH_4$, (3) H_3O^+; (e) NBS/Ph_3P.

Therefore, in the present synthesis, a compound with a known C-8 configuration could be prepared by use of the appropriate chiral system to alkylate benzyl bromide **14**. The 8*R* configuration found in (-)-schizandrin was the target of these studies since the structure given to (-)-isoschizandrin was now suspect.

Reaction of **14** with the lithium anion derived from hydrazone (*R*)-**24**[24b] afforded the alkylation product **25** in 90% yield (Scheme VIII). No resonances for a minor diastereomer could be detected by ^{1}H NMR. Thus, if present, the minor isomer would constitute less than 10% of the product mixture. A high selectivity was expected on the basis of Ender's results with benzyl bromide and (*S*)-**24**, which gave the alkylated derivative in 84% de.[24c] Attempted removal of the hydrazone by ozonolysis led to total decomposition of the material. Removal by sequential treatment with iodomethane and aqueous acid was more successful; however, yields of **15*** were low, and enolization was a problem. In this fashion, hydroxy aldehyde **15*** was obtained in 35% yield but as a 2.9:1 mixture of epimers. Due to the ready enolization of this hydroxy aldehyde, the 1:1 mixture of C-8 epimers produced earlier in the reaction of **14** with the achiral cyclohexylimine anion probably does not reflect the diastereoselectivity achieved in the alkylation.

In another attempt to prepare **15** with confirmed absolute stereochemistry at the C-8 position, the reaction of **14** with the lithium anion derived from chiral oxazoline **26**[25b] was carried out. The alkylation product **27** was obtained in 96% yield as a 14.5:1 mixture of diastereomers. Unfortunately, removal of the oxazoline by the methyl triflate/sodium borohydride/acid hydrolysis sequence[7] gave **15*** in only 25% yield as a 7.7:1 mixture of C-8 epimers. Once again, enolization en route to **15*** was significant. Nonetheless, in both asymmetric alkylations the major diastereomer had the same configuration (*R*) at the C-8 position as predicted.

The 8*R*-enriched hydroxy aldehyde (**15***, 8*R*:8*S* = 3.6:1) was subjected to the earlier reaction sequence and was converted carefully to bromide **16*** by use of *N*-bromosuccinimide/triphenylphosphine. The product was obtained in 93% yield accompanied by substantial epimerization (8*R*:8*S* = 2.3:1) Samarium diiodide induced cyclization of this 8*R*-enriched substrate (**16***) yielded a cyclooctanol mixture in 72% yield favoring the alcohols leading to isoschizandrin/schizandrin by a 2.2:1 ratio. Therefore, (-)-isoschizandrin **22** should have the 8*R* rather than 8*S* configuration.

In summary, the oxazoline-mediated biaryl coupling reaction has once again been applied successfully, this time to the total synthesis of a series of dibenzocyclooctadiene lignans in chiral nonracemic form. The present synthesis has provide an asymmetric route to (-)-schizandrin, which has been shown to maintain the 15,16*S*,7*R*,8*R* configuration, the antipode of the natural material which has the 15,16*R*,7*S*,8*S* configuration. Of greater significance, we have reached the unnatural enantiomer of isoschizandrin, which has been assigned the 15,16*S*,7*S*,8*R* configuration. The stereochemical assignment for isoschizandrin presented in the literature has now been corrected by the total synthesis of the four possible diastereomers.

Experimental Section

General Procedures. Solvents were purified under an inert atmosphere with standard procedures when this was deemed necessary. 1,2-Diiodoethane was purified immediately prior to use by washing an ether solution of the dihalide with aqueous 10% $Na_2S_2O_3$ solution and water. The ether solution was dried over $MgSO_4$, and the solvent was removed in vacuo.

Flash column chromatography was performed by use of Grace 951 silica gel (58 μm, Aldrich) or Matrex SilicaSi (20–45 μm, Amicon). Radial chromatography was done with Harrison Research Chromatotron 7924 and silica gel plates (No. 7749, Kieselgel 60 PF_{254}, Merck). Analytical gas chromatography (GC) was performed on a Hewlett-Packard Model 5890 instrument with a Hewlett-Packard 5% phenyl methyl silicone fused-silica capillary column, 30 m × 0.20 mm. Analytical HPLC was performed with one of three columns: (A) Rainin Microsorb silica (4.6 mm × 25 cm); (B) Du Pont Zorbax silica (4.6 mm × 25 cm); or (C) Waters 10/50 μPorasil.

Reactions requiring an inert atmosphere were conducted under dry argon. Temperatures are reported as bath temperatures. Organic layers were dried with $MgSO_4$, and the solvents were removed in vacuo. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. IR spectra were taken from thin films. ^1H NMR spectra were recorded at 270 or 300 MHz. ^{13}C NMR spectra were recorded at 75.5 MHz. Carbon multiplicities were obtained from DEPT experiments. Deuteriochloroform was used as the solvent unless specified otherwise. Chemical shifts are expressed (ppm) downfield from tetramethylsilane, which served as an internal reference.

2-(2-Bromo-3,4,5-trimethoxyphenyl)-1,3-dioxane (5a). A solution of 2-bromo-3,4,5-trimethoxybenzaldehyde[8] (6.24 g, 22.7 mmol) in dry benzene (100 mL) was treated with 1,3-propanediol (10 mL, 0.14 mol) and a spatula tip of *p*-toluenesulfonic acid monohydrate. The reaction mixture was heated at reflux for 3 h, cooled, and diluted with ether (125 mL). The mixture was washed with water and brine (75 mL each). The organic layer was dried and concentrated. Purification by flash chromatography with hexanes/ethyl acetate (6:1 to 3:2) afforded a colorless oil (6:1 g, 81%): IR 2965, 2937, 2854, 1573, 1485, 1450, 1387, 1107, 1006 cm^{-1}; ^1H NMR δ 1.46 (br d, 1 H, J = 13.5 Hz), 2.24 (tq, 1 H, J = 5.1, 12.8 Hz), 3.87 (s, 3 H), 3.88 (s, 3 H), 3.90 (s, 3 H), 4.03 (dt, 2 H, J = 1.9, 12.3 Hz), 4.26 (dd, 2 H, J = 5.0, 11.5 Hz), 5.76 (s, 1 H), 7.09 (s, 1 H); ^{13}C NMR δ 25.62 (t), 56.09 (q), 61.03 (q), 67.58 (t), 100.79 (d), 106.54 (d), 108.95 (s), 133.01 (s), 143.58 (s), 150.58 (s), 152.96 (s). Anal. Calcd for $C_{13}H_{17}BrO_5$: C, 46.86; H, 5.14. Found: C, 46.89; H, 5.19.

2-Bromo-3,4,5-trimethoxy-1-(methoxymethyl)benzene (5b). A solution of 2-bromo-3,4,5-trimethoxybenzyl alcohol (**5e**)[9] (1.40 g, 5.05 mmol) in dry THF (5 mL) was cooled in an ice bath and treated with sodium hydride (180 mg, 7.50 mmol). After the vigorous evolution of gas subsided, the cooling bath was removed. The suspension was stirred for 30 min, and iodomethane (0.47 mL, 7.5 mmol) was added. After 1.5 h, saturated aqueous NH_4Cl solution (10 mL) was added, and the mixture was extracted with ether (25 mL). The organic layer was dried and concentrated to a yellow oil (1.51 g). The crude product was purified by flash chromatography with hexanes/ethyl acetate (5:1) to afford a colorless oil (1.37 g, 93.2%): IR 2938, 2862, 2826, 1592, 1506, 1460, 1127 cm^{-1}; ^1H NMR δ 3.43 (s, 3 H), 3.83 (s, 6 H), 3.85 (s, 3 H), 4.43 (s, 2 H), 6.83 (s, 1 H); ^{13}C NMR δ 56.10 (q), 58.61 (q), 60.92 (t), 61.03 (q), 73.85 (t), 107.51 (d), 108.47 (s), 133.19 (s), 142.28 (s), 150.71 (s), 152.84 (s). Anal. Calcd for $C_{11}H_{15}BrO_4$: C, 45.38; H, 5.19. Found: C, 45.05; H, 5.02.

2-Bromo-1-[(*tert*-butyldimethylsiloxy)methyl]-3,4,5-trimethoxybenzene (5c). A solution of 2-bromo-3,4,5-trimethoxybenzyl alcohol (**5e**)[9] (1.40 g, 5.05 mmol) in dry CH_2Cl_2 (5 mL) was cooled in an ice bath and treated sequentially with triethylamine (1.04 mL, 7.49 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.61 mL, 7.01 mmol). The cooling bath was removed, and after 30 min, saturated aqueous NH_4Cl solution (10 mL) was added. The mixture was extracted with CH_2Cl_2 (25 mL). The organic layer was dried and concentrated. Purification by flash chromatography with hexanes/ethyl acetate (5:1) afforded a colorless oil (1.89 g, 95.6%): IR 2934, 2873, 2856, 1570, 1482, 1399, 1108 cm^{-1}; ^1H NMR δ 0.12 (s, 6 H), 0.96 (s, 9 H), 3.850 (s, 3 H), 3.854 (s, 3 H), 3.87 (s, 3 H), 4.67 (s, 2 H), 6.99 (s, 1 H); ^{13}C NMR δ −5.34 (q), 18.31 (s), 25.89 (q), 55.92 (q), 60.94 (q), 61.07 (q), 64.45 (t), 106.31 (d), 106.42 (s), 135.99 (s), 141.62 (s), 150.41 (s), 152.80 (s). Anal. Calcd for $C_{16}H_{27}BrO_4Si$: C, 49.10; H, 6.95. Found: C. 49.25; H, 6.95.

2-Bromo-3,4,5-trimethoxy-1-methylbenzene (5d). A solution of 2-bromo-3,4,5-trimethoxybenzyl alcohol (**5e**)[9] (14.4 g, 52.0 mmol) in dry CH_2Cl_2 (250 mL) was treated at ambient temperature with triphenylphosphine (17.0 g, 65.0 mmol). The solution was cooled in an ice bath, and a mixture of *N*-bromosuccinimide (11.6 g, 65.0 mmol) in CH_2Cl_2 (250 mL) was added. After 1 h, the light orange solution was washed with water (250 mL) and the aqueous layer was extracted with CH_2Cl_2 (125 mL). The combined organic layers were washed with brine (125 mL), dried, and concentrated to a deep purple oil. The crude product was purified by flash chromatography with hexanes/ethyl acetate (3:2 to 1:1) to afford 2-bromo-3,4,5-trimethoxybenzyl bromide, a white solid (15.9 g, 90.0%): mp 60–61 °C; ^1H NMR δ 3.84 (s, 3 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.57 (s, 2 H), 6.79 (s, 1 H); ^{13}C NMR δ 34.17 (t), 56.20 (q), 61.01 (q), 61.11 (q), 109.78 (d), 111.18 (s), 132.22 (s), 143.42 (s), 151.28 (s), 152.79 (s).

A solution of 2-bromo-3,4,5-trimethoxybenzyl bromide (1.70 g, 5.00 mmol) in THF (5 mL) was treated dropwise at ambient temperature with lithium triethylborohydride (10 mL, 10 mmol, 1.0 M in THF). After 30 min, water (1 mL) was added carefully at 0 °C. Aqueous 20% NaOH solution (5 mL) and 30% H_2O_2 solution (5 mL) were added. The mixture was extracted with ether (2 × 20 mL). The organic layers were dried and concentrated to a mixture of white solid and colorless oil (1.97 g). Purification by flash chromatography with hexanes/ethyl acetate (5:1) afforded **5d**, a colorless oil (969 mg, 74.2%): ^1H NMR δ 2.34 (s, 3 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 3.86 (s, 3 H), 6.59 (s, 1 H); ^{13}C NMR δ 23.18 (q), 56.08 (q), 60.83 (q), 61.08 (q), 109.56 (d), 110.84 (s), 133.38 (s), 141.11 (s), 150.84 (s), 152.30 (s). Anal. Calcd for $C_{10}H_{13}BrO_3$: C, 46.00; H, 5.02. Found: C, 46.28; H, 5.01.

General Procedure for Biaryl Coupling to Biphenyls 7a–d. A mixture of aryl bromide **5** (1.53 mmol) and magnesium powder (3.53 mmol, 20–100 mesh) in THF (8 mL) was heated at reflux and treated dropwise with a solution of 1,2-dibromoethane (2.00 mmol) in THF (4 mL) over 1.5 h. The mixture was heated for 1 h more and cooled to ambient temperature. A solution of phenyloxazoline **6**[5a] (0.51 mmol) in THF (4 mL) was added with a cannula. The solution was heated at reflux for 1–2 days, cooled, quenched with saturated aqueous NH_4Cl solution (6 mL), and partitioned with ether (25 mL). The organic layer was dried and concentrated. The crude product mixture was passed through a plug of silica gel (Amicon, ethyl acetate), and the diastereomer ratio was determined by HPLC analysis. Purification by radial chromatography with hexanes/ethyl acetate (3:1 to 1:1) afforded pure products **7a–e**.

Biphenyl 7a. The 2.8:1 = (*S*)-**7a**:(*R*)-**7a** diastereomer mixture (HPLC column C, hexanes:2-propanol = 1:1, t_R = 14.2, 17.4 min) was separable by radial chromatography (2-day reflux, 53.3%).

Major diastereomer (*S*)-7a: $[\alpha]^{22}_D$ +40.5° (*c* 1.20, $CHCl_3$); IR 2939, 2849, 1635, 1595, 1486, 1463, 1395, 1122, 1104 cm^{-1}; ^1H NMR δ 1.23–1.28 (m, 1 H), 2.02–2.19 (m, 1 H), 3.36 (s, 3 H), 3.41 (dd, 1 H, J = 7.2, 9.5 Hz), 3.49–3.70 (m, 2 H), 3.66 (s, 3 H), 3.67 (s, 3 H), 3.72 (s, 3 H), 3.80–4.08 (m, 2 H), 3.92 (s, 3 H), 3.94 (s, 3 H), 3.97 (s, 3 H), 4.11–4.15 (m, 2 H), 4.95 (d, 1 H, J = 7.8 Hz), 5.02 (s, 1 H), 7.03 (s, 1 H), 7.09–7.12 (m, 2 H), 7.20–7.29 (m, 3 H), 7.38 (s, 1 H); ^{13}C NMR δ 25.50 (t), 55.77 (q), 55.99 (q), 58.97 (q), 60.33 (q), 60.37 (q), 60.68 (q), 67.11 (t), 73.58 (d), 74.73 (t), 84.34 (d), 99.88 (d), 104.12 (d), 108.38 (d), 122.83 (s), 123.44 (s), 123.74 (s), 125.42 (d), 127.67 (d), 128.27 (d), 132.19 (s), 140.23 (s), 141.94 (s), 144.46 (s), 151.16 (s), 152.23 (s), 152.48 (s), 152.84 (s), 164.90 (s). Anal. Calcd for $C_{33}H_{39}NO_{10}$: C, 65.01; H, 6.45; N, 2.30. Found: C, 65.46; H, 6.73; N, 2.14.

Minor diastereomer (*R*)-7a: $[\alpha]^{22}_D$ +69.3° (*c* 0.43, $CHCl_3$); IR 2939, 2850, 1647, 1596, 1463, 1396, 1122, 1103 cm^{-1}; ^1H NMR δ 1.22–1.28 (m, 1 H), 2.00–2.16 (m, 1 H), 3.36 (s, 3 H), 3.38–4.16 (m, 7 H), 3.58 (s, 3 H), 3.64 (s, 3 H), 3.73 (s, 3 H), 3.93 (s, 3 H), 3.94 (s, 3 H), 3.97 (s, 3 H), 5.03 (s, 1 H), 5.12 (d, 1 H, J = 8.4 Hz), 6.86–6.89 (m, 2 H), 7.04 (s, 1 H), 7.18–7.22 (m, 4 H); ^{13}C NMR δ 25.54 (t), 55.76 (q), 56.09 (q), 59.10 (q), 60.26 (q), 60.38 (q), 60.51 (q), 60.75 (q), 67.03 (t), 67.22 (t), 74.23 (d), 74.46 (t), 84.60 (d), 99.90 (d), 104.42 (d), 108.40 (d), 122.47 (s), 123.37 (s), 124.32 (s), 125.92 (d), 127.65 (d), 128.18 (d), 132.39 (s), 140.12 (s), 142.03 (s), 144.25 (s), 151.54 (s), 152.24 (s), 152.29 (s), 153.08 (s), 165.08 (s). Anal. Calcd for $C_{33}H_{39}NO_{10}$: C, 65.01; H, 6.45; N, 2.30. Found: C, 64.52; H, 6.45; N, 1.78.

Biphenyl 7b. The 2.8:1 = (*S*)-**7b**:(*R*)-**7b** diastereomer mixture (HPLC column C, hexanes:ethyl acetate = 2:1, t_R = 25.5, 29.6 min) was inseparable by radial chromatography (2-day reflux, 40.4%): IR 2936, 2828, 1650, 1593, 1485, 1462, 1396, 1119, 1102 cm^{-1}; ^1H NMR (reflects a ~3:1 mixture) δ 3.17 (s, 0.75 H), 3.21 (s, 2.25 H), 3.37 (s, 3 H), 3.44 (dd, 1 H, J = 6.7, 9.5 Hz), 3.60 (dd, 1 H, J = 4.6, 9.8 Hz), 3.64 (s, 2.25 H), 3.66 (s, 2.25 H), 3.68 (s, 0.75 H), 3.73 (s, 0.75 H), 3.78 (s, 3 H), 3.90 (s, 2.25 H), 3.92 (s, 0.75 H), 3.94 (s, 3 H), 3.96 (s, 3 H), 4.04–4.12 (m, 1 H), 4.07 (d, 1 H, J = 12 Hz), 4.15 (d, 1 H, J = 12 Hz), 5.11 (d, 0.75 H, J = 7.5 Hz), 5.17 (d, 0.25 H, J = 7.6 Hz), 6.82 (s, 1 H), 6.82–6.86 (m, 0.5 H), 6.94–6.97 (m, 1.5 H), 7.22–7.31 (m, 4 H); ^{13}C NMR (major isomers *S*) δ 55.69 (q), 55.75 *S* (q), 55.97 *S* (q), 58.14 *S* (q), 58.17 (q), 59.04 *S* (q), 60.30 (q), 60.45 *S* (q), 60.70 *S* (q), 72.01 (t), 72.13 *S* (t), 74.02 *S* (d), 74.36 *S* (t), 74.44 (t), 83.89 *S* (d), 84.13 (d), 105.46 *S* (d), 108.81 *S* (d), 122.05 *S* (s), 123.55 (s), 123.73 *S* (s), 123.98 (s), 125.15 *S* (d), 125.37 (d), 127.65 *S* (d), 128.25 (d), 128.29

S (s), 132.64 (s), 133.09 S (s), 140.27 (s), 140.35 S (s), 140.71 S (s), 144.33 (s), 144.42 S (s), 151.27 S (s), 151.60 (s), 151.69 (s), 151.75 S (s), 152.48 S (s), 152.53 (s), 152.82 S (s), 152.94 (s), 164.84 S (s), 165.04 (s). Anal. Calcd for $C_{31}H_{37}NO_9$: C, 65.60; H, 6.57; N, 2.47. Found: C, 65.44; H, 6.59; N, 2.42.

Biphenyl 7c. The 6.2:1 = (*S*)-**7c**:(*R*)-**7c** diastereomer mixture (HPLC column B, hexanes:ethyl acetate = 3:1, t_R = 4.96, 4.18 min) was separable by radial chromatography (2-day reflux, 67.9%).

Major diastereomer (*S*)-7c: $[\alpha]^{22}_D$ +54.5° (*c* 2.97, $CHCl_3$); IR 2934, 2855, 2360, 1647, 1593, 1485, 1362, 1103 cm^{-1}; ^1H NMR δ −0.075 (s, 3 H), −0.052 (s, 3 H), 0.86 (s, 9 H), 3.36 (s, 3 H), 3.42 (dd, 1 H, *J* = 6.9, 9.7 Hz), 3.59 (dd, 1 H, *J* = 4.5, 9.7 Hz), 3.61 (s, 3 H), 3.62 (s, 3 H), 3.76 (s, 3 H), 3.88 (s, 3 H), 3.91 (s, 3 H), 3.94 (s, 3 H), 4.07 (dt, 1 H, *J* = 4.5, 7.1 Hz), 4.30 (d, 1 H, *J* = 14.2 Hz), 4.43 (d, 1 H, *J* = 14.2 Hz), 5.12 (d, 1 H, *J* = 7.5 Hz), 6.85–6.88 (m, 2 H), 6.93 (s, 1 H), 7.19 (m, 3 H), 7.25–7.27 (m, 1 H); ^{13}C NMR δ −5.49 (q), −5.39 (q), 18.23 (s), 25.84 (q), 55.61 (q), 56.04 (q), 59.16 (q), 60.52 (q), 60.80 (q), 62.62 (t), 74.08 (d), 74.48 (t), 84.03 (d), 104.22 (d), 109.03 (d), 120.01 (s), 123.47 (s), 123.93 (s), 125.17 (d), 127.65 (d), 128.31 (d), 136.25 (s), 136.25 (s), 140.00 (s), 140.38 (s), 144.49 (s), 150.97 (s), 151.53 (s), 152.48 (s), 152.71 (s), 164.96 (s). Anal. Calcd for $C_{36}H_{49}NO_9Si$: C, 64.74; H, 7.40; N, 2.10. Found: C, 64.66; H, 7.53; N, 2.12.

Minor diastereomer (*R*)-7c: $[\alpha]^{22}_D$ +70.5° (*c* 2.43, $CHCl_3$); IR 2934, 2855, 1652, 1594, 1484, 1463, 1120, 1103 cm^{-1}; ^1H NMR δ −0.087 (s, 3 H), −0.072 (s, 3 H), 0.86 (s, 9 H), 3.35 (s, 3 H), 3.40–3.46 (m, 1 H), 3.60 (dd, 1 H, *J* = 4.6, 9.7 Hz), 3.63 (s, 3 H), 3.65 (s, 3 H), 3.70 (s, 3 H), 3.89 (s, 3 H), 3.91 (s, 3 H), 3.95 (s, 3 H), 4.04–4.10 (m, 1 H), 4.24 (d, 1 H, *J* = 14.1 Hz), 4.36 (d, 1 H, *J* = 14.0 Hz), 5.15 (d, 1 H, *J* = 5.2 Hz), 6.81–6.84 (m, 2 H), 6.94 (s, 1 H), 7.16–7.25 (m, 4 H); ^{13}C NMR δ −5.49 (q), −5.42 (q), 18.26 (s), 25.89 (q), 55.62 (q), 56.14 (q), 59.20 (q), 60.43 (q), 60.56 (q), 60.62 (q), 60.86 (q), 62.46 (t), 74.18 (d), 74.56 (t), 84.36 (d), 104.30 (d), 109.19 (d), 120.07 (s), 125.46 (d), 127.75 (d), 128.37 (d), 135.55 (s), 140.09 (s), 151.40 (s), 151.51 (s), 152.61 (s), 152.90 (s), 165.18 (s). Anal. Calcd for $C_{3}36H_{49}NO_9Si$: C, 64.74; H, 7.40; N, 2.10. Found: C, 64.63; H, 7.47; N, 2.11.

Biphenyl 7d. The 6.5:1 = (*S*)-**7d**:(*R*)-**7d** diastereomer mixture (HPLC column A, hexanes:2-propanol = 3.5:1, t_R = 6.8, 7.5 min) was inseparable by radial chromatography (1-day reflux, 52.0%): IR 2937, 2830, 1646, 1592, 1486, 1463, 1393, 1331, 1104 cm^{-1}; ^1H NMR (reflects a ~7:1 mixture) δ 1.96 (s, 0.38 H), 2.00 (s. 2.62 H), 3.38 (s, 3 H), 3.44 (dd, 1 H, *J* = 6.8, 9.6 Hz), 3.62 (dd, 1 H, *J* = 5.2, 9.7 Hz), 3.64 (s, 3 H), 3.67 (s, 3 H), 3.79 (s, 3 H), 3.87 (s, 3 H), 3.94 (s, 3 H), 3.95 (s, 3 H), 4.10 (dt, 1 H, *J* = 4.5, 7.0 Hz), 5.15 (d, 0.88 H, *J* = 7.4 Hz), 5.20 (d, 0.12 H, *J* = 7.5 Hz), 6.50 (s, 0.12 H), 6.53 (s, 0.88 H), 6.82–6.85 (m, 0.24 H), 6.93–6.96 (m, 1.76 H), 7.19–7.29 (m, 4 H); ^{13}C NMR (major isomer) δ 20.26 (q), 55.78 (q), 56.05 (q), 59.16 (q), 60.47 (q), 60.58 (q), 60.60 (q), 60.84 (q), 74.16 (d), 74.54 (t), 83.99 (d), 108.21 (d), 108.97 (d), 123.24 (s), 123.91 (s), 125.17 (d), 125.29 (s), 127.70 (d), 128.39 (d), 132.79 (s), 139.72 (s), 140.59 (s), 144.55 (s), 151.51 (s), 151.70 (s), 152.38 (s), 152.42 (s), 165.22 (s). Anal. Calcd for $C_{30}H_{35}NO_8$: C, 67.02; H, 6.56; N, 2.61. Found: C, 66.78; H, 6.60; N, 2.51.

Biphenyl 7e. A solution of 2-bromo-3,4,5-trimethoxybenzyl alcohol (**5e**)[9] (426 mg, 1.54 mmol) in THF (15 mL) was cooled to −78 °C and treated dropwise with methylmagnesium chloride (0.51 mL, 1.53 mmol, 3.0 M in THF). The mixture was stirred in an ice bath for 15 min, recooled to −78 °C, and treated dropwise with *tert*-butyllithium (1.81 mL, 3.07 mmol, 1.7 M in pentane). After 1.5 h, the reaction mixture was allowed to warm to ambient temperature. A solution of phenyloxazoline **6**[5a] (200 mg, 0.516 mmol) in THF (5 mL) was added with a cannula. The yellow solution was heated at reflux for 1 day, cooled, quenched with saturated aqueous NH_4Cl solution (5 mL), and partitioned with ether (2 × 25 mL). The organic layer was dried and concentrated. Purification by radial chromatography with hexanes/ethyl acetate (1:4) afforded (*S*)-**7e** (12 mg, 4.2%) and (*R*)-**7e** (62 mg, 21.7%) as colorless oils.

Major diastereomer (*R*)-7e (lower R_f): $[\alpha]^{22}_D$ −42.2° (*c* 2.81, $CHCl_3$); IR 3288 (br), 3121, 2937, 1654, 1593, 1486, 1461, 1120, 1103 cm^{-1}; ^1H NMR δ 3.35 (s, 3 H), 3.46 (dd, 1 H, *J* = 6.0, 9.8 Hz), 3.56 (dd, 1 H, *J* = 4.1, 9.9 Hz), 3.60 (s, 3 H), 3.65 (s, 3 H), 3.79 (s, 3 H), 3.92 (s, 6 H), 3.95 (s, 3 H), 3.90–4.03 (m, 1 H), 4.24 (d, 1 H, *J* = 11 Hz), 4.31 (d, 1 H, *J* = 11 Hz), 4.90 (br s, 1 H), 5.33 (d, 1 H, *J* = 7.2 Hz), 6.86 (s, 1 H), 7.05–7.12 (m, 2 H), 7.15 (s, 1 H), 7.23–7.28 (m, 3 H); ^{13}C NMR δ 55.78 (q), 56.06 (q), 59.23 (q), 60.58 (q), 60.61 (q), 60.86 (q), 63.92 (t), 73.78 (t), 74.20 (d), 83.78 (d), 108.21 (d), 122.41 (s), 123.73 (s), 124.16 (s), 125.74 (d). 128.23 (d), 128.62 (d), 135.75 (s), 140.05 (s), 141.35 (s), 144.41 (s), 150.84 (s), 151.94 (s), 152.74 (s), 153.08 (s), 164.80 (s). Anal. Calcd for $C_{30}H_{35}NO_9$: C, 65.09; H, 6.37; N, 2.53. Found: C, 65.28; H, 6.27; N, 2.52.

Minor diastereomer (*S*)-7e (higher R_f): $[\alpha]^{22}_D$ +80.5° (*c* 4.01, $CHCl_3$); IR: 3288 (br), 2935, 1648, 1592, 1486, 1463, 1103 cm^{-1}; ^1H NMR δ 3.08 (dd, 1 H, *J* = 6.3, 9.8 Hz), 3.21 (s, 3 H), 3.29 (dd, 1 H, *J* = 4.0, 9.8 Hz), 3.65 (s, 6 H), 3.86 (s, 3 H), 3.93 (s, 6 H), 3.94 (s, 3 H), 4.12 (dt, 1 H, *J* = 4.2, 6.3 hz), 4.26 (d, 1 H, *J* = 11 Hz), 4.32 (d, 1 H, *J* = 11 Hz), 5.21 (br s, 1 H), 5.26 (d, 1 H, *J* = 6.5 Hz), 6.88 (s, 1 H), 7.12 (s, 1 H), 7.19–7.23 (m, 2 H), 7.28–7.39 (m, 3 H); ^{13}C NMR δ 55.83 (q), 56.05 (q), 58.92 (q), 60.51 (q), 60.81 (q), 63.81 (t), 73.49 (t), 73.82 (d), 83.26 (d), 108.00 (d), 108.17 (d), 122.52 (s), 123.55 (s), 124.44 (s), 125.37 (d), 128.18 (d), 128.70 (d), 135.99 (s), 140.31 (s), 141.34 (s), 144.53 (s), 150.75 (s), 151.91 (s), 152.67 (s), 153.02 (s), 164.66 (s). Anal. Calcd for $C_{30}H_{35}NO_9$: C, 65.09; H, 6.37; N, 2.53. Found: C, 65.05; H, 6.23; N, 2.46.

Structure Correlations of Biphenyl Products. Biphenyl 7e from 7c. A solution (*S*)-**7c** (448 mg, 0.671 mmol) in THF (5 mL) was treated with tetra-*n*-butylammonium fluoride (1.34 mL, 1.34 mmol, 1.0 M in THF). After being allowed to stand at ambient temperature for 1 h, the solution was concentrated. The residue was purified by flash chromatography with hexanes/ethyl acetate (1:6) to afford (*S*)-**7e** (353 mg, 95.1%), spectroscopically equivalent to material obtained from the biaryl coupling of **5e** and **6**.

Similarly, fluoride ion induced deprotection of (*R*)-**7c** provided (*R*)-**7e**.

Biphenyl (*S*)-7b from (*S*)-7e. A solution of (*S*)-**7e** (35 mg, 0.063 mmol) in THF (1 mL) was cooled in an ice bath and treated with sodium hydride (4.5 mg, 0.19 mmol). The cooling bath was removed, and after 30 min, iodomethane (0.01 mL, 0.2 mmol) was added. The mixture was stirred for 1 h, quenched with saturated aqueous NH_4Cl solution (3 mL), and extracted with ether (15 mL). The organic layer was dried and condensed to (*S*)-**7b** as a colorless oil (34 mg, 95%). This material corresponded (^1H NMR data) to the major isomer in the biaryl coupling of **5b** and **6**.

Hydroxy Amide 8, Hydrogenolysis of 7e. A solution of (*S*)-**7e** (506 mg, 0.914 mmol) in ethyl acetate (50 mL) was treated with 10% palladium on carbon (0.25 g). The system was evacuated with a water aspirator and purged with hydrogen (3×). The mixture was stirred under a hydrogen atmosphere (balloon) for 5 h, filtered through Celite, and condensed to (*S*)-**8**, a white solid (511 mg, 101%): mp 136–137 °C; $[\alpha]^{22}_D$ +31.2° (*c* 1.46, $CHCl_3$); IR 3264 (br), 3066, 2994, 2974, 2934, 2874, 1643, 1590, 1550, 1486, 1458, 1394, 1266, 1127, 1102 cm^{-1}; ^1H NMR δ 2.66 (dd, 1 H, *J* = 8.6, 14 Hz), 2.72 (dd, 1 H, *J* = 7.3, 14 Hz), 3.07 (d, 2 H, *J* = 3.6 Hz), 3.20 (s, 3 H), 3.61 (s, 3 H), 3.70 (s, 3 H), 3.85 (s, 3 H), 3.88 (s, 3 H), 3.90 (s, 3 H), 3.91 (s, 3 H), 4.19–4.24 (m, 3 H), 6.34 (d, 1 H, *J* = 8.5 Hz), 6.88 (s, 1 H), 6.90 (s, 1 H), 7.14–7.29 (m, 5 H); ^{13}C NMR δ 36.93 (t), 50.18 (d), 55.74 (q), 55.85 (q), 58.55 (q), 60.45 (q), 60.52 (q), 60.58 (q), 60.69 (q), 63.35 (t), 71.93 (t), 106.90 (d), 108.06 (d), 121.08 (s), 121.17 (s), 126.27 (d), 128.26 (d), 129.10 (d), 132.02 (s), 135.57 (s), 137.73 (s), 141.28 (s), 143.53 (s), 150.88 (s), 151.19 (s), 152.74 (s), 153.36 (s), 168.17 (s).

Similarly, hydrogenolysis of (*R*)-**7e** afforded (*R*)-**8** as a colorless oil (25 mg, 83%): ^1H NMR δ 2.54 (dd, 1 H, *J* = 9.2, 13 Hz), 2.59 (dd, 1 H, *J* = 6.0, 13 Hz), 2.97 (dd, 1 H, *J* = 3.6, 9.4 Hz), 3.07 (dd, 1 H, *J* = 3.3, 9.4 Hz), 3.20 (s, 3 H), 3.60 (s, 3 H), 3.74 (s, 3 H), 3.87 (s, 3 H), 3.90 (s, 3 H), 3.92 (s, 3 H), 3.94 (s, 3 H), 4.12–4.20 (m, 1 H), 4.24 (s, 2 H), 6.51 (d, 1 H, *J* = 8.0 Hz), 6.83 (s, 1 H), 7.05 (s, 1 H), 7.10–7.26 (m, 5 H).

Hydroxy Amide (*R*)-8 from (*R*)-7a. A solution of biphenyl (*R*)-**7a** (47 mg, 0.077 mmol) in ethyl acetate (3 mL) was treated with 10% palladium on carbon (25 mg). The system was evacuated with a water aspirator and purged with hydrogen (3×). The mixture was stirred under a hydrogen atmosphere (balloon) for 48 h, filtered through Celite, and condensed. The residue was dissolved in THF (5 mL), and 3 N HCl (3 mL) was added. The mixture was stirred for 15 h, saturated with NaCl, and extracted with ether (25 mL). The organic layer was dried and condensed. The residue (44 mg) was dissolved in methanol (3 mL), cooled in an ice bath, and treated with sodium borohydride (30 mg, 0.79 mmol). After 30 min, the reaction was quenched with saturated aqueous NH_4Cl solution (1.5 mL). The mixture was partitioned between water (1 mL) and CH_2Cl_2 (25 mL). The organic layer was dried and condensed. Purification of the crude product by preparative TLC (hexanes:ethyl acetate = 1:2.5) gave (*R*)-**8** (6 mg, 14%), equivalent to material obtained from (*R*)-**7e** (^1H NMR data).

Amide 9 from 7d. Following the hydrogenolysis procedure for **7e**, biphenyl **7d** was converted to amide **9**, which was isolated as a 7.5:1 = *S*:*R* mixture of axial diastereomers (40 mg, 97%): $[\alpha]^{22}_D$ +30.5° (*c* 1.47, $CHCl_3$); IR 3391 (br), 2937, 2844, 1651, 1591, 1564, 1483, 1325, 1103 cm^{-1}; ^1H NMR δ 1.92 (s, 0.35 H), 1.97 (s, 2.65 H), 2.62 (dd, 1 H, *J* = 8.6, 13 Hz), 2.72 (dd, 1 H, *J* = 6.1, 13 Hz), 2.85 (dd, 1 H, *J* = 4.2, 9.3 Hz), 2.98 (dd, 1 H, *J* = 3.4, 9.3 Hz), 3.15 (s, 2.65 H), 3.18 (s, 0.35 H), 3.62 (s, 0.35 H), 3.63 (s, 2.65 H), 3.73 (s, 2.65 H), 3.80 (s, 0.35 H), 3.86 (s, 2.65 H), 3.87 (s, 0.35 H), 3.89 (s, 2.65 H), 3.90 (s, 0.35 H), 3.92 (s, 3 H), 3.94 (s, 3 H), 4.09–4.22 (m, 1 H), 6.16 (d, 1 H, *J* = 8.3 Hz), 6.55 (s, 0.12 H), 6.61 (s, 0.88 H), 7.13–7.34 (m, 6 H); ^{13}C NMR (major

isomer) δ 19.96 (q), 36.92 (t), 50.51 (d), 55.72 (q), 55.81 (q), 58.49 (q), 60.46 (q), 60.55 (q), 60.68 (q), 71.56 (t), 108.03 (d), 108.78 (d), 121.83 (s), 122.14 (s), 126.12 (d), 128.21 (d), 129.21 (d), 130.71 (s), 132.65 (s), 138.00 (s), 139.98 (s), 143.95 (s), 151.06 (s), 152.58 (s), 153.06 (s), 166.90 (s).

Amide 9 from Hydroxy Amide 8. A solution of alcohol (*S*)-**8** (52 mg, 0.94 mmol) in ethyl acetate (3 mL) was treated with 10% palladium on carbon (20 mg) and perchloric acid (3 drops, 70% aqueous solution). The system was evacuated with a water aspirator and purged with hydrogen (3×). The mixture was stirred under a hydrogen atmosphere (balloon) for 24 h, filtered through Celite, and condensed. Purification by preparative TLC with hexanes/ethyl acetate (1:3) afforded (*S*)-**9** (37 mg, 73%). The ^{1}H NMR spectrum of this compound was identical with that of the major isomer of **9** from **7d**.

Similarly, acidic hydrogenolysis of (*R*)-**8** provided a sample of (*R*)-**9**. This material was compared to the minor isomer of **9** from **7d** by HPLC analysis (column A, hexanes:2-propanol = 6:1, t_R = 4.2 min (minor); 4.7 min (major)).

Diester Amide 10. A solution of oxazoline (*S*)-**7c** (1.415 g, 2.119 mmol) in THF (22 mL) was treated with powdered sodium sulfate (15.5 g, 0.109 mol), water (2.0 mL, 0.11 mol), and trifluoroacetic acid (0.87 mL, 11 mol). The suspension was stirred for 12 h, and anhydrous sodium sulfate (4.2 g, 30 mmol) was added. Filtration and concentration at <30 °C afforded the unstable ammonium salt, which was dissolved in CH_2Cl_2 (36 mL), cooled in an ice bath, and treated sequentially with acetic anhydride (7.3 mL, 77 mmol) and pyridine (11.5 mL, 0.142 mol). The reaction mixture was allowed to warm to ambient temperature over 7 h. The solution was washed with cold 3 N HCl (3 × 50 mL) and saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was dried and condensed. Purification of the crude product by radial chromatography with hexanes/ethyl acetate (1:1) afforded (*S*)-**10**, a white solid (1.040 g, 74.9%): mp 152–153 °C; $[\alpha]^{22}_D$ −0.4° (*c* 1.40, $CHCl_3$), $[\alpha]^{22}_D$ +9.91° (*c* 1.10, C_6H_6); IR 3430 (br), 3054, 2986, 2941, 1728, 1676, 1592, 1487, 1464, 1105 cm^{-1}; ^{1}H NMR δ 1.89 (s, 3 H), 1.97 (s, 3 H), 3.08 (dd, 1 H, *J* = 3.4, 9.6 Hz), 3.23 (dd, 1 H, *J* = 5.0, 9.6 Hz), 3.25 (s, 3 H), 3.42 (s, 3 H), 3.58 (s, 3 H), 3.69 (s, 3 H), 3.90 (s, 3 H), 3.95 (s, 3 H), 4.01 (s, 3 H), 4.49–4.59 (m, 1 H), 4.65 (d, 1 H, *J* = 12 Hz), 4.75 (d, 1 H, *J* = 12 Hz), 6.07 (d, 1 H, *J* = 7.0 Hz), 6.16 (d, 1 H, *J* = 8.4 Hz), 6.76 (s, 1 H), 7.07–7.11 (m, 2 H), 7.19–7.22 (m, 3 H), 7.47 (m, 1 H); ^{13}C NMR δ 20.78 (q), 23.27 (q), 52.55 (d), 55.71 (q), 56.24 (q), 58.90 (q), 60.44 (q), 60.47 (q), 60.59 (q), 60.81 (q), 64.61 (t), 71.14 (t), 74.97 (d), 107.68 (d), 109.76 (d), 123.71 (s), 124.21 (s), 125.94 (s), 126.95 (d), 128.03 (d), 128.20 (d), 129.52 (s), 137.32 (s), 141.74 (s), 145.62 (s), 150.92 (s), 151.61 (s), 152.67 (s), 152.70 (s), 166.00 (s), 169.94 (s), 170.69 (s). Anal. Calcd for $C_{34}H_{41}NO_{12}$: C, 62.28; H. 6.30; N, 2.14. Found: C, 62.28; H, 6.19; N, 2.19.

By the procedure described previously, (*R*)-**7c** (297 mg, 0.445 mmol) was converted to (*R*)-**10** (236 mg, 80.9%): $[\alpha]^{22}_D$ +14.2° (*c* 1.63, $CHCl_3$); IR 3388 (br), 2940, 1738, 1674, 1591, 1487, 1462, 1103 cm^{-1}; ^{1}H NMR δ 1.85 (s, 3 H), 1.91 (s, 3 H), 2.88–2.97 (m, 2 H), 3.19 (s, 3 H), 3.59 (s, 3 H), 3.60 (s, 3 H), 3.86 (s, 3 H), 3.93 (s, 3 H), 3.94 (s, 3 H), 3.95 (s, 3 H), 4.31–4.39 (m, 1 H), 4.54 (d, 1 H, *J* = 12 Hz), 4.75 (d, 1 H, *J* = 12 Hz), 6.02 (d, 1 H, *J* = 6.7 Hz), 6.01–6.04 (d, 1 H), 6.80 (s, 1 H), 7.13–7.16 (m, 2 H), 7.25–7.31 (m, 3 H), 7.39 (m, 1 H); ^{13}C NMR δ 20.48 (q), 22.94 (q), 52.92 (d), 55.73 (q), 55.93 (q), 58.56 (q), 60.31 (q), 60.38 (q), 60.40 (q), 60.59 (q), 64.42 (t), 70.72 (t), 75.11 (d), 108.04 (d), 109.76 (d), 123.94 (s), 124.01 (s), 125.80 (s), 126.66 (d), 128.06 (d), 128.22 (d), 129.25 (s), 137.24 (s), 141.80 (s), 145.54 (s), 150.85 (s), 151.46 (s), 152.53 (s), 152.62 (s), 166.08 (s), 169.68 (s), 170.44 (s).

Diol 11. A solution of ester (*S*)-**10** (117 mg, 0.178 mmol) in THF (5 mL) was cooled in an ice bath and treated with lithium aluminum hydride (38 mg, 1.0 mmol). The suspension was stirred for 1 h and quenched with sodium sulfate decahydrate. Anhydrous sodium sulfate was added (~0.5 g), and the mixture was stirred for 30 min. The salts were filtered and washed with CH_2Cl_2. The filtrate was condensed, and the residue was purified by flash chromatography with ethyl acetate to give (*S*)-**11**, a white solid (61 mg, 87%): mp 111–112 °C (ether/pentane) (lit.[2] mp 106–108 °C); $[\alpha]^{22}_D$ +36.3° (*c* 3.30, $CHCl_3$) (lit.[2] $[\alpha]^{24}_D$ −38.2° (*c* 0.510, $CHCl_3$) for (*R*)-**11**; ^{1}H NMR δ 3.20 (s, 2 H), 3.66 (s, 6 H), 3.89 (s, 6 H), 3.92 (s, 6 H), 4.16 (d, 2 H, *J* = 12 Hz), 4.19 (d, 2 H, *J* = 12 Hz), 6.88 (s, 2 H); ^{13}C NMR δ 55.78 (q), 60.63 (q), 60.71 (q), 63.16 (t), 108.43 (d), 121.52 (s), 135.52 (s), 141.43 (s), 150.89 (s), 153.09 (s).

By the procedure described above, (*R*)-**10** (214 mg, 0.326 mmol) was converted to (*R*)-**11** (120 mg, 93.2%): $[\alpha]^{22}_D$ −43.2° (*c* 1.98, $CHCl_3$).

Hydroxy Acid (*S*)-12. A solution of ester (*S*)-**10** (1.7 g, 2.6 mmol) in THF (65 mL) and water (55 mL) was treated with aqueous 2.5 N NaOH solution (6.7 mL, 17 mmol) and heated at 55 °C for 3 h. The mixture was cooled, and the THF was removed in vacuo. The aqueous layer was extracted with $CHCl_3$ (2 × 40 mL), cooled in an ice bath, acidified (pH ~1) with 3 N HCl, and extracted with CH_2Cl_2 (2 × 50 mL). The CH_2Cl_2 extract was dried and condensed to (*S*)-**12** (1.08 g, 100%): IR 3500–2600 (br), 2941, 1698, 1592, 1487, 1463, 1392, 1321, 1122, 1102 cm^{-1}; ^{1}H NMR δ 3.56 (s, 3 H), 3.62 (s, 3 H), 3.82 (s, 3 H), 3.88 (s, 3 H), 3.93 (s, 3 H), 3.94 (s, 3 H), 4.20 (d, 1 H, *J* = 12 Hz), 4.23 (d, 1 H, *J* = 12 Hz), 6.83 (s, 1 H), 7.36 (s 1 H); ^{13}C NMR δ 55.72 (q), 55.96 (q), 60.51 (q), 60.54 (q), 60.71 (q), 60.89 (q), 63.83 (t), 107.76 (d), 109.86 (d), 122.02 (s), 125.13 (s), 125.78 (s), 134.11 (s), 141.24 (s), 145.91 (s), 150.75 (s), 151.24 (s), 152.29 (s), 152.89 (s), 170.62 (s).

Hydroxy Silyl Ether 13. A solution of hydroxy acid (*S*)-**12** (228 mg, 0.558 mmol) in dry CH_2Cl_2 (5 mL) was treated sequentially with triethylamine (0.27 mL, 1.95 mmol), *tert*-butyldimethylsilyl chloride (252 mg, 1.67 mmol), and a spatula tip of 4-(dimethylamino)pyridine. The mixture was stirred at ambient temperature for 3 h, cooled to −78 °C, and treated with diisobutylaluminum hydride (4.8 mL, 4.8 mmol, 1.0 M DIBAL in CH_2Cl_2). After 2 h, additional DIBAL (1.2 mL) was added. The mixture was stirred for 1 h and quenched with sodium sulfate decahydrate (2.5 g). The cooling bath was removed, and anhydrous sodium sulfate (~6 g) was added at ambient temperature. The reaction mixture was filtered and condensed. Purification by radial chromatography with hexanes/ethyl acetate (4:1 to 1:1) afforded **13** as a colorless oil (253 mg, 89.1%): $[\alpha]^{22}_D$ +7.23° (*c* 1.66, $CHCl_3$); IR 3500 (br), 2934, 2873, 2856, 1597, 1582, 1572, 1462, 1102 cm^{-1}; ^{1}H NMR δ −0.032 (s, 3 H), −0.024 (s, 3 H), 0.85 (s, 9 H), 2.96 (br s, 1 H), 3.65 (s, 3 H), 3.67 (s, 3 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 3.91 (s, 3 H), 3.92 (s, 3 H), 4.14 (s, 2 H), 4.16 (d, 1 H, *J* = 13 Hz), 4.39 (d, 1 H, *J* = 13 Hz), 6.86 (s, 1 H), 6.92 (s, 1 H); ^{13}C NMR δ −5.44 (q), −5.40 (q), 18.39 (s), 25.91 (q), 55.79 (q), 55.91 (q), 60.67 (q), 60.76 (q), 60.86 (q), 60.92 (q), 63.12 (t), 63.88 (t), 106.65 (d). 108.37 (d), 120.47 (s), 121.04 (s), 135.73 (s), 135.78 (s), 140.84 (s), 141.39 (s), 150.76 (s), 151.16 (s), 152.94 (s), 153.21 (s). Anal. Calcd for $C_{26}H_{40}O_8Si$: C, 61.39; H, 7.93. Found: C, 61.44; H, 8.07.

Bromo Silyl Ether 14. A solution of monosilyl ether **13** (1.01 g, 1.99 mmol) in CH_2Cl_2 (28 mL) was cooled in an ice bath and treated sequentially with triphenylphosphine (0.78 g, 3.0 mmol) and *N*-bromosuccinimide (0.53 g, 3.0 mmol, recrystallized from water). The mixture was stirred for 40 min and partitioned between CH_2Cl_2 (50 mL) and water (25 mL). The organic layer was dried and concentrated. Purification by radial chromatography with hexanes/ethyl acetate (4:1) afforded **14** (897 mg, 79.0%) and dibromide **14a** (77 mg, 7.5%).

14 (higher R_f): $[\alpha]^{22}_D$ −7.95° (*c* 1.12, $CHCl_3$); IR 2935, 2856, 1596, 1572, 1484, 1462, 1102 cm^{-1}; ^{1}H NMR δ 0.024 (s, 6 H), 0.92 (s, 9 H), 3.66 (s, 3 H), 3.70 (s, 3 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 3.93 (s, 3 H), 3.94 (s, 3 H), 4.17 (d, 1 H, *J* = 10 Hz), 4.25 (d, 1 H, *J* = 10 Hz), 4.38 (AB, 2 H, *J* = 15 Hz), 6.87 (s, 1 H), 7.04 (s, 1 H); ^{13}C NMR δ −5.38 (q), 18.26 (s), 25.87 (q), 32.43 (t), 55.63 (q), 55.85 (q), 60.54 (q), 60.65 (q), 60.71 (q), 60.73 (q), 62.47 (t), 104.97 (d), 108.92 (d), 118.32 (s), 122.32 (s), 131.90 (s), 136.23 (s), 140.14 (s), 142.09 (s), 150.77 (s), 151.20 (s), 153.01 (s), 153.14 (s).

14a (lower R_f): $[\alpha]^{22}_D$ −0.526° (*c* 0.76, $CHCl_3$); ^{1}H NMR δ 3.73 (s, 6 H), 3.90 (s, 6 H), 3.94 (s, 6 H), 4.20 (d, 2 H, *J* = 10 Hz), 4.23 (d, 2 H, *J* = 10 Hz), 6.89 (s, 2 H); ^{13}C NMR δ 32.38 (t), 55.93 (q), 60.78 (q), 60.81 (q), 108.91 (d), 121.86 (s), 131.86 (s), 142.03 (s), 151.38 (s), 153.48 (s).

Hydroxy Aldehyde 15. A solution of diisopropylamine (3.27 mL, 23.5 mmon) in THF (25 mL) was cooled in an ice bath and treated dropwise with *n*-butyllithium (10.3 mL, 18.5 mmol, 1.80 M in hexanes). After being stirred for 20 min, a solution of *N*-propylidenecyclohexanamine[16] (3.56 g, 25.6 mmol) in THF (25 mL) was added with a cannula. After 30 min, the light yellow solution was cooled to −78 °C and treated with a solution of bromide **14** (897 mg, 1.57 mmol) in THF (25 mL). The reaction mixture was stirred for 1.5 h, quenched with saturated aqueous NH_4Cl solution (3 mL), and concentrated. The residue was diluted with THF (30 mL) and treated with aqueous 5% HCl (23 mL). After the mixture was stirred at ambient temperature for 4 h, the THF was removed in vacuo. The aqueous layer was saturated with NaCl and extracted with ether (100 mL, 50 mL). The organic layers were dried and concentrated. The crude product was purified by radial chromatography with hexanes/ethyl acetate (1:1) to afford **15** (501 mg, 73.5%). The product consisted of a 1:1 mixture of C-8 epimers; configuration assignments in the ^{1}H NMR data were obtained from the asymmetric alkylations giving **25**/**27**.

15: $[\alpha]^{22}_D$ +17.7° (*c* 0.13, $CHCl_3$); IR 3483 (br), 2938, 2844, 2719, 1719, 1596, 1570, 1485, 1459, 1394, 1319, 1125, 1104 cm^{-1}; ^{1}H NMR δ 0.88 *R* (d, 1.5 H, *J* = 6.6 Hz), 0.95 *S* (d, 1.5 H, *J* = 7.0 Hz), 1.78 (br s, 0.5 H), 2.23 *S* (dd, 0.5 H, *J* = 7.3, 14 Hz), 2.33–2.43 *R* (m, 1.5 H), 2.68–2.75 *R* (m, 0.5 H), 2.83 *S* (dd, 0.5 H, *J* = 6.8, 14 Hz), 2.90 (br s, 0.5 H), 3.65 (s, 3 H), 3.71 *R* (s, 1.5 H), 3.72 *S* (s, 1.5 H), 3.87 (s, 3 H), 3.88 (s, 3 H), 3.90 (s, 3 H), 3.94 (s, 3 H), 4.14 *S* (br s, 1 H), 4.17

R (br s, 1 H), 6.59 *S* (s, 0.5 H), 6.60 *R* (s, 0.5 H), 6.91 (s, 1 H), 9.32 *S* (d, 0.5 H, *J* = 1.7 Hz), 9.43 *R* (d, 0.5 H, *J* = 1.5 Hz); ^{13}C NMR δ 13.63 (q), 34.56 (t), 34.66 (t), 46.68 (d), 46.71 (d), 55.82 (q), 55.91 (q), 60.62 (q), 60.75 (q), 60.81 (q), 60.90 (q), 63.67 (t), 63.72 (t), 107.76 (d), 107.84 (d), 108.93 (d), 109.10 (d), 121.12 (s), 121.20 (s), 122.17 (s), 122.44 (s), 134.04 (s), 134.20 (s), 135.64 (s), 135.66 (s), 140.46 (s), 141.31 (s), 150.97 (s), 151.02 (s), 151.14 (s), 152.65 (s), 153.28 (s), 204.38 (d), 204.62 (d).

Bromo Aldehyde 16. A solution of hydroxy aldehyde **15** (501 mg, 1.15 mmol) in CH_2Cl_2 (12 mL) was cooled in an ice bath and treated sequentially with triphenylphosphine (454 mg, 1.73 mmol) and *N*-bromosuccinimide (308 mg, 1.73 mmol). The mixture was stirred for 30 min and partitioned between CH_2Cl_2 (50 mL) and water (25 mL). The organic layer was dried, passed through a plug of silica gel (Amicon, ether), and concentrated. Purification by radial chromatography with hexanes/ethyl acetate (4:1 to 1:1) afforded **16** (517 mg, 90.1%). The product consisted of a 1:1 mixture of C-8 epimers; configuration assignments in the ^{1}H NMR data were obtained from the asymmetric alkylations giving **25**/**27**.

16: $[\alpha]^{22}_D$ −3.69° (*c* 1.57, $CHCl_3$); IR 2938, 2843, 2716, 1724, 1595, 1570, 1458, 1393, 1324, 1102 cm^{-1}; ^{1}H NMR δ 0.95 *S* (d, 1.5 H, *J* = 7.0 Hz), 1.00 *R* (d, 1.5 H, *J* = 6.9 Hz), 2.20 *S* (dd, 0.5 H, *J* = 7.2, 14 Hz), 2.31 *R* (dd, 0.5 H, *J* = 7.7, 14 Hz), 2.53–2.62 (m, 1 H), 2.74 *R* (dd, 0.5 H, *J* = 6.6, 14 Hz), 2.87 *S* (dd, 0.5 H, *J* = 7.1, 14 Hz), 3.69 (s, 1.5 H), 3.70 (s, 3 H), 3.71 (s, 1.5 H), 3.87 (s, 3 H), 3.88 (s, 3 H), 3.90 (s, 1.5 H), 3.91 (s, 1.5 H), 3.93 (s, 3 H), 4.15 *S* (d, 0.5 H, *J* = 10 Hz), 4.16 *R* (d, 0.5 H, *J* = 10 Hz), 4.26 (d, 1 H, *J* = 10 Hz), 6.59 (s, 1 H), 6.89 (s, 1 H), 9.48 *R* (d, 0.5 H, *J* = 1.6 Hz), 9.54 *S* (d, 0.5 H, *J* = 1.6 Hz); ^{13}C NMR δ 13.74 (q), 13.79 (q), 32.27 (t), 34.43 (t), 46.43 (d), 46.57 (d), 55.86 (q), 60.54 (q), 60.61 (q), 60.73 (q), 108.25 (d), 108.32 (d), 108.92 (d), 121.43 (s), 123.08 (s), 131.54 (s), 131.62 (s), 134.10 (s), 134.30 (s), 140.23 (s), 142.04 (s), 151.21 (s), 151.42 (s), 152.92 (s), 153.10 (s), 204.65 (d), 204.70 (d).

Preparation of Ketones 17s and 17r. Samarium metal powder (0.75 g, 5.0 mmol, Alfa) was flamed and cooled under argon. A solution of 1,2-diiodoethane (0.71 g, 2.5 mmol) in THF (25 mL) was added at ambient temperature with a cannula. The mixture was stirred for 1.5 h and cooled in an ice bath. The deep aqua solution turned purple upon addition of HMPA (0.40 mL, 2.3 mmol). A solution of bromo aldehyde **16** (182 mg, 0.366 mmol) in THF (16 mL) was added over 1.5 h. The mixture was stirred for 2 h, quenched with saturated aqueous K_2CO_3 solution (10 mL), and extracted with ether (75 mL). The organic layer was washed with water (3 × 40 mL), dried, and concentrated. Purification by radial chromatography with hexanes/ethyl acetate (3:1 to 1:1) afforded two major product mixtures.

The products with the higher R_f (68.0 mg, 0.16 mmol) were dissolved in benzene (7.5 mL) and treated with pyridinium chlorochromate on alumina[19] (1.0 g, 1.0 mmol). The suspension was stirred for 12 h and filtered through a plug of silica gel (Amicon, ether). Purification by radial chromatography with hexanes/ethyl acetate (4:1) afforded ketone **17s** (55 mg, 36%). Similarly, the products with the lower R_f (50.8 mg, 0.12 mmol) were oxidized to **17r** (45 mg, 30%).

17s: $[\alpha]^{22}_D$ −213° (*c* 1.96, $CHCl_3$); IR 2936, 2837, 1703, 1595, 1577, 1488, 1460, 1405, 1300, 1127, 1105 cm^{-1}; ^{1}H NMR δ 1.14 (d, 3 H, *J* = 6.6 Hz), 2.41 (dd, 1 H, *J* = 12, 14 Hz), 2.56–2.64 (m, 1 H), 2.60 (dd, 1 H, *J* = 2.2, 11 Hz), 3.23 (d, 1 H, *J* = 11 Hz), 3.53 (d, 1 H, *J* = 11 Hz), 3.67 (s, 6 H), 3.88 (s, 3 H), 3.90 (s, 3 H), 3.91 (s, 3 H), 3.94 (s, 3 H), 6.70 (s, 1 H), 6.73 (s, 1 H); ^{13}C NMR δ 17.03 (q), 38.84 (t), 48.16 (t), 48.33 (d), 55.95 (q), 56.00 (q), 60.60 (q), 60.64 (q), 60.92 (q), 107.72 (d), 107.88 (d), 122.63 (s), 123.04 (s), 128.89 (s), 136.13 (s), 141.03 (s), 141.16 (s), 151.44 (s), 151.69 (s), 153.35 (s), 209.05 (s). Anal. Calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.26; H, 6.61.

17r: $[\alpha]^{22}_D$ −214° (*c* 2.42, $CHCl_3$); IR 2937, 2838, 1698, 1595, 1575, 1487, 1462, 1327, 1127, 1105 cm^{-1}; ^{1}H NMR δ 1.15 (d, 3 H, *J* = 7.2 Hz), 2.46 (dd, 1 H, *J* = 5.1, 14 Hz), 2.64–2.72 (m, 1 H), 2.81 (dd, 1 H, *J* = 3.9, 14 Hz), 3.10 (d, 1 H, *J* = 12 Hz), 3.53 (d, 1 H, *J* = 12 Hz), 3.66 (s, 3 H), 3.67 (s, 3 H), 3.89 (s, 3 H), 3.90 (s, 3 H), 3.909 (s, 3 H), 3.912 (s, 3 H), 6.69 (s, 1 H), 6.73 (s, 1 H); ^{13}C NMR δ 16.57 (q), 36.51 (t), 45.01 (d), 45.95 (t), 55.92 (q), 60.54 (q), 60.86 (q), 107.94 (d), 110.14 (d), 123.28 (s), 123.60 (s), 128.95 (s), 131.88 (s), 141.07 (s), 141.18 (s), 151.47 (s), 151.63 (s), 152.47 (s), 153.12 (s), 211.08 (s).

Equilibration of Ketones 17s and 17r, Basic Conditions. A 53:47 mixture of **17s**/**17r** (2.6 mg; GC (275 °C) t_R = 8.44, 8.76 min) was dissolved in a solution of sodium methoxide in methanol (1.5 mL, 0.26 M). The solution was stirred at ambient temperature and monitored by GC for 3 days. An equilibrium mixture of **17s**:**17r** = 70:30 was achieved within 20 h. Warming the solution to 50 °C led to decomposition of the ketones.

Acidic Conditions. A 53:47 mixture of **17s**/**17r** (2.6 mg) in benzene (1.5 mL) was treated with *p*-toluenesulfonic acid monohydrate (6 mg) and heated at 60 °C. A **17s**:**17r** = 70:30 equilibrium mixture was reached within 24 h.

Methyllithium Addition to Ketone 17s. Preparation of 18. A solution of methyllithium (2.0 mL, 2.8 mmol, 1.4 M in ether) in THF (7.5 mL) was cooled to −78 °C. Ketone **17s** (51 mg, 0.12 mmol) in THF (15 mL) was added with a cannula. The mixture was stirred for 1.5 h, quenched with saturated aqueous NH_4Cl solution (3 mL), and extracted with ether (25 mL). The organic layer was dried and concentrated. Purification by radial chromatography with hexanes/ethyl acetate (4:1 to 1:1) afforded **18** (50.3 mg, 95%). This compound comprised 99.1% of the crude product by GC analysis (285 °C, t_R 8.97 min): $[\alpha]^{22}_D$ −121° (*c* 0.50, $CHCl_3$); IR 3566 (br), 2937, 2836, 1595, 1489, 1461, 1405, 1127, 1104 cm^{-1}; ^{1}H NMR δ 1.10 (d, 3 H, *J* = 7.0 Hz, 8-Me), 1.29 (s, 3 H, 7-Me), 1.58 (br s, 1 H, O*H*), 1.58–1.69 (m, 1 H, 8-H), 2.16 (dd, 1 H, *J* = 2.0, 14 Hz, 9α-H), 2.22 (dd, 1 H, *J* = 9.6, 14 Hz, 9β-H), 2.58 (d, 1 H, *J* = 13 Hz, 6α-H), 2.64 (d, 1 H, *J* = 13 Hz, 6β-H), 3.64 (s, 6 H), 3.89 + 3.90 (2 s, 12 H), 6.55 (s, 1 H, 11-H), 6.68 (s, 1 H, 4-H); ^{13}C NMR δ 18.87 (q), 30.58 (q), 36.76 (t), 45.72 (t), 46.26 (d), 55.92 (q), 55.99 (q), 60.58 (q), 60.92 (q), 70.14 (s), 107.35 (d), 110.08 (d), 122.09 (s), 124.04 (s), 131.57 (s), 138.13 (s), 140.05 (s), 140.87 (s), 151.13 (s), 151.85 (s), 152.38 (s), 153.09 (s). Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.85; H, 7.52. Nuclear Overhauser data irradiation at δ (responsive signals (%)): 1.10 (1.29 (2.0), 1.58 (2.7), 1.58–1.69 (3.2), 2.16/2.22 (1.6)); 1.29 (1.10 (2.3), 1.58 (0.7), 1.58–1.69 (3.7), 2.64 (1.7)); 1.58 + 1.58–1.69 (1.10 (3.5), 1.29 (1.7), 2.16/2.22 (2.3), 2.58/2.64 (1.7), 6.55 (1.5), 6.68 (2.1)); 6.55 (1.58–1.69 (3.5), 2.16 (3.6)); 6.68 (1.58 (11), 26.4 (4.3)).

Olefin 19. A solution of ketone **17s** (40.0 mg, 0.0960 mmol) in CH_2Cl_2 (6 mL) was treated at ambient temperature with "aged" $CH_2Br_2/Zn/TiCl_4$ reagent[21] (~0.9 g). After 15 min, ether (20 mL) was added, and the gray-blue reaction mixture was treated slowly with a slurry of $NaHCO_3$ (2 g) and water (0.5 mL). The mixture was stirred until a dark gray slime precipitated to the bottom of the flask. The solution was decanted and washed with saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous layer was combined with the precipitate, and this mixture was extracted with ether (15 mL). The combined organic layers were dried and concentrated. The crude material was passed through a plug of silica gel (Amicon, hexane:ethyl acetate = 1:1) to afford **19** (42.7 mg, quantitative), which was used in subsequent reactions without further purification: IR 2935, 2849, 1632, 1595, 1578, 1488, 1460, 1401, 1104 cm^{-1}; ^{1}H NMR δ 1.22 (d, 3 H, *J* = 6.5 Hz), 2.20 (dd, 1 H, *J* = 11, 12 Hz), 2.24–2.32 (m, 1 H), 2.49 (d, 1 H, *J* = 12 Hz), 2.87 (d, 1 H, *J* = 13 Hz), 3.23 (d, 1 H, *J* = 13 Hz), 3.63 (s, 3 H), 3.64 (s, 3 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 3.90 (s, 3 H), 3.92 (s, 3 H), 4.74 (s, 1 H), 4.97 (s, 1 H), 6.62 (s, 1 H), 6.68 (s, 1 H); ^{13}C NMR δ 20.97 (q), 40.90 (d), 41.16 (t), 41.70 (t), 55.80 (q), 55.89 (q), 60.52 (q), 60.57 (q), 60.89 (q), 107.02 (d), 107.51 (d), 109.50 (t), 122.17 (s), 122.48 (s), 136.28 (s), 137.87 (s), 140.15 (s), 140.18 (s), 151.23 (s), 151.30 (s), 152.27 (s), 152.81 (s), 152.94 (s).

Epoxide 20. A solution of olefin **19** (42.7 mg, 0.096 mmol maximum) in CH_2Cl_2 (4.8 mL) was cooled in an ice bath and treated with *m*-chloroperoxybenzoic acid (45 mg, 0.22 mmol, 85%). After 14 h, the rose-colored reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with aqueous 10% $Na_2S_2O_3$ and saturated $NaHCO_3$ solutions (10 mL each). The organic layer was dried and concentrated. Purification by radial chromatography with hexanes/ethyl acetate (3:1) gave a pale yellow oil, whose purity was assumed by a single peak by capillary GC (34.9 mg, 84.5%): ^{1}H NMR δ 0.86 (d, 3 H, *J* = 6.9 Hz), 2.13–2.18 (m, 1 H), 2.20 (d, 1 H, *J* = 13 Hz), 2.33–2.45 (m, 1 H), 2.47 (dd, 1 H, *J* = 1.3, 13 Hz), 2.80 (dd, 1 H, *J* = 1.3, 4.0 Hz), 2.83 (d, 1 H, *J* = 4.0 Hz), 2.96 (dd, 1 H, *J* = 1.5, 13 Hz), 3.63 (s, 3 H), 3.64 (s, 3 H), 3.88 + 3.90 (2 s, 9 H), 3.92 (s, 3 H), 6.51 (s, 1 H), 6.61 (s, 1 H); ^{13}C NMR δ 17.49 (q), 38.75 (t), 39.05 (d), 42.24 (t), 47.88 (t), 55.94 (q), 60.59 (q), 60.64 (q), 60.91 (q), 61.86 (s), 107.48 (d), 108.72 (d), 121.96 (s), 123.08 (s), 133.03 (s), 136.91 (s), 140.39 (s), 140.74 (s), 151.28 (s), 151.75 (s), 152.72 (s), 153.23 (s).

Reduction of Epoxide 20. Preparation of 21. A solution of epoxide **20** (34.9 mg, 0.0811 mmol) in THF (3 mL) was treated at ambient temperature with lithium triethylborohydride (0.5 mL, 0.5 mmol, 1.0 M in THF). The solution was stirred 30 min, cooled in an ice bath, and treated dropwise with water to quench the excess hydride. Aqueous 2 N NaOH solution (1 mL) and 30% hydrogen peroxide solution (1 mL) were added. The mixture was saturated with sodium chloride and extracted with ether (30 mL). The organic layer was dried and concentrated. Analysis of the product mixture by capillary GC indicated a 10:1 mixture of **21**/**18** (285 °C, t_R = 10.1, 8.9 min). This indicated that the epoxide contained some epimeric material not detected by capillary GC. Purification by radial chromatography with hexanes/ethyl acetate (3:1) afforded **18** (1.9 mg, 5.4%) and **21** (23.0 mg, 65.5%).

21 (**lower** R_f): $[\alpha]^{22}_D$ −116° (*c* 1.02, $CHCl_3$); IR 3502 (br), 2937, 1596, 1490, 1457, 1403, 1127, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (s, 3 H), 1.10 (d, 3 H, *J* = 7.1 Hz), 1.65 (br s, 1 H), 1.65–1.78 (m, 1 H), 2.14–2.25 (m, 2 H), 2.62 (d, 1 H, *J* = 13 Hz), 2.68 (d, 1 H, *J* = 13 Hz), 3.61 (s, 6 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 3.897 (s, 3 H), 3.903 (s, 3 H), 6.56 (s, 1 H), 6.64 (s, 1 H); ^1H NMR (C_6D_6) δ 0.83 (br s, 1 H, O*H*), 0.98 (s, 3 H, 7-Me), 1.07 (d, 3 H, *J* = 7.1 Hz, 8-Me), 1.68–1.78 (m, 1 H, 8-H), 2.14 (d, 1 H, *J* = 14 Hz, 9α-H), 2.29 (dd, 1 H, *J* = 9.7, 14 Hz, 9β-H), 2.48 (d, 1 H, *J* = 13 Hz, 6β-H), 2.75 (d, 1 H, *J* = 13 Hz, 6α-H), 3.47 (s, 6 H), 3.68 (s, 3 H), 3.70 (s, 3 H), 3.87 (s, 6 H), 6.48 (s, 1 H, 4-H), 6.51 (s, 1 H, 11-H); ^{13}C NMR δ 18.85 (q), 20.71 (q), 37.05 (t), 47.94 (d), 48.24 (t), 55.91 (q), 60.57 (q). 60.89 (q), 60.94 (s), 73.81 (s), 107.12 (d), 110.43 (d), 121.69 (s), 123.34 (s), 132.79 (s), 138.17 (s), 140.11 (s), 140.56 (s), 151.26 (s), 151.46 (s), 151.96 (s), 153.10 (s). Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.35; H, 7.74. Nuclear Overhauser data, irradiation at δ (C_6D_6) (responsive signals (%)): 0.98 (1.07 (2.6), 1.68–1.78 (1.8), 2.14 (−0.4), 2.29 (3.0), 2.48 (1.5), 2.75 (0.6), 6.48 (3.5)); 1.07 (0.98 (?), 1.68–1.78 (7.5), 2.14 (2.8)); 1.68–1.78 (0.83 (7.4), 0.98 (1.2), 1.07 (2.4), 2.14 (1.8), 2.29 (−0.4), 2.48 (−1.6), 2.75 (4.2), 6.51 (3.0)); 6.48 (0.98 (2.3), 1.07 (−0.9), 2.48 (4.6), 2.75 (−2.5)); 6.51 (1.68–1.78 (4.1), 2.14 (5.8)).

Methyllithium Addition to Ketone 17r. Preparation of (−)-Isoschizandrin (22) and (−)-Schizandrin (23). A solution of methyllithium (0.8 mL, 1.1 mmol, 1.4 M in ether) in THF (1.5 mL) was cooled to −78 °C. Ketone **17r** (18.5 mg, 0.0444 mmol) in THF (3 mL) was added with a cannula. The mixture was stirred for 1.5 h, quenched with saturated aqueous NH_4Cl solution (3 mL), and extracted with ether (25 mL). The organic layer was dried and concentrated. Analysis of the product mixture by capillary GC indicated a 15:9.9:75 mixture of **17r**/**23**/**22** (285 °C, t_R = 8.9, 9.4, 10.2 min). Purification by radial chromatography with hexanes/ethyl acetate (3:1 to 1:1) afforded, in order of decreasing R_f, starting ketone (2.2 mg, 12%), **23** (1.8 mg, 9.4%), and **22** (15.1 mg, 78.6%).

The spectroscopic data (^1H and ^{13}C NMR) for **22** are the same as those reported for the natural material. A correction of the aryl resonance at 6.52 ppm ($CDCl_3$) to 6.62 ppm was noted by Dr. Ikeya: $[\alpha]^{22}_D$ −90.6° (*c* 0.62, $CHCl_3$) (lit.[3] $[\alpha]^{25}_D$ +92° (*c* 1.22, $CHCl_3$)); ^1H NMR δ 0.89 (d, 3 H, *J* = 7.0 Hz, 8-Me), 1.19 (s, 3 H, 7-Me), 1.36 (br s, 1 H, O*H*), 1.85–1.95 (m, 1 H, 8-H), 2.32 (d, 1 H, *J* = 13.1 Hz, 6β-H), 2.53–2.54 (m, 2 H, 9-H), 2.82 (d, 1 H, *J* = 13.1 Hz, 6α-H), 3.56 (s, 3 H), 3.57 (s, 3 H), 3.88 (s, 6 H), 3.89 (s, 6 H), 6.54 (s, 1 H, 11-H), 6.61 (s, 1 H, 4-H); ^{13}C NMR δ 13.53, 29.25, 35.45, 40.77, 42.21, 55.95, 60.58, 60.97, 74.10, 110.40, 110.59, 122.93, 123.35, 133.61, 140.44, 140.55, 151.70, 151.78, 151.84, 152.06. Nuclear Overhauser data, irradiation at δ (responsive signals (%)): 0.89 (1.85–1.95 (3.4), 2.32 (−0.8), 2.53–2.54 (0.5), 2.82 (1.8), 6.54 (3.0)); 1.19 (0.89 (−0.5), 1.85–1.95 (3.9), 2.32 (0.6), 2.53–2.54 (1.6), 6.61 (2.7)); 1.85–1.95 (0.89 (3.0), 1.19 (3.2), 2.53–2.54 (6.2)); 6.54 (0.89 (3.4), 2.53–2.54 (−4.9)); 6.61 (1.19 (2.6), 2.32 (6.5), 2.82 (−1.7)).

The spectroscopic data (^1H and ^{13}C NMR) for **23** are the same as those reported for the natural material: $[\alpha]^{22}_D$ −88.2° (*c* 0.11, $CHCl_3$) (lit.[2] $[\alpha]^{22}_D$ +88.7° (*c* 0.767, $CHCl_3$)); ^1H NMR ($CDCl_3$) δ 0.82 (d, 3 H, *J* = 7.2 Hz), 1.26 (s, 3 H), 1.83–1.93 (m, 1 H), 1.89 (br s, 1-O*H*), 2.37 (d, 1 H, *J* = 13 Hz), 2.38 (dd, 1 H, *J* = 7.4, 14 Hz), 2.65 (dd, 1 H, *J* = 1.5, 14 Hz), 2.67 (d, 1 H, *J* = 13 Hz), 3.58 (s, 3 H), 3.59 (s, 3 H), 3.884 (s, 3 H), 3.889 (s, 3 H), 3.894 (s, 3 H), 3.91 (s, 3 H), 6.54 (s, 1 H), 6.61 (s, 1 H); ^1H NMR (C_6D_6) δ 0.72 (d, 3 H, *J* = 7.2 Hz, 8-Me), 1.25 (s, 3 H, 7-Me), 1.76 (br s, 1-O*H*), 1.83–1.93 (m, 1 H, 8-H), 2.21 (dd, 1 H, *J* = 7.8, 14 Hz, 9α-H), 2.32 (d, 1 H, *J* = 13 Hz, 6β-H), 2.76 (d, 1 H, *J* = 13 Hz, 6α-H), 2.80 (dd, 1 H, *J* = 1.5, 14 Hz, 9β-H), 3.40 (s, 3 H), 3.46 (s, 3 H), 3.64 (s, 3 H), 3.69 (s, 3 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 6.36 (s, 1 H, 11-H), 6.59 (s, 1 H, 4-H); ^{13}C NMR δ 15.86 (q), 29.81 (q), 34.25 (t), 40.82 (t), 41.85 (d), 55.90 (q), 55.98 (q), 60.60 (q), 60.94 (q), 71.81 (s), 109.95 (d), 110.41 (d), 122.77 (s), 124.19 (s), 131.81 (s), 133.85 (s), 140.19 (s), 140.77 (s), 151.57 (s), 151.85 (s), 152.06 (s), 152.39 (s). Nuclear Overhauser data, irradiation at δ (C_6D_6) (responsive signals (%)): 0.72 (1.25 (2.2), 1.83–1.93 (4.2), 2.76 (1.4), 6.36 (2.7)); 1.25 (0.72 (1.6), 1.83–1.93 (1.5), 2.32 (1.7)); 1.83–1.93 (0.72 (3.6), 2.21 (4.6), 2.32 (1.4), 2.80 (2.9)); 6.36 (0.72 (3.1), 2.21 (6.6), 2.80 (−1.3)); 6.59 (1.76 (3.1), 2.32 (5.8), 2.76 (−1.9)).

Alkylation of 14 with RAMP-Hydrazone 24. A solution of diisopropylamine (0.25 mL, 1.8 mmol) in THF (3 mL) was cooled in an ice bath and treated dropwise with *n*-butyllithium (0.95 mL, 1.54 mmol, 1.62 M in hexanes). After being stirred for 20 min, the mixture was cooled to −78 °C and a solution of hydrazone (*R*)-**24**[24b] (262 mg, 1.54 mmol) in THF (3 mL) was added over 15 min. The solution was stirred for 1 h, transferred to an ice bath, and after 30 min, placed in a refrigerator (0 °C) for 10 h. The yellow solution was cooled to −95 °C and treated with a solution of bromide **14** (208 mg, 0.364 mmol) in THF (3 mL). The reaction mixture was stirred at this temperature for 1.5 h and allowed to warm gradually to 0 °C. Saturated aqueous NH_4Cl solution (3 mL) was added, and the mixture was extracted with ether (25 mL). The organic layer was dried and concentrated. The crude product was purified by radial chromatography with hexanes/ethyl acetate (6:1 to 1:1) to afford **25**, a viscous colorless oil (216 mg, 89.8%): $[\alpha]^{22}_D$ +41.1° (*c* 1.77, $CHCl_3$); IR 2934, 1739, 1596, 1574, 1456, 1393, 1317, 1195, 1104 cm^{-1}; ^1H NMR δ −0.029 (s, 3 H), −0.018 (s, 3 H), 0.84 (d, 3 H, *J* = 6.6 Hz), 0.88 (s, 9 H), 1.68–1.91 (m, 4 H), 2.18 (dd, 1 H, *J* = 7.6, 14 Hz), 2.39–2.58 (m, 3 H), 3.20–3.28 (m, 2 H), 3.31 (s, 3 H), 3.31–3.37 (m, 1 H), 3.49 (dd, 1 H, *J* = 3.7, 9.0 Hz), 3.59 (s, 3 H), 3.65 (s, 3 H), 3.82 (s, 6 H), 3.84 (s, 3 H), 3.89 (s, 3 H), 4.18 (d, 1 H, *J* = 14 Hz), 4.37 (d, 1 H, *J* = 14 Hz), 6.36 (d, 1 H, *J* = 5.7 Hz), 6.61 (s, 1 H), 6.98 (s, 1 H); ^{13}C NMR δ −5.46 (q), −5.44 (q), 18.23 (s), 18.76 (q), 21.99 (t), 25.84 (q), 26.42 (t), 36.82 (d), 38.47 (t), 50.16 (t), 55.55 (q), 55.75 (q), 59.05 (q), 60.39 (q), 60.42 (q), 60.68 (q), 62.44 (t), 63.46 (t), 74.65 (t), 104.56 (d), 108.11 (d), 119.92 (s), 121.98 (s), 135.05 (s), 135.82 (s), 139.81 (s), 140.08 (s), 143.16 (d), 150.90 (s), 151.06 (s), 152.21 (s), 152.57 (s).

Hydrolysis of Hydrazone 25. Preparation of Hydroxy Aldehyde 15*. A solution of **25** (129 mg, 0.195 mmol) in iodomethane (1.5 mL) was heated at reflux (oil bath: 60 °C) for 12 h. The orange solution was cooled and concentrated. The residue was treated sequentially with pentane (6 mL) and aqueous 10% HCl solution (3 mL). The biphasic mixture was stirred for 2 h, and ether (6 mL) was added. The mixture was stirred for 30 min, diluted with ether (25 mL), and washed with water (2 × 5 mL). The organic layer was dried, filtered through a plug of silica gel (Amicon, ether), and concentrated. Purification by radial chromatography (with hexanes/ethyl acetate (1:1) gave **15***, a colorless oil (30.0 mg, 35.4%). Analysis by ^1H NMR (integration of signals for the aldehyde protons) indicated a 2.9:1 mixture of 8*R* and 8*S* epimers. This data permitted assignment of resonances in the ^1H NMR spectrum of **15** to a given C-8 epimer.

Alkylation of 14 with Chiral Oxazoline 26. A solution of diisopropylamine (0.13 mL, 0.92 mmol) in THF (3 mL) was cooled in an ice bath and treated dropwise with *n*-butyllithium (0.46 mL, 0.74 mmol, 1.62 M in hexanes). After being stirred for 20 min, the mixture was cooled to −78 °C and a solution of oxazoline (*R*,*R*)-**26**[25b] (203 mg, 0.926 mmol) in THF (3 mL) was added over 15 min. The solution was stirred for 1 h, cooled to −100 °C, and stirred for 30 min. A solution bromide **14** (162 mg, 0.283 mmol) in THF (3 mL) was added over 15 min. The reaction mixture was stirred at this temperature for 1.5 h and allowed to warm gradually. Saturated aqueous NH_4Cl solution (3 mL) was added after 1.5 h (bath temperature: −50 °C). The mixture was partitioned between water (5 mL) and ether (25 mL). The organic layer was dried and concentrated. The crude product was purified by radial chromatography with hexanes/ethyl acetate (6:1 to 1:1) to afford **27**, a colorless oil (193 mg, 96.2%). Analysis by ^1H NMR indicated a 14.5:1 mixture of 8*R* and 8*S* epimers: ^1H NMR δ −0.056 (s, 6 H), 0.88 (s, 9 H), 1.09 (d, 3 H, *J* = 6.0 Hz), 2.42–2.59 (m, 2 H), 2.69–2.78 (m, 1 H), 3.32–3.35 (m, 1 H), 3.36 (s, 3 H) 3.56 (dd, 1 H, *J* = 4.4, 9.5 Hz), 3.66 (s, 3 H), 3.71 (s, 3 H), 3.80 (s, 3 H), 3.84 (s, 3 H), 3.90 (s, 6 H), 3.97–4.03 (m, 1 H), 4.32 (d, 1 H, *J* = 14 Hz), 4.42 (d, 1 H, *J* = 14 Hz), 5.16 (d, 0.935 H, *J* = 6.7 Hz), 5.50 (d, 0.065 H, *J* = 9.2 Hz), 6.67 (s, 1 H), 7.01–7.04 (m, 3 H), 7.25–7.31 (m, 3 H).

Removal of the Oxazoline in 27. Preparation of Hydroxy Aldehyde 15*. A solution of oxazoline **27** (193 mg, 0.272 mmol) in dry CH_2Cl_2 (3.5 mL) was treated dropwise at ambient temperature with methyl trifluoromethanesulfonate (0.036 mL, 0.32 mmol) and stirred for 3 h. The solution was cooled in an ice bath, and absolute ethanol (0.4 mL) and sodium borohydride (21 mg, 0.56 mmol) were added. After 45 min, additional sodium borohydride (100 mg) was added. The mixture was stirred to ambient temperature over 1.5 h, quenched with saturated aqueous NH_4Cl solution (1.5 mL), and partitioned between water (3 mL) and CH_2Cl_2 (25 mL). The organic layer was condensed, and the residue was dissolved in THF (4 mL) and water (1 mL). Oxalic acid dihydrate (0.35 g, 2.8 mmol) was added. After being stirred for 12 h, the solution was saturated with NaCl and extracted with ether (25 mL). The organic layer was dried, filtered through a plug of silica gel (Amicon, ether), and concentrated. Purification by radial chromatography with hexanes/ethyl acetate (1:1) gave **15***, a colorless oil (30 mg, 25%). Analysis by ^1H NMR (integration of signals for the aldehyde protons) indicated a 7.7:1 mixture of 8*R* and 8*S* epimers. This data permitted assignment of resonances in the ^1H NMR spectrum of **15** to a given C-8 epimer.

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