JOC Article

Convergent Enantioselective Synthesis of Vinigrol, an Architecturally Novel Diterpenoid with Potent Platelet Aggregation Inhibitory and Antihypertensive Properties. 1. Application of Anionic Sigmatropy to Construction of the Octalin Substructure

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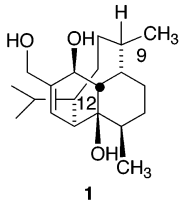
The coupling of building blocks **15** and **36e** in the presence of $MgBr_2 \cdot OEt_2$ at 0 °C proceeds with an exo stereoselectivity (3.2:1) considerably more advantageous for the acquisition of carbinol **37e** than in the absence of the additive (exo/endo = 1:5.7). The pivotal transformation that sets all of the relevant stereocenters of the *cis*-octalin **55** is the oxyanionic-accelerated [3,3]-sigmatropic rearrangement of **37e**. A salient feature is the structurally enforced adoption of a boatlike transition state that serves to properly set four vicinal methine hydrogens in an all-cis arrangement. The ensuing conversion of **55** into iodo sulfone **62** has permitted X-ray crystallographic confirmation of all absolute stereochemical assignments since the isopropyl substituent was initially installed enantioselectively via the Evans oxazolidinone protocol. No intramolecular anionic cyclization of **62** to generate the tricyclic framework was seen. This absence of reactivity is attributed to conformational factors that inhibit attainment of the proper S_N2 reaction trajectory.

Fungi have been the source of a wide variety of structurally unique and pharmacologically active compounds. In 1987/1988, a group of scientists from the Fujisawa Pharmaceutical Co. reported the isolation from *Virgaria nigra* and the structural elucidation of a diterpenoid, the antihypertensive and platelet-inhibiting properties of which held unusual promise.[2] Spectroscopic studies, capped by an X-ray crystallographic analysis, established this substance, named vinigrol, to possess a totally unprecedented decahydro-1,5-butanonaphthalene framework as defined by **1**. These unusual structural features, and the subsequent discovery that vinigrol is also a powerful tumor necrosis factor antagonist and an agent capable of arresting the progression of the AIDS-related complex to AIDS,[3] have fueled interest in **1** as a challenging synthetic objective.[4−6] Despite the application of several imaginative strategies to this problem, a de novo route to **1** has not yet been achieved. Herein we describe, with full experimental detail, a route to an advanced precursor of vinigrol. The present investigation highlights the utility of anionic oxy-Cope chemistry for constructing an extensively functionalized octalin ring system having the dual *R* configuration present in appendages housing both C9 and C12.



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Results and Discussion

Retrosynthetic Analysis. In line with our long-range plan to advance to **1** in nonracemic fashion, the strategy as defined in Scheme 1 was based on the expectation that the cyclization of **3** or a close relative thereof would lead via **2** to the enantiopure diterpenoid target. With the focus on **3**, proper access to this intermediate by methodology capable of accommodating the proper juxtapositioning of six contiguous stereogenic centers was accorded attention. It was reasoned that this important objective

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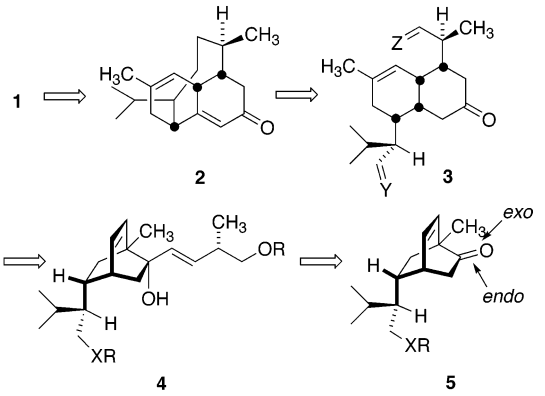
SCHEME 1



could be realized in a single step by anionic oxy-Cope rearrangement[7] of the tertiary bicyclo[2.2.2]octenol **4**. Another attractive feature of **4** is the convenient allowance provided by it for convergent assembly. Thus, we envisioned that ketones such as **5** and appropriately substituted vinylic halides would serve as reaction partners. Proper delineation of the stereoselectivity associated with the coupling of these building blocks was also mandated. Nucleophilic addition to **5** from the π surface opposite the unsaturated bridge would give rise to a diastereomer having olefinic centers too remote for possible engagement in charge-accelerated [3,3]sigmatropic rearrangement. We therefore hoped to skirt its formation. The degree of control available from solvent, temperature, and precise nature of the organometallic reagent was not a priori predictable, and we planned to launch a systematic study in order to define conditions leading to maximum exo stereoselectivity. The impact of changes in the chemical nature of the XR substituent was also to be probed.

Synthesis of Representative Bicyclo[2.2.2]octenones. After brief, unprofitable encounters with routes to **5** based on Diels−Alder and Ireland−Claisen protocols as key transformations,[8] attention was directed instead to a pathway featuring a Michael−Michael sequence for elaboration of the structural framework. The route began by acylation of the lithiated form of (*S*)-oxazolidinone **6**[9] with isovaleryl chloride (Scheme 2).[10] Excellent levels of diastereoselectivity (dr > 95:5) were subsequently realized in the alkylation[11] of **7** with allyl bromide. Traces of the minor reaction component were conveniently removed by preparative HPLC to give **8** of very high quality (>99% ee). Some difficulties were experienced in removing the chiral auxiliary resident in **8**.[12] The use of $LiAlH_4$ resulted in the formation of a significant amount of ring-cleaved amino alcohol. Although Damon's two-step procedure involving the use of lithium benzyl mercaptide was effective on a 100 mg scale,[13] only a 12% yield of **9** was realized at the 10 g level. In contrast, the hindered acyl oxazolidinone responded well to the action of lithium borohydride in THF containing 1 equiv of ethanol.[14] The absence of racemization during formation of alcohol **9** was ascertained by Mosher ester analysis [15] (>97% ee).

Protection of **9** as the *tert*-butyldimethylsilyl ether followed by ozonolysis afforded aldehyde **11**. While the direct alkylation of aldehydes is recognized to be sluggish and competitive with concomitant operation of unwanted aldol condensations or Cannizarro type reactions,[16] prior conversion to an enamine, hydrazone, or imine derivative has been reported to allow alkylations to proceed efficiently.[17] From these options, the pyrrolidine enamine alternative proved most successful in conjunction with methyl vinyl ketone, giving rise to **12** in 84% yield. The best conditions uncovered for the cyclization of the resulting keto aldehyde were adapted from those developed in Burke's quadrone synthesis.[18] Following the heating of **12** with potassium hydroxide and dibenzo-18-crown-6 in benzene, there was isolated 46% of **13** (dr = 1.7:1) and 47% of the intermediate β-hydroxy ketones. Resubmission of the latter to the basic reaction conditions resulted in an increase of the overall yield of cyclohexenones to 80%.

Following the α'-monomethylation of **13**, compound **14** so obtained was subjected to a double-Michael reaction[19] involving phenyl vinyl sulfoxide as the co-reactant. Without purification, the intermediate bicyclic adducts were heated in toluene containing calcium carbonate in order to induce the direct thermal extrusion of benzenesulfenic acid.[20] Although the overall yield in which **15** and **16** were formed was modest (41%), these diastere-

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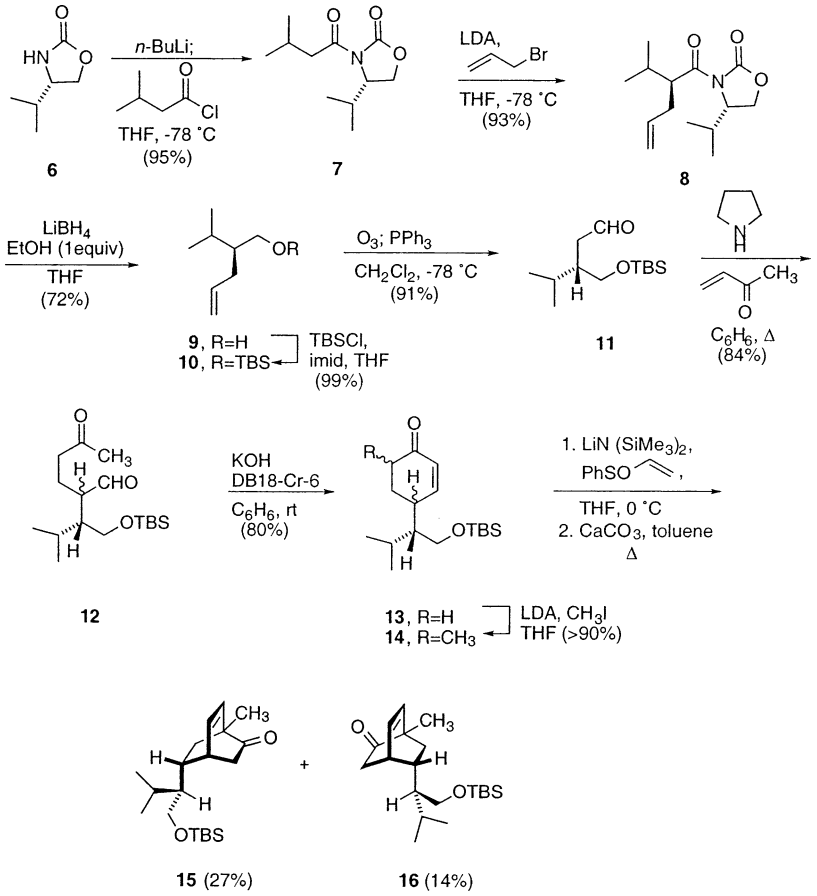
SCHEME 2



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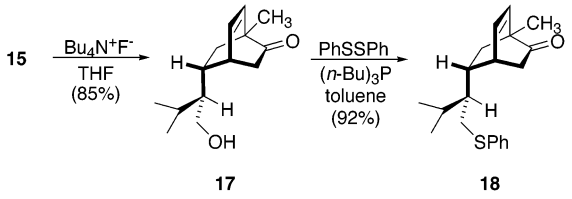

omeric β,γ-unsaturated ketones were conveniently amenable to chromatographic separation.

Deprotection of **15** with TBAF smoothly gave **17** and made possible the ensuing conversion to the phenylthio derivative **18** through the combined action of diphenyl disulfide and tri-*n*-butylphosphine[21] (Scheme 3). We were now in a good position to examine the possible role of different heteroatomic groups on π-face diastereoselection.

Construction of the Nucleophilic Synthons. A rich collection of O-substituted derivatives of methyl (*R*)-2-(hydroxymethyl) propionate has been described in the prior art.[22] Of these, **19a**−**e** were selected for evaluation (Scheme 4). Reduction of these esters with $LiAlH_4$ or Dibal-H furnished the corresponding alcohols. Subsequent careful oxidation of intermediates **20** under Swern conditions[23] or with the perruthenate reagent[24] was implemented without any obvious epimerization. However, stereochemical integrity could not be ensured if the aldehydes were stored for any extended time period, even at low temperatures. Immediate submission of **21** to the Takai reaction[25] was observed to lead almost exclusively to the *E* vinyl iodide **22**. At this point, effort was expended for the purpose of determining the extent of configurational loss during the reaction sequence. To this end, the unstable vinyl iodide **22a** was hydrogenated over plati-

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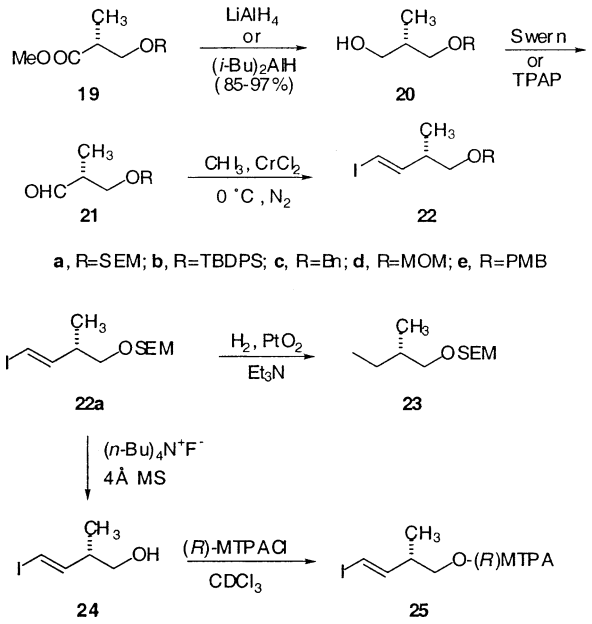
SCHEME 4



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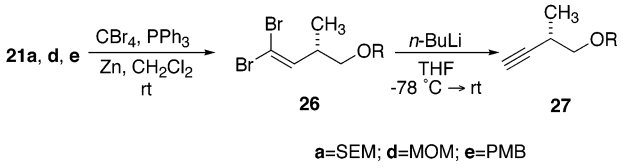
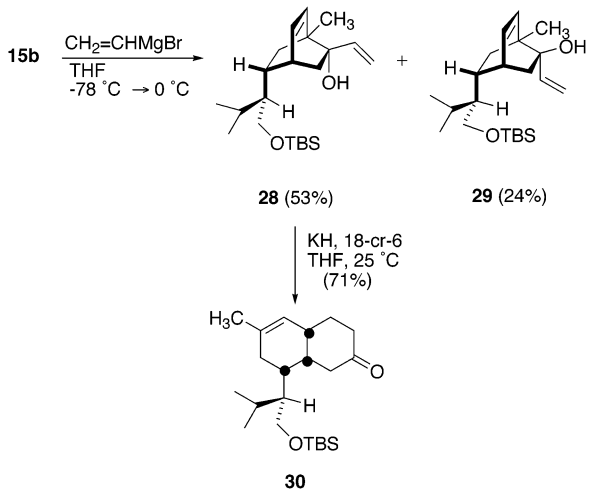


num oxide in the presence of triethylamine.[26a] This process gave rise to **23**, which was independently prepared from pure (*S*)-(−)-2-methyl-1-butanol.[27] Comparison of $[\alpha]_D$ values indicated the enantiomeric excess to be 75%. The same sample of **22a** was treated as well with anhydrous tetra-*n*-butylammonium fluoride at 80 °C under reduced pressure[26b] to provide alcohol **24**. Mosher ester analysis of **25** by ^{1}H and ^{19}F NMR established more reliably that the enantiomeric excess was greater than 90% and therefore suited for further deployment. Parallel behavior was seen with **22b** and **22c**.

To gain greater quantitative appreciation of the stereoselectivity of nucleophilic capture by bicyclic ketones **15** and **18**, the alkynes **27a**, **27d**, and **27e** were also produced (Scheme 5). The Corey−Fuchs procedure[28] was selected among several options and found to be satisfactory for our purposes.

Stereochemical Course of the Coupling Reactions. The ultimate acquisition of **4** requires that 1,2-addition to the carbonyl group in **15** and **18** occur predominantly from the direction syn to the double bond. The consequences of methyl substitution at the proximal bridgehead site and of the endo-oriented side chain on reaction trajectories were not known. Consequently, feasibility studies involving vinylmagnesium bromide were initially undertaken. The conversion to **28** and **29**,

SCHEME 6



realized in anhydrous THF at −78 to 0 °C, proceeded with minimal competing enolization. Column chromatography conveniently separated the less polar **28** (53%) from its more polar counterpart **29** (24%) (Scheme 6). The exo orientation of the vinyl substituent in **28** was easily recognized on the basis of NOE studies. The significant amount of **29** formed under these circumstances was not entirely expected because of the postulate that the bulky group projected to the endo surface might well sterically impede approach from this direction.

The literature precedent in this area is limited and rather disparate. At one extreme such as that involving the conjugate reduction of **31** with $LiAlH_4$, hydride delivery occurs stereospecifically from the exo direction to give **32**.[29] In a related alkylation example, treatment of ketone **33** with LDA and 1-iodobutane produced the exo product (75%), equilibration of which with methanolic sodium hydroxide produced a 73:27 exo/endo mixture.[30] Where direct addition to the carbonyl is involved, product ratios are significantly less imbalanced. For example, the coupling of vinylmagnesium bromide to parent ketone **34** gives rise to a 2:1 mixture of the exo adduct and its epimer.[31] Higher levels of substitution as in **35**, a ketone more structurally allied to **15b**, have little obvious impact on product distribution. The exposure of **35** to 2-lithiodihydropyran has been reported to lead to a 1.5:1 distribution of exo and endo carbinols.[32]

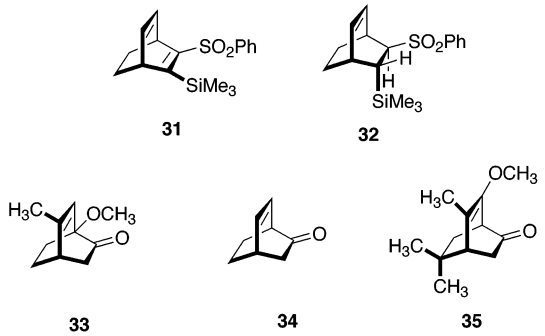


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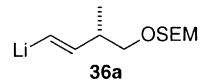
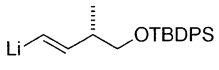
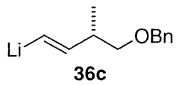
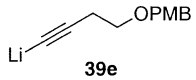
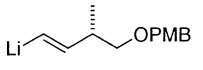
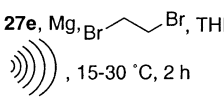
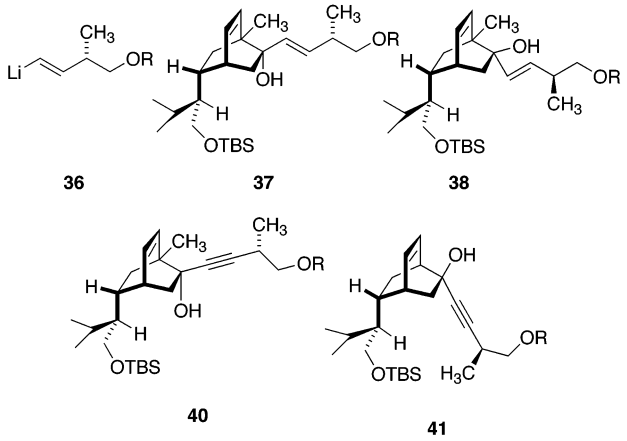
TABLE 1. Stereochemical Course of 1,2-Addition to Bicyclo[2.2.2]octenones 15 and 18 (THF, −78 °C)

expt	ketone	organometallic reagt	yield,%	exo/endo ratio
1	**15**	CH_2=CHMgBr	77	2.2:1
2	**15**	 **36a**	72	1:3.5
3	**15**	 **36b**	73	1:3.6
4	**15**	 **36c**	93	1:4.8
5	**15**	 **39e**	47	1:5.7
6	**18**	 **36e**	58	1:3.5
7	**15**	**27e**, C_2H_5MgBr, THF	30	1:1.8
8	**15**	**27e**, Mg,  , 15-30 °C, 2 h	33	1.5:1
9	**15**	**22e**, *t*-BuLi; $MgBr_2$•OEt_2, ether, -78 °C → 0 °C	60	1.9:1
10	**15**	**22e**, *t*-BuLi; $MgBr_2$•OEt_2 ether, 0 °C, 2h	83	3.2:1

As a result of the above, we defined as an interim goal a clearer definition of those conditions most conducive to production of the appropriate exo isomers. The compatibility of those structural feature resident in **28** to a potential synthesis of vinigrol was brought to the fore when its sigmatropic rearrangement to **30** was found to occur readily at room temperature in the presence of potassium hydride and 18-crown-6 in tetrahydrofuran.

The ready availability of the lithiated alkenes **36** by metal−halogen exchange involving *tert*-butyllithium in THF at −78 °C[33] prompted their initial exploitation. Following chromatographic separation of the less polar **37** from the more polar **38**, it was possible to ascertain by NOE analysis that the preferred π-facial stereoselectivity was in fact opposite to that observed with vinylmagnesium bromide (Table 1). The proportion of **38** varied from 3.5:1 when R was the SEM protecting group to 5.7:1 for the *p*-methoxybenzyl (PMB) derivative. Recourse to HMPA as cosolvent on the basis of its capability to disrupt lithium aggregates[34] had no effect on the isomer distribution. The replacement of THF by ether led to extensive enolization of **15** and **18**, resulting in low-yielding conversion to addition products. The ability of methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) to influence facial selectivity is well recognized.[35] However, the precomplexation of **18** with MAD did not result in a change of product composition at very short exposure times. When reactions were allowed to proceed beyond 20 min at −78 °C, extensive decomposition was noted.

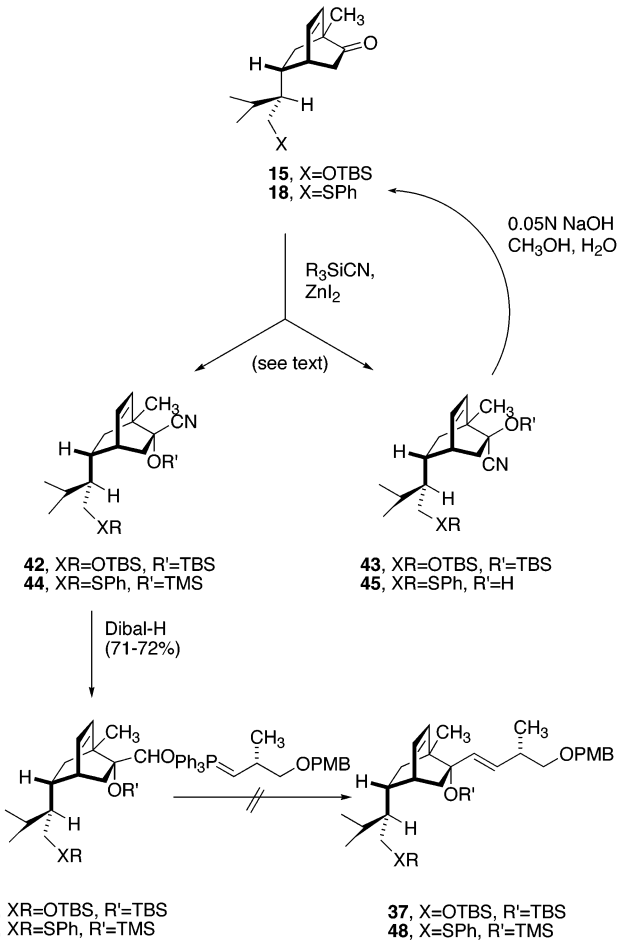


Although recourse to the vinyl cerates[36] and zincates[37] was also ineffective and lithium acetylides afforded no advantage, Grignard reagents proved more ideally suited to preferred exo addition, provided that proper conditions were employed (Table 1, expts 7−10). Although the direct entrainment method involving the metalation of alkyne **27e** with ethylmagnesium bromide in THF failed to give rise to a useful distribution of **40** and **41** (expt 7), significant improvements were noted when sonication of the vinyl iodides in the presence of magnesium metal and 1,2-dibromoethane was utilized (expt 8). More serviceable yet were those conditions involving exposure of the vinyl iodide **22e** to *tert*-butyllithium followed by magnesium bromide etherate (expts 9 and 10). The 3.2:1 exo/endo ratio observed in the last of these experiments accorded us the opportunity to access reasonable quantities of **37e** for the continuation of our studies as discussed in the sequel.

Probe of Possible Cyanohydrin and Enol Ether Alternatives. Although the preceding results proved to be reproducible, we simultaneously probed other possible means for stereocontrolled carbinol synthesis. The alternative interim goal was the construction of α-hydroxy aldehydes of the type **46**, **47**, or **52**, which possess an exo carbonyl group potentially suited to Wittig and related condensations. To this end, **15** was treated with *tert*-butyldimethylsilyl cyanide[38] in the presence of a catalytic

(31) Berson, J. A.; Jones, M., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 5019.
(32) (a) Oplinger, J. A.; Paquette, L. A. *Tetrahedron Lett.* **1987**, *28*, 5441. (b) For a more recent pertinent example, consult: Kim, D.; Shim, P. J.; Lee, J.; Park, C. W.; Hong, S. W.; Kim, S. *J. Org. Chem.* **2000**, *65*, 4864.
(33) Evans, D. A.; Thomas, R. C.; Walker, J. A. *Tetrahedron Lett.* **1976**, 1427.
(34) Chang, N.-C.; Day, H. M.; Lu, W. F. *J. Org. Chem.* **1989**, *54*, 4083.
(35) (a) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573. (b) Hirukawa, T.; Shudo, T.; Kato, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 217. (c) Preparation of MAD: Stern, A. J.; Rohde, J. J.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 4413.
(36) (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T.; Sugiura, Y. *J. Organomet. Chem.* **1985**, *285*, C21. (c) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107. (d) Greeves, N.; Lyford, L. *Tetrahedron Lett.* **1992**, *33*, 4759.
(37) Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198.

SCHEME 7



amount of zinc iodide. Chromatography on silica gel was necessary to separate the nonpolar adducts **42** and **43**, which were formed quantitatively in a reasonably favorable 2:1 ratio. These isomers were distinguished spectroscopically and on the basis of the readiness with which **43** was converted to **15** in the presence of 0.05 N NaOH in aqueous methanol (Scheme 7).

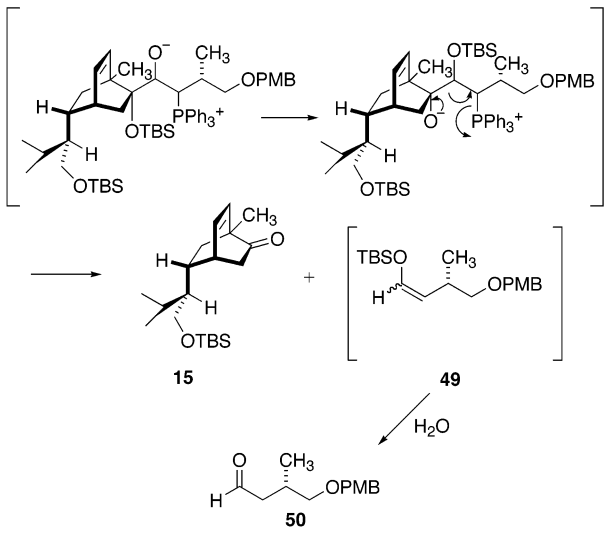
The desired isomer **42** proved inert to these conditions during overnight stirring.

Therefore, the recycling process could, if warranted, be used advantageously to produce exclusively the exo nitrile **42**, the reduction of which to aldehyde **46** with Dibal-H was conveniently accomplished in 72% yield.

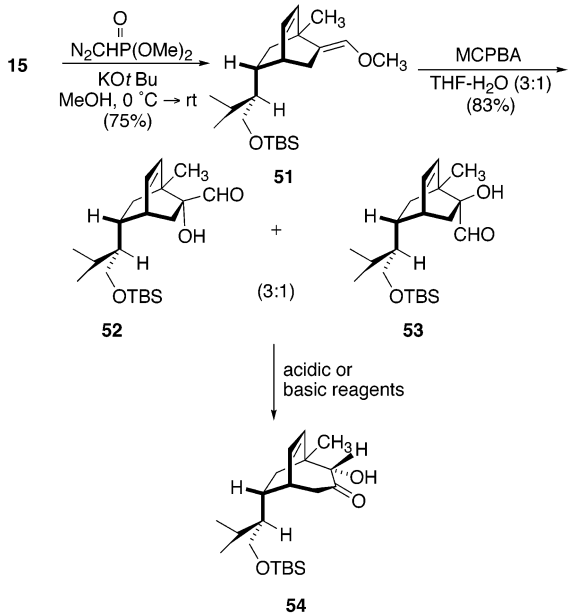
Comparable exposure of **18** to trimethylsilyl cyanide[39] gave rise to a less favorable 1.4:1 mixture of **44** and **45**. As expected, these adducts and the derived aldehyde **47** proved to be somewhat more sensitive compounds as a result of the sterically smaller, more reactive nature of the protecting group. The hydrolysis leading to **45** during chromatography is noteworthy.

The attempted homologation of **46** and **47** to **37** and **48**, respectively, proved to be unsuccessful. Neither Wittig methylenation nor Julia olefination[40] resulted in

SCHEME 8



SCHEME 9

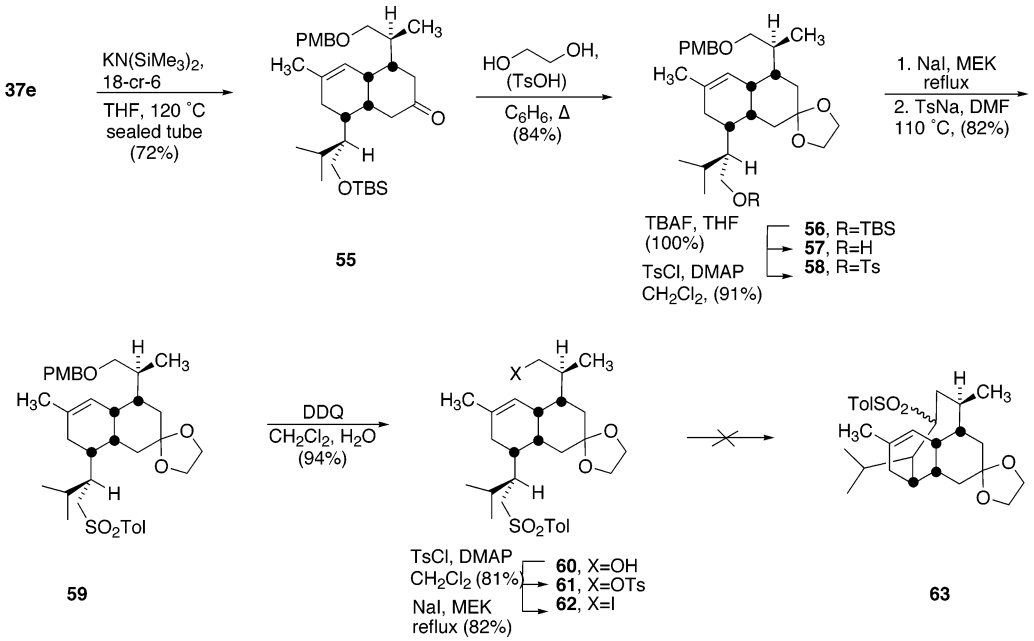


generation of the desired olefin. In the first instance, modest amounts of aldehyde **50** were isolated in addition to the starting ketone **15**. On this basis, it would appear that the mechanistic pathway shown in Scheme 8 may be operative.[41] This fragmentative option results in the expulsion of silyl enol ether **49**, the hydrolysis of which gave rise to **50**.

Our requirements for highly controlled exo orientation of the unsaturated side chain at C-2 of the bicyclooctanol were also met by homologation of **15** to enol ether **51** with dimethyl diazomethylphosphonate[42] and oxidation of the latter with *m*-chloroperbenzoic acid[43] (Scheme 9). These conditions afforded **52** and **53** as a 3:1 mixture in good

(38) Narasaka, K.; Iwakura, K.; Okauchi, T. *Chem. Lett.* **1991**, 423.
(39) (a) Lidy, W.; Sundermeyer, W. *Chem. Ber.* **1973**, *106*, 587. (b) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914.
(40) Marko, I. E.; Murphy, F.; Dolan, S. *Tetrahedron Lett.* **1996**, *37*, 2089 and relevant references therein.
(41) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
(42) Gilbert, J. C.; Weerasooriya, V.; Wiechman, B.; Ho, L. *Tetrahedron Lett.* **1980**, *21*, 5003.
(43) (a) Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3190. (b) Martin, S. F.; Assercq, J.-M.; Austin, R. E.; Dantanarayana, A. P.; Fishpaugh, J. R.; Gluchowski, C.; Guinn, D. E.; Hartmann, M.; Tanaka, T.; Wagner, R.; White, J. B. *Tetrahedron* **1995**, *51*, 3455.

SCHEME 10



yield. The sensitivity of these compounds to acidic and basic conditions precluded their chromatographic separation. Furthermore, all attempts to protect their tertiary hydroxyl group or to effect chain extension generally resulted in operation of an α-ketol rearrangement to give **54**. This result prompted cessation of this phase of the effort and solidified the stance that further advance would be made via the route defined by experiment 10 in Table 1.

Construction of the Octalin Core. Given the ease with which **28** was noted to undergo oxyanionic sigmatropy to form **30**, the expectation was that **37e** and its congeners would likewise rearrange at or slightly above room temperature. Quite to the contrary, exposure of **37e** to potassium hexamethyldisilazide and 18-crown-6 in THF between −78 and 30 °C induced only gradual degradation of the carbinol. After considerable experimentation, it was determined that rapid heating of such samples to 120 °C in sealed tubes for 1 h with subsequent rapid cooling provided **55** in yields exceeding 70% (Scheme 10). That a structurally enforced boatlike transition state had been adopted to set the four contiguous methine hydrogens of the newly crafted octalin ring system in a rigorous all-cis relationship was ultimately confirmed by X-ray crystallographic studies (see below).

To develop the functional group array in **55** while simultaneously addressing the unconfirmed stereochemical issues, we chose to venture forward via the acetal **56**. Following temporary masking of the ketone carbonyl in this manner, desilylation was implemented and the hydroxyl group so uncovered was transformed via tosylate **58** to sulfone **59**. A comparable few steps transformed the *p*-methoxybenzyloxy-terminated side chain into a primary iodide. These advances made available the highly crystalline substance **62**, single crystal X-ray analysis of which confirmed the original stereochemical assumptions while simultaneously defining its solid state conformational features (Figure 1). This rigorous evidence establishes all stereogenic centers to be of the proper vinigrol absolute configuration as a consequence of their relative relationship to C-17, which was installed in enantiocontrolled fashion. Beyond that, the pair of heavily functionalized side chains are clearly seen to be strongly directed to the equatorial plane. A major consequence of this orientational preference, the origins of which are obviously steric in nature, is to position the incipient nucleophilic center neighboring the sulfone sulfur (viz. C-21) remotely from the electrophilic carbon bonded to iodine (C-15). Although it is quite likely that this conformation of **62** or a closely related variant is also preferentially adopted in solution, no information is available concerning the topological flexibility of this *cis*-octalin. *cis*-Decalins are well recognized to be mobile systems subject to being biased toward one of two chair−chair arrangements depending on the locus of substitution.[44] In *cis*-octalins, the situation is somewhat more complex since the double bond introduces an added degree of rigidification.

Attempted Tricycle Formation via Intramolecular Nucleophilic Displacement. The next major goal in the synthesis was cyclization to close the eight-membered ring. The various basic reagents that we chose to employ, ranging from potassium hexamethyldisilazide to potassium hydride, proved to be uniformly incapable of generating **63**. Depending on the specific conditions, either unreacted **62** was returned or elimination of HI was seen. Based on these results, it would appear that intramolecular nucleophilic attack is impeded by an inability of the reaction centers to orient themselves properly along the necessary collinear trajectory. We recognize that S_N2 displacement reactions represent perhaps the most stereoelectonically demanding carbon−carbon bond-forming reactions. For that reason, recourse to this tactic for medium-ring construction has been most often applied only when favorable low energy conformations are populated.[45] MM2 transition structures based

(44) *Stereochemistry of Organic Compounds*; Eliel, E. L., Wilen, S. H., Mander, L. M., Eds.; John Wiley and Sons: New York, 1994; pp 776−781.

(45) Takahashi, T. *Stud. Nat. Prod. Chem.* **1991**, *8*, 175−204.

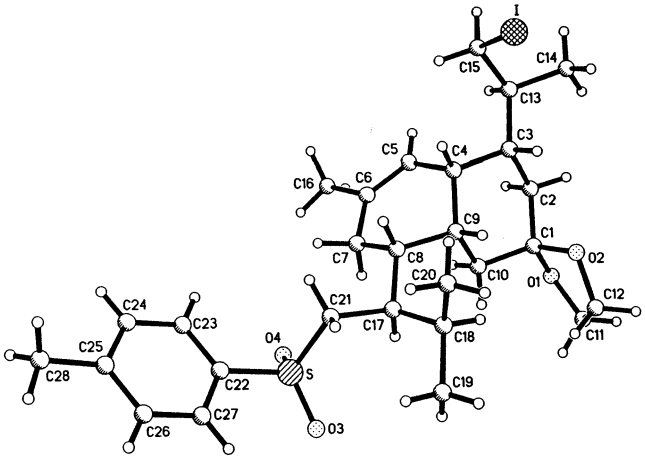
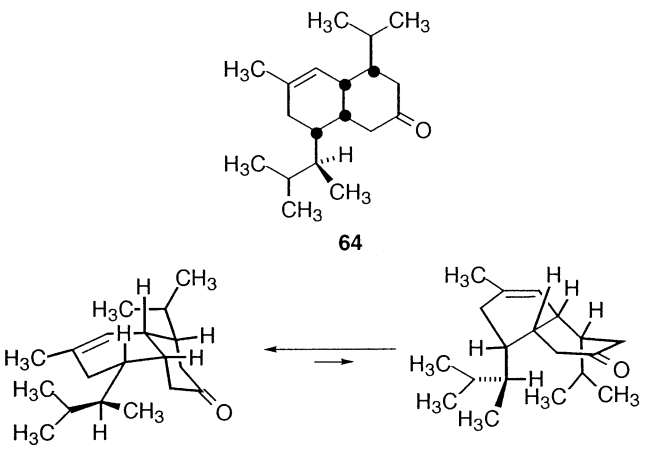


FIGURE 1. Perspective plot of **62** in the solid state.



15.497 kcal/mol	ΔE_{strain}	28.172 kcal/mol
-92.083 kcal/mol	ΔH_f	-79.408 kcal/mol
25.58 kcal/mol	ΔE_{total}	38.25 kcal/mol

FIGURE 2. Energy separating the diequatorial and diaxial conformers of **64**.

on ab initio calculations hold reasonably good predictive ability. Our modeling of the structural prototype **64** has provided indication that the diequatorial conformer is approximately 12.5 kcal/mol less strained than the diaxial arrangement (Figure 2). These considerations provide insight into the extent to which the framework resident in **62** is precluded from aligning the two reacting centers suitably for intramolecular backside displacement. This restriction can be expected to apply to other anionic C−C bond-forming reactions that have been used for medium-ring construction such as the aldol reaction and conjugate additions.[46,47] Somewhat greater latitude is recognized to be associated with radical cyclizations,[47,48] samarium(II)- and manganese(III)-mediated processes,[47] and ring-closing olefin metatheses,[47,49] since comparably high levels of stereoalignment no longer lurk as a complicating factor. These and related protocols are currently under active investigation.

(46) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.
(47) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881.
(48) Yet, L. *Tetrahedron* **1999**, *55*, 9349.

Experimental Section

[(4*S*)-*N*-(3-Methylbutanoyl)-4-(1-methylethyl)-2-oxazolidinone (7). To a solution of (4*S*)-4-isopropyl-2-oxazolidinone (**6**, 100 g, 0.78 mol) in THF (1000 mL) was added 1.6 M *n*-butyllithium in hexanes (509 mL, 0.81 mol) at −60 °C. After being vigorously stirred for 20 min at −50 °C, the thick white slurry was slowly treated with isovaleryl chloride (100 g, 0.85 mol). The resulting homogeneous reaction mixture was stirred for 1 h at 0 °C and treated with saturated K_2CO_3 solution (300 mL). The aqueous layer was extracted with several portions of CH_2Cl_2. The combined organic layers were washed with brine, dried, and concentrated in vacuo. Purification of the residue by distillation gave 157 g (95%) of **7** as a colorless oil: bp 112−115 °C (1 Torr); IR (neat, cm^{-1}) 1780, 1700; ^1H NMR (300 MHz, $CDCl_3$) δ 4.45 (dt, J = 8, 4 Hz, 1H), 4.24 (dd, J = 9, 8 Hz, 1H), 4.17 (dd, J = 9, 4 Hz, 1H), 2.93 (dd, J = 18, 7 Hz, 1H), 2.67 (dd, J = 18, 8 Hz, 1H), 2.35 (heptet x d, J = 7, 4 Hz, 1H), 2.16 (heptet, J = 7 Hz, 1H), 0.98 (d, J = 5 Hz, 3H), 0.96 (d, J = 5 Hz, 3H), 0.90 (d, J = 7 Hz, 3H), 0.86 (d, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 (s), 153.9 (s), 63.1 (t), 58.2 (d), 43.8 (t), 28.3 (d), 25.1 (d), 22.4 (q), 22.2 (q), 17.8 (q), 14.5 (q); MS m/z (M^+) calcd 213.1365, obsd 213.1368; $[\alpha]^{20}_D$ +79.5 (c 1.60, $CHCl_3$).

[(4*S*)-4-Isopropyl-3-[(2*S*)-2-isopropyl-4-pentenoyl]-2-oxazolidinone (8). To an LDA solution prepared at 0 °C from diisopropylamine (66 mL, 0.70 mol) and 1.6 M *n*-butyllithium in hexanes (320 mL, 0.51 mmol) in THF (1500 mL) was slowly added at −65 °C a solution of **7** (100 g, 0.47 mol) in THF (500 mL). The resulting yellow reaction mixture was vigorously stirred at −65 °C for 3 h, warmed to 0 °C over 1 h, cooled back to −65 °C, and treated with freshly distilled allyl bromide (120 mL, 1.41 mol). The resulting solution was stirred at 0 °C overnight and quenched at −50 °C with saturated NH_4Cl solution (500 mL). The resulting aqueous layer was extracted with CH_2Cl_2 (300 mL). The combined organic phases were dried and concentrated in vacuo. Purification of the residue by chromatography (silica gel, elution with 10% ethyl acetate in hexanes) afforded 110 g (93%) of **8** as a colorless oil (de >95%): IR (neat, cm^{-1}) 1780, 1700, 1640; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (m, 1H), 5.03 (br d, J = 17 Hz, 1H), 4.96 (br d, J = 10 Hz, 1H), 4.45 (m, 1H), 4.18 (m, 2H), 3.86 (m, 1H), 2.36 (m, 3H), 1.92 (octet, J = 7 Hz, 1H), 0.94 (d, J = 5 Hz, 3H), 0.92 (d, J = 5 Hz, 3H), 0.88 (d, J = 7 Hz, 3H), 0.83 (d, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7 (s), 153.8 (s), 135.5 (d), 116.7 (t), 62.8 (t), 58.6 (d), 48.1 (d), 33.9 (t), 30.2 (d), 28.3 (d), 20.8 (q), 19.2 (q), 18.0 (q), 14.5 (q); MS m/z (M^+) calcd 253.1678, obsd 253.1683; $[\alpha]^{20}_D$ +92.2 (c 1.06, $CHCl_3$).

Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15. Found: C, 66.63; H, 9.31.

(2*S*)-2-Isopropyl-4-penten-1-ol (9). To a solution of **8** (27.6 g, 0.109 mol) in ether (600 mL) were added absolute ethanol (6.1 mL, 0.11 mol) and a 2.0 M solution of lithium borohydride in THF (60 mL, 0.12 mol) at 0 °C under N_2. The reaction mixture was stirred at 0−5 °C overnight under N_2, quenched with 1 M NaOH solution, stirred until both layers were clear, and poured into ether and water. The ether layer was washed with brine, dried, and concentrated in vacuo. Chromatography of the residue on TLC grade silica gel (elution with 10% ethyl acetate in petroleum ether) or by MPLC (silica gel, elution with

(49) (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833. (c) Fürstner, A. *Topics Catal.* **1997**, *4*, 285. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (e) Pariya, C.; Jayaprakash, K. N.; Sarkar, A. *Coord. Chem. Rev.* **1998**, *168*, 1 (f) Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A.: Chem. 1998*, **133**, 29 (g) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (h) Ivin, K. *J. Mol. Catal. A.: Chem.* **1998**, *133*, 1. (i) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211.

30% ether and 10% CH_2Cl_2 in petroleum ether) afforded 10.04 g (72%) of **9** as a colorless liquid: IR (neat, cm^{-1}) 3400 (br), 1635; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.05 (br d, J = 17 Hz, 1H), 4.99 (br d, J = 10 Hz, 1H), 3.57 (m, 2H), 2.15 (m, 1H), 2.03 (m, 1H), 1.78 (m, 1H), 1.74 (br s, 1H), 1.42 (m, 1H), 0.90 (d, J = 7 Hz, 3H), 0.89 (d, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1 (d), 115.8 (t), 63.6 (t), 46.4 (d), 32.9 (t), 27.9 (d), 19.8 (q), 19.3 (q); MS m/z (M^+) calcd 128.1201, obsd 128.1187; $[\alpha]^{20}_D$ +10.2 (c 0.49, $CHCl_3$).

Anal. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.84; H, 12.63.

***tert*-Butyl[[(2*R*)-2-isopropyl-3-butenyl]oxy]dimethylsilane (10).** To a solution of **9** (11.67 g, 0.09 mol) and imidazole (18.62 g, 0.27 mol) in dry DMF (10 mL) was added *tert*-butyldimethylsilyl chloride (20.61 g, 0.14 mol). The viscous reaction mixture was stirred for 2 days under N_2 at rt, poured into distilled water (150 mL), and extracted thoroughly with several portions of pentane. The combined organic layers were dried and concentrated in vacuo. Purification of the residue by column chromotagraphy (silica gel, elution with petroleum ether) afforded 19.8 g (90%) of **10** as a colorless liquid: IR (neat, cm^{-1}) 1645, 1470, 1440, 1395; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (m, 1H), 5.01 (br d, J = 17 Hz, 1H), 4.96 (br d, J = 10 Hz, 1H), 3.53 (d, J = 5.6 Hz, 2H), 2.06 (m, 2H), 1.80 (m, 1H), 1.37 (m, 1H), 0.90 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.88 (d, J = 6.8 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3 (d), 115.3 (t), 63.0 (t), 46.4 (d), 32.4 (t), 27.7 (d), 25.9 (q, 3C), 19.9 (q), 19.5 (q), 18.3 (s), −5.4 (q, 2C); MS m/z (M^+) calcd 242.2066, obsd 242.2038; $[\alpha]^{20}_D$ +11.9 (c 1.08, $CHCl_3$).

Anal. Calcd for $C_{14}H_{30}OSi$: C, 69.35; H, 12.47. Found: C, 69.72; H, 12.56.

The ^{19}F signals for the Mosher esters in ($CDCl_3$) were seen at −72.74 and −73.04 ppm.

(3*S*)-3-[(*tert*-Butyldimethylsiloxy)methyl]-4-methylvaleraldehyde (11). Ozone was bubbled through a solution of **10** (4.0 g, 17 mmol) in acid-free MeOH (10 mL) and CH_2Cl_2 (45 mL) buffered with $NaHCO_3$ at −78 °C until the appearance of a persistent deep blue color. The reaction mixture was subsequently purged with a flow of dry N_2, treated with methyl sulfide (8 mL) at −78 °C, slowly warmed to rt, and stirred overnight. The volatiles were removed in vacuo, and the residue was purified by column chromatography on Florisil (elution with 10% ether in petroleum ether) to give 3.8 g (91%) of **11** as a colorless oil: IR (neat, cm^{-1}) 1735, 1470, 1395, 1260; ^1H NMR (300 MHz, C_6D_6) δ 9.57 (dd, J = 2, 1 Hz, 1H), 3.51 (dd, J = 10, 5.1 Hz, 1H), 3.40 (dd, J = 10, 6.9 Hz, 1H), 2.14 (ddd, J = 16.3, 8.5, 2.7 Hz, 1H), 2.01 (ddd, J = 16.3, 4.4, 1.4 Hz, 1H), 1.90 (m, 1H), 1.62 (septet, J = 5 Hz, 1H), 0.98 (s, 9H), 0.76 (d, J = 7 Hz, 3H), 0.72 (d, J = 7 Hz, 3H), 0.60 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 200.9 (s), 64.5 (t), 43.6 (t), 42.1 (d), 28.5 (d), 26.0 (q, 3C), 20.2 (q), 19.3 (q), 18.4 (s), −5.5 (q, 2C); MS m/z (M^+) calcd 244.1859, obsd 244.1828; $[\alpha]^{20}_D$ +16.8 (c 1.02, $CHCl_3$).

Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.88; H, 11.55. Found: C, 63.50; H, 11.54.

2-[(*R*)-1-[(*tert*-Butyldimethylsiloxy)methyl]-2-methylpropyl]-5-oxohexanal (12). Water was azeotropically removed from a refluxing solution of **11** (13.0 g, 53.2 mmol) and freshly distilled (from Na) pyrrolidine (18 mL, 215 mmol) in benzene (400 mL) via a Dean−Stark apparatus for 24 h. The resulting solution was concentrated in vacuo to give 15 g (95%) of a moisture-sensitive, pale yellow oil which was used in the next step without further purification: IR (neat, cm^{-1}) 3060, 2940, 1650, 1465, 1390, 1370, 1260, 1100, 940, 850, 780; ^1H NMR (300 MHz, C_6D_6) δ 6.22 (d, J = 13.6 Hz, 1 H), 4.03 (dd, J = 13.6, 9.2 Hz, 1 H), 3.75 (m, 2 H), 2.86 (m, 4 H), 2.20 (m, 1 H), 1.52 (m, 4 H), 1.12 (d, J = 7 Hz, 3 H), 1.07 (s, 9 H), 1.06 (d, J = 7 Hz, 3 H), 0.16 (s, 6 H); ^{13}C NMR (50 MHz, C_6D_6) ppm 137.7 (d), 95.3 (d), 66.9 (t), 50.3 (d), 49.1 (t, 2C), 28.2 (d), 26.2 (q, 3C), 25.0 (t, 2C), 21.7 (q), 18.6 (s), 17.9 (q), −5.4 (q), −5.2 (q).

To a solution of the above enamine (15.0 g, 50.5 mmol) in dry benzene (300 mL) was added freshly distilled methyl vinyl ketone (22.2 mL, 266 mmol). The resulting pale yellow reaction mixture, which became darker yellow as the reaction proceeded, was refluxed for 48 h under N_2, treated at 0 °C with aqueous oxalic acid solution (13 g in 200 mL of distilled water), and stirred for 1 h. The aqueous phase was extracted with several portions of ether (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried, and concentrated in vacuo. Chromatography of the residue (Florisil, elution with 10% ether in petroleum ether) gave 14.1 g (84%) of **12** as a colorless, oily, inseparable 1.2:1 diastereomeric mixture: IR (neat, cm^{-1}) 1725, 1470, 1410, 1390; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (d, J = 2 Hz, 1H), 9.57 (br s, 1H), 3.60 (m, 1H), 3.52 (dd, J = 10, 5.5 Hz, 1H, minor), 3.40 (dd, J = 10, 9.1 Hz, 1H, major), 2.38 (m, 1H), 2.14 (m, 2H), 1.98−1.70 (series of m, 2H), 1.69 (m, 1H), 1.68 (s, 3H, major), 1.67 (s, 3H, minor), 1.53 (m, 1H, major), 1.38 (m, 1H, minor), 0.98 (s, 9H), 0.91 (d, J = 6.7 Hz, 3H, minor), 0.89 (d, J = 6.8 Hz, 3H, major), 0.84 (d, J = 6.7 Hz, 3H, minor), 0.83 (d, J = 6.8 Hz, 3H, major), 0.07 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) (major isomer) δ 205.8 (s), 202.8 (d), 61.9 (t), 51.0 (d), 47.9 (d), 41.5 (t), 29.0 (q), 27.0 (d), 25.6 (q, 3C), 21.3 (q), 20.5 (q), 18.0 (s), 17.9 (t), −6.0 (q, 2C); (minor isomer) δ 205.5 (s), 202.7 (d), 60.5 (t), 51.2 (d), 49.6 (d), 40.9 (t), 29.0 (q), 26.4 (d), 25.6 (q, 3C), 21.2 (t), 21.2 (q), 19.5 (q), 18.0 (s), −6.0 (q, 2C); MS m/z (M^+) calcd 314.2277, obsd 314.2304.

4-[1-(*tert*-Butyldimethylsiloxy)methyl]-2-methylpropyl]-2-cyclohexen-1-one (13). To a vigorously stirred solution of the above enamine (14.1 g, 44.9 mmol) (1.2:1 ratio) in dry benzene (1600 mL) was added a finely ground suspension of KOH (three crushed pellets) and dibenzo-18-crown-6 (0.4 g, 1.1 mmol). The reaction mixture was stirred under N_2 for 64 h, treated with saturated NH_4Cl solution (300 mL), and extracted with several portions of ether (4 × 200 mL). The combined organic layers were dried and concentrated in vacuo. The crude residue was filtered through a pad of silica gel to remove most of the dibenzo-18-crown-6 (elution with 15% ether in petroleum ether) and purified by column chromatography (silica gel, elution with 15% ether in petroleum ether) to give 6.1 g (46%) of **13** (1.7:1 ratio) as a very pale yellow oil and 6.8 g (47%) of β-hydroxy ketone isomers, which were resubjected to the previous reaction conditions for 3 days. After one recycling, a total of 10.6 g (80%) of **13** (1.5:1 ratio of diastereoisomers) was obtained: IR (neat, cm^{-1}) 1680, 1470, 1390; ^1H NMR (300 MHz, $CDCl_3$) δ 7.07 (br d, J = 10.3 Hz, 0.4H), 6.94 (br d, J = 10.3 Hz, 0.6H), 5.96 (m, 1H), 3.67 (m, 2H), 2.76 (m, 1H), 2.51 (m, 1H), 2.34 (m, 1H), 1.98 (m, 2H), 1.84 (m, 1H), 1.47 (m, 0.6H), 1.34 (m, 0.4H), 0.97 (m, 6H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) (major diastereoisomer) δ 200.2 (s), 157.1 (d), 128.5 (d), 61.5 (t), 50.4 (d), 37.9 (t), 37.3 (d), 25.5 (t), 26.9 (d), 25.8 (q, 3C), 21.8 (q), 20.3 (q), 18.1 (s), −5.6 (q, 2C); (minor isomer) δ 200.1 (s), 156.1 (d), 128.3 (d), 60.9 (t), 50.5 (d), 38.0 (t), 36.7 (d), 27.6 (t), 26.9 (d), 25.8 (q, 3C), 21.5 (q), 20.3 (q), 18.1 (s), −5.5 (q, 2C); MS m/z (M^+ − t-Bu) calcd 239.1467, obsd 239.1402.

Anal. Calcd for $C_{17}H_{32}O_2Si$: C, 68.86; H, 10.88. Found: C, 69.19; H, 10.94.

4-[1-(*tert*-Butyldimethylsiloxy)methyl]-2-methylpropyl]-6-methyl-2-cyclohexen-1-one (14). To an LDA solution prepared at 0 °C from diisopropylamine (3.1 mL, 22.2 mmol) and a 1.3 M solution of *n*-butyllithium (14.7 mL, 19 mmol) in THF (120 mL) was slowly added at 0 °C a solution of **13** (4.7 g, 16 mmol) in THF (50 mL). After being stirred for 15 min, the reaction mixture was treated with purified methyl iodide (1.3 mL, 20 mmol), treated 1.5 h later with saturated NH_4Cl solution (100 mL), and extracted with several portions of ether. The combined organic layers were washed with brine, dried, and concentrated in vacuo. Chromatography of the residue on silica gel (elution with 5% ether in petroleum ether) gave 240 mg (5%) of the axial methylated epimer as a pale yellow oil, 3.7 g (75%) of the equatorial isomer **14** as a pale yellow oil

(1.5:1 ratio of 2 diastereoisomers) and 987 mg (20%) of more polar unreacted **13** which can be recycled.

For **14**: IR (neat, cm^{-1}), 1690, 1625, 1480, 1400; ^1H NMR (250 MHz, $CDCl_3$) δ 7.01 (dd, J = 10.3, 2.8 Hz, 1H, minor), 6.90 (dd, J = 10.2, 2.8 Hz, 1H, major), 5.91 (m, 1H), 3.67 (m, 2H), 2.80 (m, 1H), 2.55 (m, 1H), 2.10 (m, 1H), 1.84 (m, 2H), 1.50 (m, 1H, major), 1.41 (m, 1H, minor), 1.15 (d, J = 7 Hz, 3H, minor), 1.13 (d, J = 7 Hz, 3H, major), 0.98 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H, major), 0.94 (d, J = 6.8 Hz, 3H, minor), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (62 MHz, $CDCl_3$) (major diastereoisomer) δ 203.2 (s), 155.1 (d), 127.7 (d), 61.5 (t), 49.8 (d), 39.3 (d), 33.4 (d), 32.1 (t), 27.1 (d), 25.8 (q, 3C), 21.8 (q), 19.9 (q), 18.1 (s), 15.5 (q), −5.6 (q, 2C); (minor isomer) δ 203.0 (s), 154.8 (d), 127.4 (d), 61.0 (t), 49.9 (d), 39.4 (d), 33.7 (t), 32.8 (d), 27.4 (d), 25.8 (q, 3C), 21.6 (q), 19.6 (q), 18.1 (s), 15.6 (q), −5.6 (q, 2C); MS m/z ($M^+ - CH_3$) calcd 295.2093, obsd 295.2119.

Anal. Calcd for $C_{18}H_{34}O_2Si$: C, 69.62; H, 11.04. Found: C, 69.88; H, 11.13.

(1*S*,4*S*,8*R*)-8-[(*R*)-1-[(*tert*-Butyldimethylsiloxy)methyl]-2-methylpropyl]-1-methylbicyclo[2.2.2]oct-5-en-2-one (15) and (1*R*,4*R*,8*S*)-8-[(*R*)-1-[(*tert*-Butyldimethylsiloxy)methyl]-2-methylpropyl]-1-methylbicyclo[2.2.2]oct-5-en-2-one (16). To a cold (0 °C) solution of hexamethyldisilazane (8.2 mL, 38.9 mmol) in THF (36 mL) was added *n*-butyllithium in hexanes (20.1 mL, 32.2 mmol). After 30 min, **14** (4.0 g, 12.9 mmol) dissolved in dry THF (515 mL) was introduced, and the brownish mixture was stirred at 0 °C for 30 min, treated with phenyl vinyl sulfoxide (4.12 g, 27.1 mmol) in THF (65 mL) via a syringe pump during 3 h at 3−6 °C, and quenched with saturated NH_4Cl solution (40 mL). The aqueous phase was extracted several times with ether, and the combined organic layers were dried and concentrated. The residue was taken up in ether, filtered through a pad of Celite, and concentrated. The residue was dissolved in toluene (40 mL), calcium carbonate (2.6 g, 26 mmol) was added, and the yellow suspension was heated at reflux for 24 h. After filtration of the cooled mixture through a pad of Celite, the filtrate was evaporated and the residue was chromatographed on silica gel (elution with 9% ethyl acetate in hexanes) to give 2.5 g (58%) of a mixture of **15** and **16**. Further purification by MPLC afforded 1.16 g (27%) of pure **15** and 609 mg (14%) of **16**.

For **15**: colorless solid; mp 38−40 °C; IR (neat, cm^{-1}) 1730, 1470, 1415, 1390; ^1H NMR (300 MHz, C_6D_6) δ 6.21 (dd, J = 8, 7 Hz, 1H), 5.83 (br d, J = 8 Hz, 1H), 3.55 (dd, J = 10.5, 3 Hz, 1H), 3.39 (dd, J = 10.5, 5 Hz, 1H), 2.48 (m, 1H), 2.01 (dd, J = 18, 2 Hz, 1H), 1.88−1.76 (series of m, 2H), 1.67 (septet × d, J = 7, 3 Hz, 1H), 1.59 (dd, J = 13, 10.5 Hz, 1H), 1.26 (s, 3H), 1.24 (dd, J = 13, 6 Hz, 1H), 0.99 (m, 1H), 0.92 (d, J = 7 Hz, 3H), 0.91 (s, 9H), 0.87 (d, J = 7 Hz, 3H), 0.00 (s, 6H); ^1H NMR (300 MHz, $CDCl_3$) δ 6.54 (dd, J = 7.4, 7.1 Hz, 1H), 5.83 (d, J = 7.7 Hz, 1H), 3.68 (dd, J = 10.5, 3.5 Hz, 1H), 3.61 (dd, J = 10.5, 5 Hz, 1H), 2.88 (br s, 1H), 2.17 (dd, J = 18.5, 1.6 Hz, 1H), 1.90 (ddd, J = 18.5, 3.3, 1.6 Hz, 1H), 1.88 (m, 1H), 1.69 (dd, J = 13.2, 10.5 Hz, 1H), 1.37 (dd, J = 13.2, 6 Hz, 1H), 1.24 (m, 2H), 1.19 (s, 3H), 0.99 (d, J = 7 Hz, 3H), 0.90 (d, J = 7 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 210.4 (s), 138.4 (d), 133.9 (d), 61.7 (t), 49.3 (s), 48.6 (d), 37.2 (t), 36.3 (d), 34.5 (t), 33.8 (d), 27.9 (d), 26.0 (q, 3C), 21.8 (q), 18.3 (s), 18.1 (q), 17.8 (q), −5.5 (q), −5.6 (q); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.5 (s), 138.5 (d), 133.5 (d), 61.6 (t), 49.4 (s), 48.7 (d), 37.1 (t), 36.4 (d), 34.7 (t), 33.6 (d), 27.7 (d), 25.9 (q, 3C), 21.7 (q), 18.1 (s), 17.6 (q), 17.5 (q), −5.5 (q), −5.6 (q); MS m/z (M^+) calcd 336.2485, obsd 336.2481; $[\alpha]^{20}_D$ −273 (c 1.35, $CHCl_3$).

Anal. Calcd for $C_{20}H_{36}O_2Si$: C, 71.37; H, 10.78. Found: C, 71.56; H, 10.87.

For **16**: IR (neat) 1730, 1470, 1415, 1390; ^1H NMR (300 MHz, C_6D_6) δ 6.33 (dd, J = 8, 7 Hz, 1H), 5.66 (br d, J = 8 Hz, 1H), 3.46 (dd, J = 10.5, 3 Hz, 1H), 3.40 (dd, J = 10.5, 4.5 Hz, 1H), 2.89 (m, 1H), 2.30 (dd, J = 18, 2 Hz, 1H), 1.96 (ddd, J = 18, 3.5, 2 Hz, 1H), 1.77 (m, 1H), 1.57 (septet x d, J = 7, 3 Hz, 1H), 1.42 (dd, J = 13, 10.5 Hz, 1H), 1.25 (s, 3H), 1.05 (m, 1H), 1.00 (dd, J = 13, 6 Hz, 1H), 0.92 (s, 9H), 0.87 (d, J = 7 Hz, 3H), 0.71 (d, J = 7 Hz, 3H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 210.7 (s), 138.9 (d), 133.5 (d), 61.3 (t), 49.2 (d), 49.1 (s), 38.7 (d), 37.0 (t), 34.9 (t), 34.5 (d), 28.5 (d), 25.9 (q, 3C), 22.4 (q), 18.2 (s), 18.1 (q), 17.1 (q), −5.5 (q), −5.6 (q); MS m/z (M^+) calcd 336.2485, obsd 336.2482; $[\alpha]^{20}_D$ +278 (c 1.1, $CHCl_3$).

Anal. Calcd for $C_{20}H_{36}O_2Si$: C, 71.37; H, 10.78. Found: C, 71.51; H, 10.78.

(1*S*,4*S*,8*R*)-8-[(1*R*)-1-(Hydroxymethyl)-2-methylpropyl]-1-methylbicyclo[2.2.2]oct-5-en-2-one (17). To a solution of **15** (200 mg, 0.6 mmol) in THF (20 mL) was added at 0 °C a 1 M solution of TBAF in THF (1.4 mL, 1.4 mmol). After being stirred at 0 °C for 5 h and at rt for 10 h, the reaction mixture was treated with saturated NH_4Cl solution (30 mL). The aqueous layer was extracted with ether (5 × 60 mL) and the combined organic layers were dried. Purification of the residue by chromatography (Florisil, elution with 10% ethyl acetate in petroleum ether) gave 113 mg (85%) of **17** as a colorless oil; IR (neat, cm^{-1}) 3446 (br), 1714, 1616, 1453; ^1H NMR (300 MHz, C_6D_6) δ 6.19 (dd, J = 8, 7 Hz, 1H), 5.63 (br d, J = 8 Hz, 1H), 3.35 (m, 2H), 2.44 (m, 1H), 1.99 (br d, J = 18 Hz, 1H), 1.76 (br d, J = 18 Hz, 1H), 1.64 (m, 2H), 1.47 (dd, J = 13, 10.5 Hz, 1H), 1.23 (br s, 1H), 1.22 (s, 3H), 1.15 (dd, J = 13, 6 Hz, 1H), 0.91 (d, J = 7 Hz, 3H), 0.91 (m, 1 H), 0.80 (d, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 211.3 (s), 138.4 (d), 133.8 (d), 61.5 (t), 49.3 (s), 49.0 (d), 37.1 (t), 36.6 (d), 34.5 (t) 33.8 (d), 27.8 (d), 21.7 (q), 18.0 (q), 17.5 (q); MS m/z (M^+) calcd 222.1620, obsd 222.1619.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 10.03. Found: C, 75.84; H, 10.03.

(1*S*,4*S*,8*R*)-8-[(1*R*)-1-(Phenylthiomethyl)-2-methylpropyl]-1-methylbicyclo[2.2.2]oct-5-en-2-one (18). A solution of **17** (500 mg, 2.25 mmol) and diphenyl disulfide (970 mg, 4.44 mmol) in toluene (5 mL) was treated with tri-*n*-butylphosphine (1.1 mL, 4.4 mmol), stirred overnight at rt, and directly charged onto a column of silica gel. Elution with 0−10% of ethyl acetate in hexanes gave **18** (650 mg, 92%) as a white solid: mp 82.5−83.5 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.24 (m, 4H), 7.19−7.14 (m, 1H), 6.53 (t, J = 7.4 Hz, 1H), 5.83 (d, J = 7.4 Hz, 1H), 2.95 (dd, J = 5.7, 12.4 Hz, 1H), 2.89 (m, 1H), 2.82 (ddd, J = 1.0, 3.6, 12.4 Hz, 1H), 2.17 (ddd, J = 1.0, 1.7, 18.5 Hz, 1H), 2.11−1.80 (m, 3 H), 1.69−1.49 (m, 1H), 1.40−1.35 (m, 2 H), 1.18 (s, 3 H), 1.02 (d, J = 6.9 Hz, 3 H), 0.96 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.8, 138.2, 137.7, 133.7, 129.3 (2C), 128.8 (2C),126.0, 49.2, 46.9, 39.6, 37.0, 34.5, 33.9 (2C), 28.4, 21.0, 17.5, 16.9; MS m/z (M^+) calcd 346.1780, obsd 346.1768; $[\alpha]^{20}_D$ +303 (c 6.6, $CHCl_3$).

Anal. Calcd for $C_{20}H_{26}OS$: C, 76.38; H, 8.33. Found: C, 76.34; H, 8.37.

Methyl (2*R*)-3-(*p*-Methoxybenzyloxy)-2-methylpropionate (19e). To an ice-cold suspension of sodium hydride (500 mg, 20 mmol) in dry ether (25 mL) was added dropwise a solution of *p*-methoxybenzyl alcohol (25 g, 0.20 mol) in dry ether (40 mL) over a 15 min period. After an additional 30 min, trichloroacetonitrile (19 mL, 0.89 mol) was introduced dropwise at ice-bath temperature. The mixture was stirred overnight and concentrated to leave the imidate as an oil (46.4 g, 90%).

To a mixture of methyl (*R*)-2-(hydroxymethyl)propionate (10.0 g, 0.085 mol) and the freshly prepared imidate (46 g) in CH_2Cl_2 (20 mL) and petroleum ether (40 mL) was added at 0 °C a solution of triflic acid (0.024 mL, 0.094 mmol) in CH_2Cl_2 (2 mL) under N_2. The reaction mixture was stirred for 30 min at rt, diluted with ice−water, and filtered with the aid of hexane. The aqueous layer of the filtrate was extracted with hexanes, and the combined organic phases were washed with brine, dried, and evaporated. Purification by chromatography on silica gel gave **19e** (9.6 g, 47%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 9.0 Hz, 2H), 4.34 (s, 2H), 3.69 (s, 3H), 3.57 (s, 3H), 3.52 (dd, J = 9.1, 7.4 Hz, 1H), 3.35 (dd, J = 9.1, 5.9 Hz, 1H), 2.67 (ddd, J = 7.4, 7.1, 5.9 Hz, 1H), 1.06 (d, J = 7.1 Hz, 3H).

***p*-Methoxybenzyl (2*S*,3*E*)-4-Iodo-2-methyl-3-butenyl Ether (22e).** A cold (−78 °C) solution of **19e** (480 mg, 2.01 mmol) in dry ether (10 mL) was treated dropwise with a solution of diisobutylaluminum hydride in hexanes (2.1 mL of 1 M, 2.1 mmol), stirred at −78 °C for 1.5 h, quenched with saturated NH_4Cl solution, and allowed to warm to rt. The product was extracted into ethyl acetate, the combined organic layers were washed with brine, dried, and evaporated, and the residual aldehyde (420 mg) was used immediately.

To a cold (0 °C) suspension of dry chromium(II) chloride (1.4 g) in anhydrous THF (10 mL) and dioxane (4 mL) was added dropwise a solution of the above aldehyde and iodoform (1.5 g, 3.8 mmol) in dry THF (8 mL). The reaction mixture was stirred at 0 °C for 1 h and at rt for 4 h prior to being quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried and concentrated. Purification of the residue on silica gel (elution with 0−3% ethyl acetate in hexanes) gave 322 mg (42% over two steps) of **22e** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 8.9 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 6.51 (dd, J = 7.4, 14.5 Hz, 1H), 6.08 (d, J = 14.5 Hz, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.30 (m, 2H), 2.50 (m, 1H), 1.02 (d, J = 6.9 Hz, 3H); MS m/z (M^+) calcd 332.0273, obsd 332.0266; $[\alpha]^{20}_D$ −4.2 (*c* 0.17, $CHCl_3$).

(1*S*,2*S*,4*S*,8*R*)-2-[(1*E*,3*S*)-4-(*p*-Methoxybenzyloxy)-3-methyl-1-butenyl]-8-[(1*R*)-1-[(*tert*-butyldimethylsiloxy)-methy]-2-methylpropyl]-1-methylbicyclo[2.2.2]oct-5-en-2-ol (37e) and (1*S*,2*R*,4*S*,8*R*)-2-[(1*E*,3*S*)-4-(4-Methoxybenzyloxy)-3-methyl-1-butenyl]-8-[(1*R*)-1-[(*tert*-butyldimethylsiloxy)methyl]-2-methylpropyl]-1-methylbicyclo-[2.2.2]oct-5-en-2-ol (38e). A. By Barbier-Type Reaction. A mixture of magnesium turnings (270 mg, 0.81 mmol), 1,2-dibromoethane (0.03 mL, 0.35 mmol), **22e** (270 mg, 0.81 mmol), and **15** (95 mg, 0.28 mmol) in dry THF (3 mL) was sonicated for 2 h at 15−20 °C. After being cooled to 0 °C, the reaction mixture was quenched with saturated NH_4Cl solution (1 mL) and diluted with ether. The organic phase washed with brine, dried, and concentrated to leave a residue that was purified chromatographically (silica gel, elution with 5% ethyl acetate in hexanes) to give 31 mg (20%) of **37e** and 20 mg (13%) of **38e**.

For **37e**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3400, 1627, 1439; ^{1}H NMR (300 MHz, C_6D_6) δ 7.28 (d, J = 6.8 Hz, 2H), 6.81 (d, J = 6.8 Hz, 2H), 6.27 (dd, J = 8.0, 7.1 Hz, 1H), 5.88 (d, J = 8.0 Hz, 1H), 5.58 (m, 2H), 4.31 (br s, 2H), 3.76 (dd, J = 10.5, 2.5 Hz, 1H), 3.72 (dd, J = 10.5, 4.1 Hz, 1H), 3.32 (s, 3H), 3.28 (m, 1H), 3.20 (m, 1H), 2.51 (br q, J = 6.0 Hz, 1H), 2.42 (br s, 1H), 2.02 (dd, J = 13, 4.5 Hz, 1H), 1.87 (m, 1H), 1.75 (m, 2H), 1.55 (ddd, J = 13, 2.1, 1.3 Hz, 1H), 1.40−1.20 (m, 3H), 1.08 (d, J = 7.0 Hz, 3H),1.06 (d, J = 6.3 Hz, 3H), 1.02 (s, 3H), 0.96 (s, 9H), 0.93 (d, J = 7.0 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 159.4 (s), 138.4 (s), 138.1 (d), 135.8 (d), 129.0 (s), 128.7 (d, 2C), 127.4 (d), 113.7 (d, 2C), 77.2 (s), 75.2 (t), 72.6 (t), 62.3 (t), 54.4 (d), 47.7 (d), 41.9 (s), 38.0 (t), 36.9 (d), 36.1 (d), 34.0 (t), 32.7 (d), 27.9 (d), 25.6 (q, 3C), 21.8 (q), 18.9 (q), 18.4 (s), 17.5 (q), 17.4 (q), −5.5 (q), −5.7 (q); MS m/z (M^+ − C_8H_9O) calcd 421.3138, obsd 421.3128; $[\alpha]^{20}_D$ −71 (*c* 1.8, $CHCl_3$).

Anal. Calcd for $C_{33}H_{54}O_4Si$; C, 73.01; H, 10.03. Found: C, 72.93; H, 10.07.

For **38e**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (t, J = 8.4 Hz, 1H), 5.90 (d, J = 8.4 Hz, 1H), 5.63 (m, 2H), 3.62 (dd, J = 6.9, 2.1 Hz, 1H), 3.51 (dd, J = 6.8, 3.1 Hz, 1H), 3.39 (dd, J = 8.1, 4.1 Hz, 1H), 2.55 (br s, 1H), 2.41 (m, 1H), 1.85 (m, 3H), 1.55 (m, 1H), 1.26−1.20 (m, 1H), 1.21 (br s, 3H), 1.05 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.88 (2s, 18H), 0.81 (d, J = 7.1 Hz, 3H), 0.05 (4s, 12H); MS m/z (M^+ − C_8H_9O) calcd 421.3138, obsd 421.3142.

B. Use of Magnesium Bromide Etherate at −78 → 0 °C. A cold (−78 °C) solution of **22e** (186 mg, 0.56 mmol) in dry ether (3 mL) was treated with *tert*-butyllithium (0.75 mL of 1.7 M in pentane, 1.28 mmol) until a pale yellow color appeared. After 10 min of stirring, magnesium bromide etherate (excess) and a solution of **15** (95 mg, 0.28 mmol) were introduced at this temperature, and the reaction mixture was allowed to warm to 0 °C over 2 h. After the reaction mixture was quenched with saturated NH_4Cl solution (1 mL), the mixture was diluted with ether, and the organic phase was washed with brine, dried, and concentrated. Chromatography of the residue as above afforded 60 mg (39%) of **37e** and 32 mg (21%) of **38e**.

C. Use of Magnesium Bromide Etherate at 0 °C. A cold (−78 °C) solution of **22e** (101 mg, 0.30 mmol) in dry ether (2 mL) was treated with *tert*-butyllithium (0.4 mL of 1.7 M in pentane, 0.68 mmol) until a pale yellow color appeared. After 10 min of stirring, magnesium bromide etherate (excess) was introduced at this temperature and the reaction mixture was warmed directly to 0 °C, stirred for 20 min, and treated with a solution of **15** (51 mg, 0.15 mmol) in THF (2 mL). After 2 h of stirring at 0 °C, the above workup was applied, and there was isolated 52 mg (63%) of **37e** and 16 mg (20%) of **38e**.

Compound 55. To a cold (0 °C) solution of **37e** (177 mg, 0.326 mmol) and 18-crown-6 (86 mg, 0.33 mmol) in dry THF (6 mL) was added potassium hexamethyldisilazide (2 mL of 0.5 M in toluene, 1 mmol). After being stirred for 5 min at 0 °C, the yellowish mixture was directly heated at 120 °C for 1 h in a sealed tube, returned to 0 °C, quenched with saturated NH_4Cl solution, and diluted with ether. The organic phase was washed with brine, dried, and concentrated. The residue was purified by chromatography on silica gel (elution with 8:1 ether/hexanes) to give 127 mg (72%) of **55**: colorless oil; IR (neat, cm^{-1}) 1710, 1510, 1460; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (br d, J = 8.6 Hz, 2H), 6.86 (br d, J = 8.6 Hz, 2H), 5.35 (br s, 1H), 4.47 (d, J = 11.6 Hz, 1H), 4.40 (d, J = 11.6 Hz, 1H), 3.79 (s, 3H), 3.69−3.62 (m, 2H), 3.48 (dd, J = 9.1, 3.7 Hz, 1H), 3.38 (dd, J = 9.0, 6.2 Hz, 1H), 2.61(br s, 1H), 2.31 (br d, J = 11.6 Hz, 1H), 2.20−2.02 (m, 6H), 1.94−1.70 (m, 4H), 1.70 (br s, 3H), 1.12−1.07 (m, 1H), 1.02 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.89 (d, J = 7.0 Hz, 3H), 0.05 (br s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.7, 159.1, 136.9, 130.7, 129.0 (2C), 118.1, 113.7 (2C), 73.1, 72.8, 60.4, 55.2, 46.7, 43.7, 41.5, 38.2, 37.3, 37.0, 36.6, 34.7, 32.1, 26.7, 25.9 (3C), 23.7, 21.7, 18.1, 17.5, 16.2, −5.5, −5.7; MS m/z (M^+ − CH_3) calcd 527.3557, obsd 527.3536; $[\alpha]^{23}_D$ +5.9 (*c* 1.60, $CHCl_3$).

Compound 56. A solution of **55** (185 mg, 0.34 mmol), ethylene glycol (0.38 mL, 6.8 mmol), and *p*-toluenesulfonic acid (19 mg, 0.1 mmol) in benzene (4 mL) was refluxed for 4 h under a Dean−Stark trap, cooled to rt, and quenched with saturated $NaHCO_3$ solution. After dilution with ether, the organic phase was washed with additional bicarbonate solution, dried, and evaporated. Chromatography of the residue on silica gel (elution with 10:1 hexanes/ethyl acetate) afforded 168 mg (84%) of **56**: colorless oil; IR (neat, cm^{-1}) 1610, 1510, 1450; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (br d, J = 8.4 Hz, 2H), 6.86 (br d, J = 8.3 Hz, 2H), 5.22 (br s, 1H), 4.47 (d, J = 11.6 Hz, 1H), 4.40 (d, J = 11.6 Hz, 1H), 3.93 (br s, 4H), 3.80 (s, 3H), 3.70−3.60 (m, 2H), 3.54 (dd, J = 9.0, 3.5 Hz, 1H), 3.32−3.26 (m, 1H), 2.40 (br s, 1H), 2.09−1.91 (m, 4H), 1.84−1.58 (m, 4H), 1.64 (br s, 3H), 1.43−1.16 (m, 4H), 1.05 (d, J = 6.5 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H), 0.89 (br s, 9H), 0.88 (d, J = 7.9 Hz, 3H), 0.05 (br s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 135.9, 131.0, 129.0 (2C), 118.7, 113.6 (2C), 109.9, 73.5, 72.6, 64.1, 63.9, 60.9, 55.2, 46.9, 40.8, 38.1, 36.4, 34.5, 34.2, 34.0, 32.6, 29.3, 26.7, 25.9 (3C), 23.7, 21.6, 18.1, 17.8, 16.4, −5.5, −5.6; MS m/z (M^+) calcd 586.4054, obsd 586.4023; $[\alpha]^{23}_D$ +10.2 (*c* 1.40, $CHCl_3$).

Compound 57. A solution of **56** (54 mg, 0.092 mmol) in dry THF (4 mL) was treated with a 1 M solution of TBAF in THF (0.28 mL, 0.28 mmol), stirred at rt for 14 h, diluted with hexanes, and filtered through a short plug of silica gel. The evaporated filtrate was purified by chromatography (silica gel, elution with 2:1 hexanes/ethyl acetate) to give **57** (43 mg, 100%) as a colorless oil: IR (neat, cm^{-1}) 3420, 1600, 1500, 1430; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (br d, J = 8.4 Hz, 2H), 6.85

(br d, J = 8.6 Hz, 2H), 5.21 (br s, 1H), 4.45 (d, J = 11.7 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 3.91 (br s, 4H), 3.79 (s, 3H), 3.77−3.67 (m, 2H), 3.49 (dd, J = 9.0, 3.6 Hz, 1H), 3.28 (dd, J = 9.0, 7.1 Hz, 1H), 2.37 (br s, 1H), 2.11−1.83 (m, 4H), 1.82−1.57 (m, 4H), 1.64 (br s, 3H), 1.43−1.18 (m, 5H), 1.02 (d, J = 6.5 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 135.6, 130.9, 129.0 (2C), 118.9, 113.6 (2C), 109.8, 73.3, 72.6, 64.2, 63.9, 61.2, 55.2, 47.4, 40.7, 38.0, 36.5, 34.5, 34.1, 34.0, 32.7, 29.2, 26.5, 23.7, 21.6, 17.7, 16.4; MS m/z (M^+ + H) calcd 473.3267, obsd 473.3285; $[\alpha]^{23}_D$ +7.6 (*c* 1.53, $CHCl_3$).

Compound 58. To a stirred solution of **57** (43 mg, 0.091 mmol) and DMAP (67 mg, 0.55 mmol) in CH_2Cl_2 (4 mL) was added *p*-toluenesulfonyl chloride (52 mg, 0.27 mmol), and the mixture was stirred overnight at rt, quenched with saturated $NaHCO_3$ solution, and extracted with ether. The combined organic phases were dried and evaporated to leave a residue that was chromatographed on silica gel. Elution with 2.5:1 hexanes/ethyl acetate gave 52 mg (91%) of tosylate as a colorless gum: IR (neat, cm^{-1}) 1590, 1505, 1440, 1350; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (br d, J = 8.2 Hz, 2H), 7.34 (br d, J = 8.1 Hz, 2H), 7.24 (br d, J = 8.5 Hz, 2H), 6.86 (br d, J = 8.6 Hz, 2H), 5.18 (br s, 1H), 4.45 (d, J = 11.7 Hz, 1H), 4.23 (d, J = 11.7 Hz, 1H), 4.09−3.29 (series of m, 2H), 3.89 (br s, 4H), 3.79 (s, 3H), 3.47 (dd, J = 9.0, 3.5 Hz, 1H), 3.26 (dd, J = 8.8, 7.2 Hz, 1H), 2.45 (s, 3H), 2.34 (br s, 1H), 2.00−1.80 (m, 3H), 1.76−1.48 (m, 5H), 1.54 (br s, 3H), 1.43−1.15 (m, 4H), 1.00 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 144.7, 135.0, 132.9, 130.8, 129.8 (2C), 129.0 (2C), 128.0 (2C), 119.0, 113.6 (2C), 109.6, 73.2, 72.6, 68.9, 64.1, 63.9, 55.2, 44.6, 40.6, 37.8, 35.9, 34.4, 34.0, 33.6, 32.1, 29.1, 26.2, 23.4, 21.6, 21.2, 17.2, 16.3; MS m/z ($M^+ - CH_3$) calcd 611.3043, obsd 611.3054; $[\alpha]^{23}_D$ +9.2 (*c* 2.43, $CHCl_3$).

Compound 59. A mixture of **58** (52 mg, 0.083 mmol) and sodium iodide (124 mg, 0.83 mmol) in methyl ethyl ketone (5 mL) was refluxed for 1.5 h under N_2, cooled to rt, diluted with ether, and washed with saturated sodium thiosulfate solution. The organic phase was dried and evaporated. The residue was taken up in DMF (4 mL), treated with sodium *p*-toluenesulfinate (148 mg, 0.83 mmol), and heated at 110 °C for 11 h. The cooled reaction mixture was diluted with ether and washed with brine. The aqueous phase was extracted with ether, and the combined organic layers were dried and concentrated. Purification of the product was accomplished by flash chromatography on silica gel (elution with 3:1 hexanes/ethyl acetate) to furnish 42 mg (82%) of **59** as a colorless gum: IR (neat, cm^{-1}) 1590, 1460, 1440; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (br d, J = 8.2 Hz, 2H), 7.35 (br d, J = 8.0 Hz, 2H), 7.25 (br d, J = 8.9 Hz, 2H), 6.86 (br d, J = 8.6 Hz, 2H), 5.16 (br s, 1H), 4.45 (d, J = 11.7 Hz, 1H), 4.35 (d, J = 11.7 Hz, 1H), 3.95−3.86 (m, 4H), 3.78 (br s, 3H), 3.45 (dd, J = 9.0, 3.5 Hz, 1H), 3.25 (dd, J = 8.9, 7.0 Hz, 1H), 3.07 (dd, J = 15.2, 4.3 Hz, 1H), 2.86 (dd, J = 15.2, 3.7 Hz, 1H), 2.44 (s, 3H), 2.34 (br s, 1H), 2.13−2.04 (m, 1H), 1.93−1.90 (m, 2H), 1.80−1.49 (m, 5H), 1.54 (br s, 3H), 1.46−1.17 (m, 4H), 1.00 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 144.5, 137.6, 135.3, 130.8, 129.8 (2C), 129.0 (2C), 128.2 (2C), 118.8, 113.6 (2C), 109.5, 73.3, 72.6, 64.2, 64.0, 56.4, 55.2, 40.6, 40.01, 39.96, 38.1, 34.6, 34.4, 34.0, 32.5, 29.0, 27.1, 23.5, 21.5, 20.4, 16.3, 16.2; MS m/z (M^+) calcd 610.3328, obsd 610.3292; $[\alpha^{23}_D$ +1.1 (*c* 2.00, $CHCl_3$).

Compound 60. A mixture of **59** (42 mg, 0.069 mmol) and DDQ (23 mg, 0.1 mmol) in 18:1 CH_2Cl_2/H_2O (4 mL) was stirred at rt for 1.5 h, quenched with saturated $NaHCO_3$ solution, and diluted with ether. The aqueous phase was extracted with ether, and the combined organic layers were dried and concentrated. The residue was purified by flash chromatography (silica gel, elution with 1:1 hexanes/ethyl acetate) to provide 32 mg (94%) of **60** as a colorless gum: IR (neat, cm^{-1}) 3460, 1590, 1370; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (br d, J = 8.3 Hz, 2H), 7.35 (br d, J = 8.2 Hz, 2H), 5.18 (br s, 1H), 3.95−3.91 (m, 4H), 3.67 (dd, J = 10.6, 3.3 Hz, 1H), 3.47 (dd, J = 10.5, 6.0 Hz, 1H), 3.06 (dd, J = 15.2, 4.4 Hz, 1H), 2.85 (dd, J = 15.2, 3.8 Hz, 1H), 2.67 (d, J = 8.7 Hz, 2H), 2.44 (s, 3H), 2.35 (br s, 1H), 2.09−1.96 (m, 1H), 1.95−1.90 (m, 2H), 1.78−1.52 (m, 5H), 1.55 (s, 3H), 1.30−1.20 (m, 3H), 0.99 (d, J = 6.2 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 137.6, 135.8, 129.8 (2C), 128.2 (2C), 118.5, 109.5, 65.9, 64.2, 64.0, 56.4, 40.1, 40.0, 39.9, 38.1, 35.8, 34.7, 34.5, 32.5, 28.9, 27.1, 23.5, 21.6, 20.5, 16.2, 15.6; MS m/z (M^+) calcd 490.2753, obsd 490.2754; $[\alpha]^{23}_D$ −4.1 (*c* 1.78, $CHCl_3$).

Compound 61. To a mixture of **60** (32 mg, 0.065 mmol) and DMAP (48 mg, 0.39 mmol) in CH_2Cl_2 (3 mL) was added *p*-toluenesulfonyl chloride (37 mg, 0.19 mmol). After being stirred overnight at rt, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with ether. The combined organic layers were dried and concentrated to leave a residue that was purified by flash chromatography (silica gel, elution with 2.5:1 hexanes/ethyl acetate). There was isolated 34 mg (81%) of **61** as a colorless gum: IR (neat, cm^{-1}) 1590, 1440, 1340; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (br d, J = 8.3 Hz, 2H), 7.75 (br d, J = 8.4 Hz, 2H), 7.35 (br d, J = 8.1 Hz, 2H), 7.31 (br d, J = 8.1 Hz, 2 H), 4.98 (br s, 1H), 4.05 (dd, J = 9.4, 3.4 Hz, 1H), 3.93−3.85 (m, 5H), 3.07 (dd, J = 15.2, 4.3 Hz, 1H), 2.84 (dd, J = 15.0, 3.7 Hz, 1H), 2.45 (s, 3H), 2.43 (s, 3H), 2.18 (br s, 1H), 2.04−1.96 (m, 1H), 1.94−1.67 (m, 4H), 1.66−1.47 (m, 3H), 1.53 (br s, 3H), 1.47−1.14 (m, 4H), 0.92 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 144.5, 137.6, 136.4, 133.1, 129.9 (2C), 129.7 (2C), 128.2 (2C), 127.9 (2C), 117.5, 109.2, 73.2, 64.2, 64.1, 56.3, 39.93, 39.89, 39.82, 37.7, 34.5, 34.3, 33.3, 32.5, 28.9, 27.1, 23.5, 21.61, 21.57, 20.4, 16.2, 15.6; MS m/z (M^+) calcd 644.2841, obsd 644.2863; $[\alpha]^{23}_D$ −3.0 (*c* 2.49, $CHCl_3$).

Compound 62. A mixture of **61** (12 mg, 0.019 mmol) and sodium iodide (28 mg, 0.19 mmol) in methyl ethyl ketone (3 mL) was heated at reflux temperature for 1.5 h, cooled to rt, diluted with ether, and washed with saturated sodium thiosulfate solution. The organic phase was dried and evaporated, and the residue was purified by flash chromatography (silica gel, elution with 4:1 hexanes/ethyl acetate) to furnish 9 mg (82%) of **62** as a white solid: mp 193 °C; IR (neat, cm^{-1})1580, 1420, 1360; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (br d J = 8.2 Hz, 2H), 7.36 (br d, J = 8.0 Hz, 2H), 5.10 (br s, 1H), 3.94 (br s, 4H), 3.34 (dd, J = 9.8, 2.6 Hz, 1H), 3.22 (dd, J = 9.7, 5.2 Hz, 1H), 3.08 (dd, J = 15.2, 4.3 Hz, 1H), 2.86 (dd, J = 15.1, 3.8 Hz, 1H), 2.45 (s, 3H), 2.38 (br s, 1H), 2.15−1.90 (m, 3H), 1.84−1.50 (m, 5H), 1.58 (br s, 3H), 1.46−1.20 (m, 4H), 1.01 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H), 0.74 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 137.7, 136.6, 129.9 (2C), 128.2 (2C), 117.6, 109.4, 64.3, 64.1, 56.4, 42.6, 40.04, 39.96, 37.5, 34.4, 34.3, 33.5, 32.6, 28.9, 27.2, 23.5, 21.6, 20.4, 19.7, 17.5, 16.2; MS m/z (M^+) calcd 600.1770, obsd 600.1761; $[\alpha]^{23}_D$ +7.6 (*c* 0.87, $CHCl_3$).

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Supporting Information Available: Experimental details for those compounds not involved in the direct route to **62**, tables of the X-ray crystal data, atomic coordinates, and equivalent isotropic displacement parameters, and positional parameters for the hydrogen atoms of **62**. This material is available free of charge via the Internet at http://pubs.acs.org.

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