layer was washed with brine, dried, and evaporated to an oil, which was chromatographed with 25% EtOAc in hexane as eluant. Evaporation of the collected fractions gave 170 mg (89%) of **27**, which solidified under vacuum: mp 100 °C; $[\alpha]^{20}_D$ 234° (*c* 1.43, $CHCl_3$); ^1H NMR δ 0.66 (t, 3 H, J = 7.4), 1.22 (m, 2 H), 2.07 (m, 1 H), 2.8 (dd, 1 H, J = 4, 10.6), 3.02 (dd, 1 H, J = 4, 10.5), 7.1–7.8 (m, 13 H); $C_{23}H_{23}NO$: C, 83.9; H, 7.0; N, 4.3. Found: C, 83.8; H, 7.0; N, 4.2.

Reduction of Vinylglycinol *S*-21 to 2-Aminobutanol 27. A solution of vinylglycinol *S*-**21** (30 mg, 0.09 mmol) in MeOH (3 mL) was treated with platinum oxide (10 mg) and stirred under 1 atm of hydrogen for 3 h. The catalyst was removed by filtration through diatomaceous earth, which was washed with MeOH (3 × 5 mL). The combined organic layer was evaporated to give 30 mg (99%) of **27**, which was directly coupled to *N*-(tolylsulfonyl)-L-alaninyl-*N*-methylimidazolium triflate as described below.

***N*-(Tolylsulfonyl)-L-alanine (*R*)- and (*S*)-2-[*N*-(9-Phenylfluoren-9-yl)amino]butanol Esters (28).** A solution of carbonyldiimidazole (50 mg, 0.32 mmol) in nitromethane (0.4 mL) was treated with 70 μL of methyl trifluoromethanesulfonate as described[14] and then treated with *N*-(tolylsulfonyl)-L-alanine (73 mg, 0.3 mmol) and stirred 10 min. To the solution was added a solution of (*R*)- or (*S*)-2-[*N*-(9-phenylfluoren-9-yl)amino]butanol (**27**, 30 mg, 0.09 mmol) in nitromethane (0.4 mL), the mixture was stirred at 0 °C for 30 min, and then EtOAc (12 mL) and water (3 mL) were added. The organic phase was extracted with NaH_2PO_4 (8 mL) and $NaHCO_3$ (4 × 8 mL), washed with 10 mL of brine, dried, and evaporated to an oil, which was redissolved, filtered through a short plug of silica gel with 25% EtOAc in hexane as eluant, and reevaporated to an oil, which was used for ^1H NMR analysis.[20]

***N*-(Tolylsulfonyl)-L-alanine (*S*)-2-[*N*-(9-phenylfluoren-9-yl)amino]butanol ester:** ^1H NMR δ (benzene-d_6) 0.59 (t, 3 H, J = 7.5), 1.04 (d, 3 H, J = 7.1), 1.1 (m, 2 H), 1.86 (s, 3 H), 2.2 (m, 1 H), 3.35 (dd, 1 H, J = 3.7, 11), 3.48 (dd, 1 H, J = 4.8, 11), 3.97 (m, 1 H), 5.4 (d, 1 H, J = 8.3), 6.7–7.9 (m, 17 H).

***N*-(Tolylsulfonyl)-L-alanine (*R*)-2-[*N*-(9-phenylfluoren-9-yl)amino]butanol ester:** ^1H NMR δ (benzene-d_6) 0.56 (t, 3 H, J = 7.3), 1.1 (m, 2 H), 1.12 (d, 3 H, J = 7.1), 1.92 (s, 3 H), 2.14 (m, 1 H), 3.4 (m, 2 H), 3.94 (m, 1 H), 5.28 (d, 1 H, J = 8.4), 6.75–7.85 (m, 17 H).

Acknowledgment. We thank Timothy F. Jamison, President's Undergraduate Fellow, for his able assistance in supplying intermediates. The crystal structure analysis was performed under the supervision of Dr. F. J. Hollander, Staff crystallographer at the University of California, Berkeley, X-ray Crystallographic Facility (CHEXRAY).

Supplementary Material Available: The X-ray crystallographic determination of **7** and **10**, listings of fractional atomic coordinates with their estimated standard deviations, temperature factors, intramolecular distances and angles, and least-square planes (6 pages). Ordering information is given on any current masthead page.

Enantioselective Robinson Annulation: Synthesis of (+)-*O*-Methyljoubertiamine

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The α-formyl ester derived from 2-(1-naphthyl)-3-borneol, as the potassium salt in moist dimethoxymethane, adds to methyl vinyl ketone to give two adducts in a ratio of 95:5. The relative configuration of the major diastereomer has been confirmed by X-ray crystallography. This diastereomer is readily carried on to (+)-*O*-methyljoubertiamine. The addition of such naphthylbornyl esters to Michael acceptors should constitute a general laboratory-scale procedure for the enantioselective construction of enantiomerically pure quaternary stereogenic centers.

The two most common methods for the construction of cyclohexane derivatives are Diels–Alder cycloaddition and Robinson annulation. While a great deal of work has been directed toward enantioselective Diels–Alder cycloaddition,[2] work on the Robinson annulation has been limited to cyclic donors.[3] We now report the development of an enantiomerically pure Michael donor,[4-7] the optimization of selectivity in the Michael addition, and the

(1) D.F.T. and J.F.M. thank A.L.R. and S.J.G. for carrying out the X-ray diffraction analysis of **9**.

(2) For leading references to enantioselective Diels–Alder cycloaddition, see: (a) Walborsky, H. M.; Barash, L.; Davis, T. C. J. *Tetrahedron* **1963**, *19*, 2333. (b) Ensley, H. E.; Parnell, C. A.; Corey, E. J. *J. Org. Chem.* **1978**, *43*, 1610. (c) Oppolzer, W.; Chapuis, C.; Kelley, M. *Helv. Chim. Acta* **1983**, *66*, 4781. (d) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261. (e) Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095.

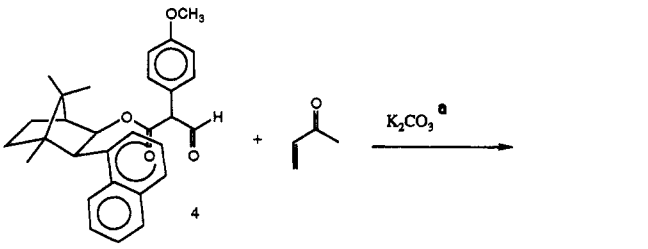
(3) (a) Early efforts toward enantioselective Robinson annulation focused on asymmetric aldol condensation of the symmetrical adduct of a 1,3-diketone: Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Conditions for enantioselective Robinson annulation of *cyclic* ketones have been reported: Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273.

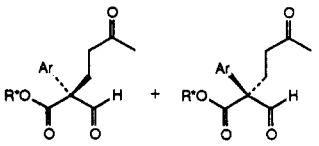
(4) Enantioselective addition of an acyclic ketone enolate in a Michael sense is a long-sought goal. Progress to date has for the most part been based on the use of imine anions derived from enantiomerically pure amines: (a) Otani, G.; Yamada, S. *Chem. Pharm. Bull.* **1973**, *21*, 2130. (b) Yamamoto, K.; Iijima, M.; Ogimura, Y. *Tetrahedron Lett.* **1982**, *23*, 3711. (c) Enders, D.; Papadopoulos, K. *Tetrahedron Lett.* **1983**, *24*, 4967. (d) Ito, Y.; Sawamura, M.; Kominami, K.; Saegusa, T. *Tetrahedron Lett.* **1985**, *26*, 5303. (e) Stetin, C.; De Jeso, B.; Pommier, J.-C. *J. Org. Chem.* **1985**, *50*, 3863. (f) Tomioka, K.; Ando, K.; Yasuda, K.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 715. (g) Tomioka, K.; Seo, W.; Ando, K.; Koga, K. *Tetrahedron Lett.* **1987**, *28*, 6637.

(5) For the enantioselective construction of quaternary centers by intermolecular *alkylation*, see: (a) For an early review, see: ApSimon, J. W.; Seguin, R. P. *Tetrahedron* **1979**, *35*, 2797. (b) Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *J. Am. Chem. Soc.* **1984**, *106*, 2718. (c) Frater, G.; Muller, U.; Gunther, W. *Tetrahedron* **1984**, *40*, 1269. (d) Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 2463. (e) Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 5891.

0022-3263/89/1954-3831$01.50/0

Table I. Solvent Effect on Michael Addition





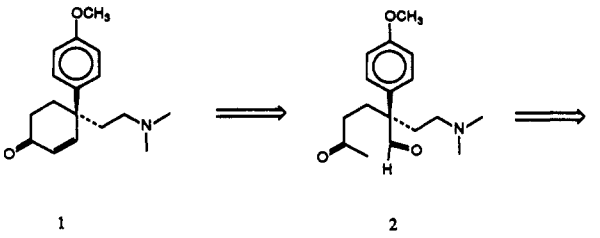
solvent/additive	ratio[b]	yield,[c] %
$PhCH_3$	88:12	54
$PhCH_3/Bu_4NBr$	50:50	77
CH_2Cl_2	75:25	45
hexane	88:12	56
$Meo)_2CH_2$[d]	82:18	83
$MeO)_2CH_2/H_2O$[d,e]	95:5	76

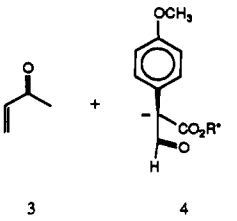
[a] Finely powdered, oven-dried K_2CO_3 was used throughout these studies. [b] Ratios were determined by integrating the ^1H NMR signals for the formyl protons of the two diastereomers. [c] Yields reported are for pure chromatographed material, based on 4 consumed. Conversions for these runs ranged from 70 to 95%. [d] Dimethoxymethane was distilled from Na/benzophenone. [e] Water (0.1 volume %) was added to the dry distilled dimethoxymethane.

conversion of the crystalline Michael adduct to the enantiomerically pure mesembrane alkaloid (+)-*O*-methyljoubertiamine (1),[8-11] the enantiomer of the natural product.

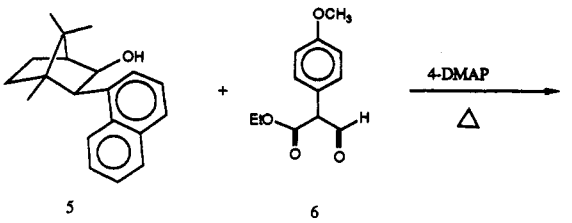
Construction of the Michael Donor

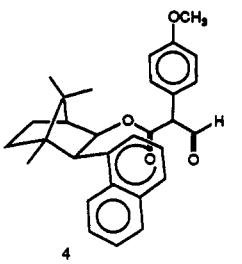
It was apparent that *O*-methyljoubertiamine (1) could be assembled by Michael addition followed by aldol condensation and that the quaternary stereogenic center of 1 would be established in the Michael addition step. We therefore set out to design a Michael donor, 4, that would show selectivity in this step.





Alcohol 5, readily prepared from (+)-camphor,[12,13] was already in hand. We had previously shown that the β-keto esters of 5 could readily be prepared by 4-(dimethylamino)pyridine-catalyzed ester exchange.[14] We have found that the α-formyl ester 6 also readily exchanges, to give 4.





We[12] as well as others[13] have shown that bornyl esters such as 4 exist in an extended conformation, with the adjacent substituent, in this case the naphthyl ring, in a parallel plane. Thus, one face of the ester is selectively shielded. While necessary, such blocking does not directly impart selectivity to the bond-forming reaction. Enolate 7 would react to give one diastereomer of the product, while enolate 8 would give the other. We therefore set out to define conditions such that one of these two trisubstituted enolates could selectively be prepared.

Development of the Michael Conditions

The starting point (Table I) for this investigation was the deliberate preparation of a mixture of the two diastereomeric Michael adducts, to establish analytical procedures. We found, as expected (entry 2) that with an

(6) For leading references to enantiomerically pure Michael acceptors, see: (a) Asami, M.; Mukaiyama, T. *Chem. Lett.* **1979**, 569. (b) Posner, G. H.; Kogan, T. P.; Hulce, M. *Tetrahedron Lett.* **1984**, *25*, 383. (c) Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* **1985**, *68*, 212.

(7) For reports of enantioselective *intra*molecular Michael addition, see: (a) Stork, G., Saccomano, N. A. *Nouv. J. Chem.* **1986**, *10*, 677. (b) Hirai, Y.; Tereda, T.; Yamazaki, T. *J. Am. Chem. Soc.* **1988**, *110*, 958.

(8) (a) For the isolation of *O*-methyljoubertiamine, see: Nieuwenhuis, J. J.; Strelow, F.; Strauss, H. F.; Wiechers, A. *J. Chem. Soc., Perkin Trans. I* **1981**, 284. (b) Racemic *O*-methyl joubertiamine had previously been synthesized. For leading references, see: Stevens, R.V.; Wentland, M. P. *J. Am. Chem. Soc.* **1968**, *90*, 5580. Strauss, H. F.; Weichers, A. *Tetrahedron* **1978**, *34*, 127. Martin, S. F.; Puckette, T. A.; Colapret; J. A. *J. Org. Chem.* **1979**, *44*, 3391. (c) An enantioselective synthesis of (−)-*O*-methyljoubertiamine was reported very recently: Asaoka, M.; Fujii, N.; Takei, H. *Chem. Lett.* **1988**, 1655.

(9) For enantioselective routes to the mesembrane alkaloids, see: (a) Otani, G.; Yamada, S. *Chem. Pharm. Bull.* **1973**, *21*, 2130. (b) Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479. (c) Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776.

(10) For leading references to other routes to the mesembrane alkaloids, see: (a) Winkler, J. D.; Muller, C. L.; Scott, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 4831. (b) Kametani, T.; Nishimura, M.; Higurashi, K.; Suzuki, Y.; Tsubuki, M.; Honda, T. *J. Org. Chem.* **1987**, *52*, 5233. (c) Hackett, S.; Livinghouse, T. *J. Org. Chem.* **1986**, *51*, 1629. (d) Sanchez, I. H.; Lemini, C.; Hernandez, C.; Larrazza, M. I.; Flores, H. J.; Garcia, R.; Machin, G. *Synth. Commun.* **1983**, *13*, 43.

(11) For an alternative route to 4,4-dialkylcyclohexenones of high enantiomeric purity, see: Gilbert, J. C.; Giamalva, D. H.; Baze, M. E. *J. Org. Chem.* **1985**, *50*, 2557.

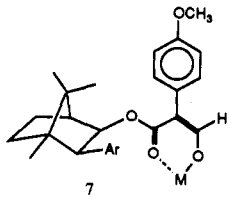
(12) For the preparation of 5, see: Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28.

(13) Concurrently with our work, others have investigated chiral induction with modified bornyl esters. For leading references, see: Helmchen, G.; Schmierer, R. *Tetrahedron Lett.* **1983**, *24*, 1235. Oppolzer, W.; Chapuis, C. *Tetrahedron Lett.* **1983**, *24*, 4665. Somfai, P.; Tanner, D.; Olsson, T. *Tetrahedron* **1985**, *41*, 5973.

(14) Taber, D. F.; Deker, P. B.; Gaul, M. D. *J. Am. Chem. Soc.* **1987**, *109*, 7488.

(15) Ainsworth, C. *Org. Synth.* **1959**, *39*, 27.

(16) Taber, D. F.; Amedio, J. C.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618.



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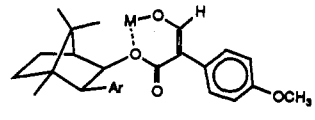


8

ammonium counterion,[17] which would be expected to be non-chelating, a 1:1 mixture of adducts was obtained. The formyl protons of these two adducts differed by 0.3 ppm in the ^1H NMR spectrum. The ratio of these two very sharp singlets was taken, throughout this study, to be the ratio of diastereomers from the addition.

We have found K_2CO_3 to be the optimal base for these additions.[18] This is easily understood. Addition of the initial stabilized enolate to the acceptor enone gives a less stable, more reactive ketone enolate, which tends to add another equivalent of acceptor. The $KHCO_3$ generated by formyl ester deprotonation may be serving to quench this initial ketone enolate.

A brief survey (Table I) has shown that hydrocarbon solvents give better ratios than chlorinated hydrocarbon solvents and that ethereal solvents give even better ratios. The optimal solvent we have found so far is dimethoxymethane, distilled from sodium/benzophenone, to which, after distillation, 0.1% water has been added. With K_2CO_3 as base, this solvent gives a 95:5 ratio of diastereomers **9** and **10**.

The diastereomeric adducts are readily deformylated under the reaction conditions. Optimal yields are achieved by running to about 70% conversion. Under these conditions, averaging over several runs, a 51% chromatographed yield of the **9**/**10** mixture is achieved (76% with recycling of **4**). Trituration of the chromatographed material with ether gives pure crystalline **9** in 59% chemical yield from **4**.

The relative (and thus absolue) stereochemistry of **9** was confirmed by X-ray analysis (Figure 1).[1,19] It follows that the reactive rotamer in the Michael addition must be **8**, which might be chelated, not through the ester carbonyl but through the other oxygen of the ester.

Synthesis of (+)-*O*-Methyljoubertiamine

We had anticipated receiving **10** as the major diastereomer from Michael addition. The conversion of **9** to *O*-methyljoubertiamine (Scheme I), developed first in the racemic series, thus led to the enantiomer of the natural product. It should be noted that the quaternary center in adduct **9** bears two oxygenated one-carbon substituents. In principle, *either* enantiomer of a desired product should be available from such an intermediate.

Several aspects of the conversion of **9** to **1** are interesting. Adduct **9** is very readily deformylated, so direct aldol condensation was not pursued. Instead, bis-thioketalization,[20] followed by $LiAlH_4$ reduction, gave the stable, crystalline alcohol **11**, at the same time returning naphthylborneol **5** for recycling.

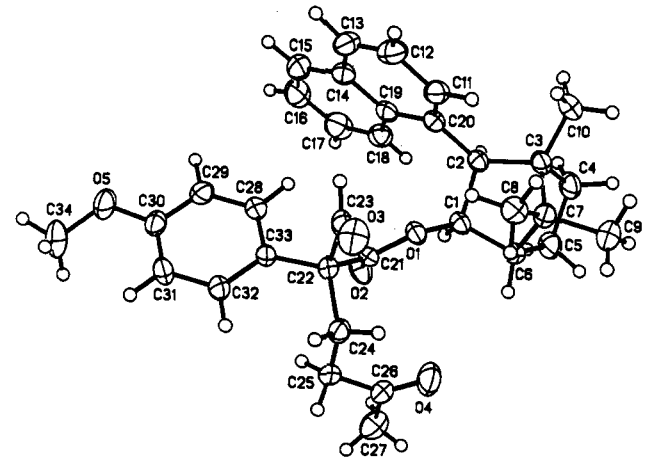


Figure 1. X-ray structure of **9**.

As expected, all attempts to effect direct displacement at the very hindered alcohol methylene of **11** failed. We therefore condensed the aldehyde **12** with (methoxymethylene)triphenylphosphorane. Efficient generation of this sometimes maligned ylide required, in our hands, the use of *phenyl* lithium.[22]

Hydrolysis of the intermediate enol ether proceeded smoothly, to give the homologated aldehyde **13**. The keto-aldehyde derived from reduction of **13**, followed by hydrolysis, underwent smooth aldol condensation, but the isolated product was bicyclic, resulting from Michael addition of the side-chain alcohol to the enone.[10a] The alcohol derived from **13** was therefore protected as the benzyl ether, to give **14**.

Treatment of enone **15** with excess TMSCl/NaI,[23] followed by exposure of the resultant iodide to aqueous dimethylamine, gave (+)-*O*-methyljoubertiamine (**1**). The synthetic material showed $[\alpha]^{25}_D$ +50.3° (c = 0.003, CH_3OH), indicating high enantiomeric purity (lit.[8a] for the enantiomer $[\alpha]^{25}_D$ = −51°, c = 1.45, CH_3OH).

The use of enantiomerically pure imine anions as enantioselective Michael donors has been described.[4] Diastereomeric ratios of adducts are, however, significantly better when the approach described herein is used. Further, the covalently attached naphthylborneol serves to render the adducts crystalline, easing purification. As naphthylborneol **5** is easily prepared (and recycled),[12] the Michael addition described should be a general[24] laboratory-scale method for the enantioselective assembly of quaternary alkylated and aminated[25] stereogenic centers.

A significant amount of attention has been focused on elucidating the stereochemical course of Michael addition.[26] This work is the first report of a stereochemically well-defined acyclic Michael donor. Elucidation of the stereochemical course of addition of *β-substituted* acceptors should serve to further define the Michael transition state.

(17) For the use of K_2CO_3/toluene with R_4NI as a solid/liquid phase-transfer catalyst, to do Michael additions, see: Kryshtal, G. V.; Kulganek, V. V.; Kucherof, V. F.; Yanovskaya, L. A. *Synthesis* **1979**, 107.

(18) Other base/solvent combinations surveyed were less effective. Among these tried were $Et_3N/PhCH_3$, Et_3N/DMF, DBU/DMF, $K_2CO_3/PhCH_3$ with Bu_4NBr, $Li_2CO_3/PhCH_3$, $Na_2CO_3/PhCH_3$, $Ni(acac)_2$, $KH/PhCH_3$, NaH/THF, and KO-*t*-Bu/*t*-BuOH.

(19) X-ray data for $C_{34}H_{38}O_5$ (**9**): triclinic, $P1$, a = 9.536 (2), b = 9.645 (2), and c = 9.886 (3) Å, α = 62.68 (3)°, β = 62.64 (3)°, γ = 82.45 (3)°, V = 7.13.9 (2) Å^3, Z = 1, D(calcd) = 1.23 g cm^{-3}. Of 4464 data collected, 4021 independent and observed data [Nicolet R3m/μ, Mo Kα, 293 K, 2θ(max) = 48°, $F_o \geq 3\sigma(F_o)$] were used in the solution and refinement of the structure. With all non-hydrogen atoms anisotropic, and all hydrogen atoms found and isotropic: $R(F)$ = 3.38%, R(wF) = 4.26%, GOF = 1.255, N_o/N_v = 8.2, Δ/σ = 0.07, $\Delta/(\rho)$ = 0.32 e Å^{-3}.

(20) Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* **1983**, *24*, 169.

(21) Wittig, G.; Schlosser, M. *Chem. Ber.* **1961**, *94*, 1373.

(22) Vedejs, E.; Fuchs, P. L. *J. Org. Chem.* **1971**, *36*, 366.

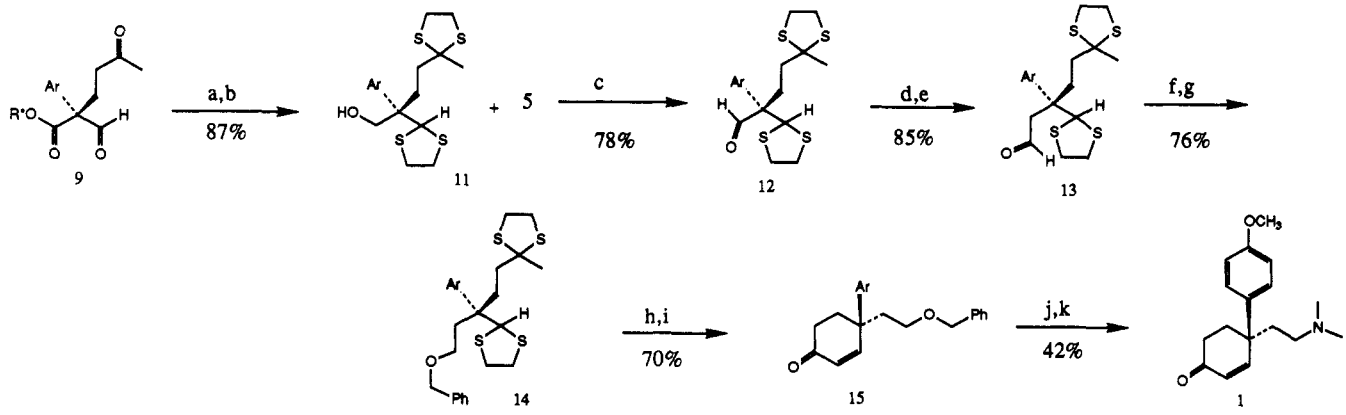
(23) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.

(24) For the use of alternative Michael acceptors and also the use of other β-oxo esters derived from **5** as donors, see: Mack, J. F. Ph.D. Dissertation, University of Delaware, 1989.

(25) For the conversion of esters such as **9** to enantiomerically pure quaternary amino acids, see: Georg, G. I.; Guan, I. X.; Kant, K. *Tetrahedron Lett.* **1988**, *29*, 403.

(26) For leading references to the ongoing investigation of diastereoselection in the intermolecular Michael addition, see: Heathcock, C. H.; Uehling, D. E. *J. Org. Chem.* **1986**, *51*, 279.

Scheme I. Synthesis of *O*-Methyljoubertiamine[a]



[a] (a) $Zn(OTf)_2$/ethanedithiol; (b) $LiAlH_4$; (c) pyridinium dichromate; (d) $CH_3OCH{=}P(Ph)_3/Et_2O$; (e) aqueous HCl; (f) $NaBH_4/CH_3OH$; (g) benzyl bromide/NaH; (h) $HgO/BF_3{\cdot}Et_2O$; (i) *p*-toluenesulfonic acid; (j) $CH_3SiCl/NaI/CH_3CN$; (k) aqueous $(CH_3)_2NH$.

Work in this direction is currently in progress.

Experimental Section

General. ^1H and ^{13}C NMR spectra were obtained on a Brucker WM-250 spectrometer as solutions in $CDCl_3$. Carbon signals were assigned by an INEPT pulse sequence, u = methylene or quaternary, d = methyl or methine. The infrared (IR) spectra were determined as solutions in CCl_4 and are reported in cm^{-1}. Unless otherwise specified, samples for determination of optical rotation were purified by column chromatography, followed by bulb-to-bulb distillation. Substances for which C,H analyses are not reported were purified as specified and gave spectroscopic data consistent with being >95% of the assigned structure. Organic chemicals were purchased from Aldrich Chemical Co. THF and Et_2O were distilled from sodium metal/benzophenone. The solvent mixtures used for chromatography are volume/volume mixtures. R_f values indicated refer to thin-layer chromatography on Analtech 2.5 × 10 cm, 250 μM analytical plates coated with silica gel GF. Column chromatography was carried out with TLC-mesh silica gel, following the procedure we have described.[27] Unless otherwise specified, all reactions were carried out in flame-dried glassware under an atmosphere of N_2.

Ethyl 2-(4-Methoxyphenyl)-3-oxopropanoate (6). *p*-Methoxyphenylacetic acid (100.0 g, 0.602 mol), absolute ethanol (200 mL), and concentrated sulfuric acid (0.5 mL) were combined, and the mixture was maintained at reflux for 18 h. The reaction mixture was concentrated in vacuo and then partitioned between diethyl ether and saturated aqueous Na_2CO_3. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. The residue was bulb-to-bulb distilled ($bp_{1\,mm}$ (bath) = 110–115 °C) to give 101.2 g (0.521 mol, 87% yield) of the ester as a colorless oil: R_f (30% EtOAc/hexanes) = 0.57; ^1H NMR δ 7.18 (d, *J* = 8.3 Hz, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 4.11 (g, *J* = 7.1 Hz, 2 H), 3.74 (s, 3 H), 3.52 (s, 2 H), 1.22 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR δ 171.9 (u), 158.7 (u), 130.3 (d) × 2, 126.3 (u), 114.0 (d) × 2, 60.7 (u), 55.1 (d), 40.5 (u), 14.2 (d); IR 3006, 2990, 1738, 1619, 1521, 1472, 1256, 1185, 1158, 1039; MS 194 (33), 122 (19), 121 (100), 78 (17), 77 (13); exact mass found 194.094, calcd for $C_{11}H_{14}O_3$ 194.0942.

Following a modification of the method of Ainsworth,[15] 47.9 g (0.247 mol) of the above ester, 33.0 g (0.446 mol, 1.8 equiv) of ethyl formate, anhydrous ether (300 mL), and 6.8 g (0.296 mol, 1.2 equiv) of sodium metal were combined. The reaction mixture was cooled in an ice/water bath and absolute ethanol (2.5 mL) was added all at once. After 2 h at 0 °C, stirring was continued at room temperature overnight (~14 h). Anhydrous ether (300 mL) and ethanol (15 mL) were added, and the reaction was stirred for an additional 2 h and then partioned between diethyl ether and water. The organic layer was dried over $MgSO_4$ and then concentrated in vacuo. The residue was bulb-to-bulb distilled to give 14.27 g (0.073 mol, 30%) of recovered starting ester.

The combined aqueous layer from above was acidified with 1% aqueous HCl (450 mL) and then partioned between aqueous NaCl and diethyl ether. The organic extract was washed with aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was bulb-to-bulb distilled (bp_1 (bath) = 120–138 °C) to give 33.8 g (0.152 mol, 62% yield, 88% yield based on unrecovered starting ester) of **6** as a colorless oil: R_f (30% EtOAc/hexanes) = 0.57; ^1H NMR δ 12.05 (d, *J* = 12.6 Hz, 1 H), 7.24 (d, *J* = 12.6 Hz, 1 H), 7.17 (d, *J* = 8.8 Hz, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 3.79 (s, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR δ 171.9 (u), 162.9 (d), 158.8 (u), 130.6 (d) × 2, 126.5 (u), 113.7 (d) × 2, 108.1 (u), 60.9 (u), 55.2 (d), 14.2 (d); IR 2985, 2955, 1729, 1663, 1609, 1514, 1243, 1171; MS 222 (18), 194 (11), 177 (18), 176 (100), 148 (18), 133 (19), 121 (32), 120 (75), 119 (16), 105 (20); exact mass found 222.089, calcd for $C_{12}H_{14}O_4$ 222.089.

(2*R*,3*R*)-1,7,7-Trimethyl-2-(1-naphthyl)bicyclo[2.2.1]-hept-3-yl 2-(4-Methoxyphenyl)-3-oxopropanoate (4). Alcohol **5** (2.0 g, 7.14 mmol), ester **6** (6.4 g, 28.8 mmol, 4 equiv), and 4-(dimethylamino)pyridine (0.219 g, 1.80 mmol, 0.25 equiv) in toluene (7.5 mL) were warmed to reflux overnight (18 h). The reaction mixture was partioned between aqueous NH_4Cl and CH_2Cl_2, and the organic layer was dried (Na_2SO_4) and concentrated in vacuo. Excess ester **6** was removed by bulb-to-bulb distillation. The pot residue was chromatographed to give **4** (2.3 g, 5.0 mmol, 71% yield) as a white solid, mp = 99–102 °C from diethyl ether: R_f (20% EtOAc/petroleum ether) = 0.62; ^1H NMR δ 1.80 (d, *J* = 12.5 Hz, 1 H), 8.03 (d, *J* = 8.4 Hz, 1 H), 7.76 (d, *J* = 7.9 Hz, 1 H), 7.65 (d, *J* = 7.9 Hz, 1 H), 7.50–7.20 (m, 4 H), 6.83 (d, *J* = 12.5 Hz, 1 H), 6.44 (d, *J* = 8.7 Hz, 2 H), 5.97 (d, *J* = 8.7 Hz, 2 H), 5.69 (d, *J* = 8.8 Hz, 1 H), 4.01 (d, *J* = 8.8 Hz, 1 H), 3.67 (s, 3 H), 1.95–1.15 (m, 5 H), 1.12 (s, 3 H), 0.90 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR δ 170.8 (u), 162.2 (d), 158.0 (u), 135.2 (u), 133.5 (u), 133.2 (u), 130.2 (d) × 2, 128.8 (d), 127.3 (d), 126.6 (d), 126.0 (d), 125.4 (u), 125.0 (d), 124.6 (d), 123.4 (d), 112.9 (d) × 2, 107.9 (u), 80.5 (d), 55.1 (d), 54.9 (d), 51.3 (d), 49.4 (u), 48.1 (u), 42.3 (u), 23.9 (u), 23.1 (d), 21.4 (d), 14.8 (d); IR 3052, 2962, 1659, 1614, 1518, 1393, 1353, 1277, 1252, 1171, 1046, 1026; MS 456 (M^+) (4), 263 (17), 262 (11), 207 (16), 179 (15), 176 (29), 171 (20), 170 (100), 169 (16), 165 (19), 149 (16), 142 (25), 141 (41), 121 (20), 120 (15); exact mass found 456.231, calcd for $C_{30}H_{32}O_4$ 456.23.

Anal. Calcd for $C_{30}H_{32}O_4$: C, 78.98; H, 7.07. Found: C, 78.54; H, 7.07.

(2*R*,3*R*)-1,7,7-Trimethyl-2-(1-naphthyl)bicyclo[2.2.1]-hept-3-yl (2*R*)-2-(4-Methoxyphenyl)-2-(3-oxobutyl)-3-oxopropanoate (9). An oven-dried, desiccator-cooled 5-mL reactivial was charged with **4** (0.0885 g, 0.194 mmol), freshly powdered potassium carbonate (0.0394 g, 0.286 mmol, 1.47 equiv), and 0.1% aqueous dimethoxymethane (0.2 mL). The resulting solution was stirred for 1 h at room temperature to preform the enolate and then cooled to −50 °C and maintained there for 10 min. Methyl vinyl ketone preserved with methylene blue (0.03 mL, 0.361 mmol, 1.85 equiv) was then added via syringe. The reaction was stirred at −50 °C for 12 h and then poured directly into a 10-mL reservoir

(27) Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351.

of petroleum ether above a 4-g silica gel column. The petroleum ether solution was eluted, and the column was then eluted with 10% EtOAc/petroleum ether to give recovered 4 (0.028 g), followed by a mixture of 9 and 10 (0.0513 g, 0.098 mmol, 51% yield, 74% yield based on consumed 4) as a colorless oil, in a 94:6 ratio. The ratio of diastereomers varied from 94:6 and 96:4, with an average of 95:5, over several runs. The major diastereomer (41 mg, 48% from 4) can be crystallized from the oily mixture by using ether (0.5 mL), mp = 124–126 °C: R_f (30% EtOAc/hexanes) = 0.41; ^{1}H NMR δ 8.22 (s, 1 H), 8.14 (d, J = 8.5 Hz, 1 H), 7.9–7.2 (m, 6 H), 6.58 (d, J = 8.9 Hz, 2 H), 6.24 (d, J = 8.7 Hz, 2 H), 5.67 (d, J = 8.8 Hz, 1 H), 4.11 (m, 1 H), 3.73 (s, 3 H), 2.3–1.3 (m, 12 H), 1.24 (s, 3 H), 1.11 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR δ 206.8 (u), 194.5 (d), 170.3 (u), 159.0 (u), 134.9 (u), 133.7 (u), 133.1 (u), 129.4 (d), 128.3 (d) × 2, 127.5 (d), 127.1 (d), 126.4 (d), 125.7 (u), 125.4 (d), 124.9 (d), 123.5 (d), 114.3 (d) × 2, 80.90 (d), 63.6 (u), 55.3 (d), 55.2 (d), 51.3 (d), 49.5 (u), 48.4 (u), 42.4 (u), 38.4 (u), 29.8 (d), 23.9 (u) × 2, 23.8 (d), 21.6 (d), 14.5 (d); IR 3000, 2961, 1746, 1720, 1550, 1514, 1255 cm^{-1}.

Anal. Calcd for $C_{34}H_{38}O_5$: C, 77.50; H, 7.27. Found: C, 77.20; H, 7.35.

(*S*)-2-(4-Methoxyphenyl)-2-[2-(1,3-dithiolanyl)]-4-[2-(2-methyl-1,3-dithiolanyl)]butan-1-ol (11). Ethanedithiol (0.27 mL, 3.25 mmol, 2.04 equiv) was added dropwise to a mixture of zinc triflate (1.159 g, 3.19 mmol, 2 equiv) and keto-aldehyde 9 (0.837 g, 1.59 mmol) in petroleum ether (3 mL) at 0 °C. After being stirred for 1.5 h at room temperature, the reaction mixture was chromatographed directly to give the bis(thioketal) (1.5 g, 1.55 mmol, 97% yield) as a white solid, mp = 71–75 °C: R_f (30% EtOAc/petroleum ether) = 0.67; ^{1}H NMR δ 8.15 (d, J = 8 Hz, 1 H), 7.85 (d, J = 8.2 Hz, 1 H), 7.7 (d, J = 8.5 Hz, 1 H), 7.6–7.3 (m, 3 H), 6.87 (d, J = 8.9 Hz, 2 H), 6.60 (d, J = 8.9 Hz, 2 H), 5.7 (d, J = 8 Hz, 1 H), 4.63 (s, 1 H), 4.18 (m, 1 H), 3.74 (s, 3 H), 3.35–3.1 (m, 4 H), 2.65–2.44 (m, 2 H), 2.1–1.3 (m, 9 H), 1.48 (s, 3 H), 1.26 (s, 3 H), 1.25 (s, 3 H), 1.11 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR δ 172.9 (u), 158.1 (u), 134.2 (u), 133.4 (u), 130.6 (u) × 2, 128.7 (d), 128.0 (d), 127.5 (u), 126.7 (d), 125.7 (d), 124.8 (d), 124.5 (d), 123.5 (d), 111.6 (d) × 2, 81.2 (d), 66.3 (u), 59.3 (u), 58.4 (d), 54.7 (d), 54.5 (d), 51.1 (d), 49.5 (u), 47.8 (u), 41.7 (u), 39.6 (u), 38.8 (u), 37.6 (u), 37.4 (u), 33.5 (u), 31.8 (d), 23.7 (u), 23.5 (d), 21.3 (d), 14.1 (d); IR 3056, 2959, 1723, 1515, 1253, 1182 cm^{-1}.

Bis(thioketal) from above (1.05 g, 1.55 mmol) in THF (3 mL) was added dropwise to lithium aluminum hydride (0.054 g, 1.55 mmol) in THF (3 mL). After 30 min, the reaction was quenched by the sequential addition of water (0.05 mL), 10% aqueous sodium hydroxide (0.05 mL), and water (0.15 mL). The suspension was vacuum filtered, and the resulting solution was dried (Na_2SO_4) and concentrated in vacuo. The residual oil was chromatographed to give recovered 5 (427 mg, 1.53 mmol, 98% yield), TLC R_f (20% EtOAc/hexane = 0.65, followed by 11 (558 mg, 1.39 mmol, 90% yield) as a viscous oil: R_f (20% EtOAc/hexanes) = 0.35; ^{1}H NMR δ 7.37 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 4.98 (s, 1 H), 4.29 (d, J = 10.8 Hz, 1 H), 3.91 (d, J = 10.8 Hz, 1 H), 3.76 (2, 3 H) 3.40–3.15 (m, 5 H), 3.06 (br s, 1 H), 3.05–2.85 (m, 2 H), 2.70–1.75 (m, 6 H), 1.74 (s, 3 H); ^{13}C NMR δ 157.7 (u), 131.2 (u), 128.7 (d) × 2, 112.5 (d) × 2, 66.7 (u), 64.8 (u), 62.2 (d), 54.6 (d), 48.8 (u), 39.4 (u), 39.3 (u), 39.1 (u), 38.0 (u), 37.7 (u), 31.6 (d), 31.5 (u); IR 3485 (br), 2958, 2928, 1608, 1518, 1463, 1294, 1275, 1251, 1191, 1045; MS (CH_4, CI) 403 (23), 385 (13), 373 (19), 311 (13), 310 (24), 309 (100), 298 (22), 220 (31), 216 (35), 121 (73), 119 (36), 105 (49); exact mass found 403.089, calcd for $C_{18}H_{27}O_2S_4$ 403.0893; $[\alpha]^{25}_D$ = −8.2° (c = 0.016, EtOH).

(*S*)-2-(4-Methoxyphenyl)-2-[2-(1,3-dithiolanyl)]-4-[2-(2-methyl-1,3-dithiolanyl)]butanal (12). Following a modification of the procedure of Corey,[20] alcohol 11 (2.41 g, 5.99 mmol) in CH_2Cl_2 (15 mL) was added dropwise to pyridinium dichromate (3.38 g, 8.98 mmol, 1.5 equiv) and anhydrous sodium acetate (0.500 g, 6.1 mmol, 1 equiv) in CH_2Cl_2 (25 mL) at 0 °C. After 6 h, the mixture was diluted with ether (30 mL) and filtered through a column of Florisil, eluting with ether (100 mL). The combined organic fraction was concentrated in vacuo. The residue was chromatographed to give unreacted 11 (0.241 g, 0.6 mmol), as well as the aldehyde 12 (1.67 g, 4.18 mmol, 68% yield, 78% yield based on 11 consumed) as a colorless oil: R_f (30% EtOAc/hexanes) = 0.50; ^{1}H NMR δ 9.85 (s, 1 H), 7.28 (d, J = 8.9 Hz, 2 H), 6.91 (d, J = 8.9 Hz, 2 H), 5.14 (s, 1 H), 3.81 (s, 3 H), 3.40–3.20 (m, 4 H), 3.02–2.92 (m, 2 H), 2.70–2.45 (m, 2 H), 2.42–2.30 (m, 2 H), 1.90–1.75 (m, 2 H), 1.73 (s, 3 H); ^{13}C NMR δ 202.5 (u), 158.9 (u), 130.0 (d) × 2, 127.4 (u), 113.3 (d) × 2, 66.3 (u), 60.6 (u), 57.6 (d), 54.9 (d), 39.8 (u), 39.7 (u), 39.0 (u), 38.5 (u), 38.0 (u), 32.6 (u), 31.9 (d); IR 2989, 2928, 1742, 1725, 1610, 1514, 1373, 1255, 1242, 1188, 1044; MS (CI) 401 (M + H$^+$) (3), 204 (13), 171 (12), 130 (10), 119 (11), 107 (12), 105 (100); $[\alpha]^{25}_D$ = −30.7° (c = 0.016, EtOH).

Anal. Calcd for $C_{18}H_{24}O_2S_4$: C, 53.96; H, 6.04. Found: C, 54.26; H, 6.12.

(*R*)-3-(4-Methoxyphenyl)-3-[2-(1,3-dithiolanyl)]-5-[2-(2-methyl-1,3-dithiolanyl)]pentan-1-al (13). Phenyllithium (55.3 mL of a 1.39 M solution in ether, 76.9 mmol, 7 equiv) was added dropwise to (methoxymethyl)triphenylphosphonium bromide (28.2 g, 82.4 mmol, 7.5 equiv) in anhydrous ether (50 mL) at 0 °C. The ice bath was removed, and the deep red solution was stirred at room temperature for an additional 10 min. The solution was again cooled in an ice/water bath, and aldehyde 12 (4.4 g, 10.98 mmol) in ether (20 mL) was added dropwise. After 1 h, the reaction mixture was partitioned between EtOAc and water. The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed to give 3.2 g (87%) of enol ether.

Aqueous HCl (1 mL of 10%) followed by concentrated aqueous HCl (1 mL) was added to a portion of the enol ether (1.89 g, 4.4 mmol) in Et_2O (5 mL). After 15 h, the reaction mixture was partitioned between Et_2O and water. The combined organic layer was washed with saturated aqueous Na_2CO_3, followed by water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed to give 13 (1.8 g, 4.35 mmol, 85% yield based on 12) as a white solid, mp = 74–77 °C from Et_2O: R_f (20% EtOAc/petroleum ether) = 0.38; ^{1}H NMR δ 9.88 (s, 1 H), 7.30 (d, J = 8.5 Hz, 2 H), 6.88 (d, J = 8.5 Hz, 2 H), 5.03 (s, 1 H), 3.81 (s, 3 H), 3.40–2.80 (m, H), 2.40–2.20 (m, H); ^{13}C NMR δ 199.6 (d), 158.0 (u), 133.5 (u), 127.8 (d) × 2, 113.3 (d) × 2, 66.2 (u), 63.7 (d), 54.8 (d), 49.3 (u), 46.5 (u), 39.6 (u), 39.4 (u), 39.3 (u), 38.6 (u), 38.4 (u), 36.8 (u), 31.7 (d); IR 2955, 2928, 2838, 1720, 1705, 1608, 1518, 1257, 1191, 1039; MS (CH_4, CI) 416 (M + H$^+$) (38), 321 (27), 309 (24), 303 (24), 237 (14), 187 (16), 148 (14), 121 (22), 119 (100), 104 (50); $[\alpha]^{25}_D$ = −20.6° (c = 0.016, EtOH).

Anal. Calcd for $C_{19}H_{26}O_2S_4$: C, 55.03; H, 6.32. Found: C, 54.71; H, 6.09.

(*R*)-1-(Phenylmethoxy)-3-(4-methoxyphenyl)-3-[2-(1,3-dithiolanyl)]-5-[2-(2-methyl-1,3-dithiolanyl)]pentane (14). Aldehyde 13 (620 mg, 1.5 mmol) dissolved in methanol (2 mL) was added dropwise to $NaBH_4$ (57 mg, 1.5 mmol) in absolute methanol (2 mL) at 0 °C. After 5 min the reaction mixture was partitioned between 5% aqueous HCl and EtOAc. The combined organic layer was dried (Na_2SO_4) and then concentrated in vacuo. The residual oil was chromatographed to give the alcohol (0.544 g, 1.31 mmol, 89% yield) as a colorless oil: R_f (20% EtOAc/hexanes) = 0.18; ^{1}H NMR δ 7.40 (d, J = 8.9 Hz, 2 H), 6.76 (d, J = 8.9 Hz, 2 H), 4.76 (s, 1 H), 3.72 (s, 3 H), 3.75–3.60 (m, 3 H), 3.30–3.20 (m, 5 H), 2.85–2.78 (m, 2 H), 2.40–1.80 (m, 7 H), 1.75 (s, 3 H); ^{13}C NMR δ 158.1 (u), 132.6 (u), 129.5 (d) × 2, 112.5 (d) × 2, 71.7 (u), 66.9 (u), 64.0 (d), 59.0 (u), 58.9 (d), 55.0 (d), 47.1 (u), 40.0 (u), 39.8 (u), 39.7 (u), 38.2 (u), 38.1 (u), 38.1 (u), 33.5 (u), 32.3 (d); IR: 3631, 3485 (br), 2953, 2928, 1742, 1608, 1518, 1463, 1372, 1251, 1191, 1033; MS (CH_4, CI) 417 (M + H$^+$) (59), 399 (18), 339 (10), 325 (15), 324 (26), 323 (100), 311 (40), 189 (26), 147 (27), 121 (19), 119 (75); $[\alpha]_D$ = −1.7° (c = 0.016, $CHCl_3$).

A portion of the above alcohol (0.465 g, 1.12 mmol) dissolved in DME (0.8 mL) was added dropwise to NaH (67 mg of a 60 wt % suspension in mineral oil, 1.675 mmol, 1.5 equiv) in DME (1.2 mL). Benzyl bromide (0.27 mL, 2.23 mmol, 2 equiv) and TBAI (41 mg, 0.111 mmol, 0.1 equiv) were added at room temperature, and then the reaction was heated to 80 °C for three 1-min periods, being allowed to cool after each period. After another 10 h at room temperature, the reaction mixture was partitioned between water and EtOAc. The combined organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed to give 14 (0.423 g, 0.834 mmol, 76% yield from aldehyde 13) as a colorless oil: R_f (30% EtOAc/hexanes) = 0.74; ^{1}H NMR δ 7.52 (d, J = 8.8 Hz, 2 H), 7.38–7.29 (m, 5 H), 6.86 (d, J = 8.7 Hz, 2 H), 4.88 (s, 1 H), 4.54 (s, 2 H), 3.81 (s, 3 H), 3.67–3.57 (m, 2 H), 3.40–3.20 (m, 5 H), 2.90–2.80 (m, 2 H), 2.60–1.80 (m, 7 H), 1.76 (s, 3 H); ^{13}C NMR δ 157.8 (u), 138.1 (u), 132.3 (u), 129.4 (d) ×

2, 128.1 (d) × 2, 127.3 (d) × 2, 127.2 (d), 112.2 (d) × 2, 72.7 (u), 66.7 (u), 66.3 (u), 63.8 (d), 54.8 (d), 47.0 (u), 39.7 (u), 39.6 (u), 39.5 (u), 38.0 (u), 37.8 (u), 34.9 (u), 33.2 (u), 31.9 (d); IR 3031, 2955, 2928, 1609, 1549, 1514, 1464, 1454, 1364, 1254, 1190, 1101, 1041; MS (CH_4, CI) 507 ($M + H^+$) (4), 401 (14), 399 (16), 323 (10), 205 (15), 151 (11), 147 (21), 121 (21), 119 (64), 107 (43), 91 (100); $[\alpha]^{25}_D = +7.4$ ($c = 0.012$, $CHCl_3$).

(*S*)-4-(4-Methoxyphenyl)-4-[2-(phenylmethoxy)eth-1-yl]-cyclohex-2-en-1-one (15). Red mercuric oxide (0.235 g, 1.08 mmol, 4.1 equiv) and boron trifluoride etherate (0.13 mL, 1.06 mmol, 4 equiv) were combined, followed 1 min later by THF/H_2O (0.6 mL of an 85:15 mixture). The orange suspension was stirred 10 min, and then compound **14** (0.134 g, 0.265 mmol) in THF (0.3 mL) was added dropwise. After 70 min the reaction mixture was diluted with water (0.5 mL) and filtered through a pipet of silica gel. The resulting liquid was extracted with ethyl acetate (3 × 0.5 mL). The combined organic extract was dried ($MgSO_4$), concentrated in vacuo, and diluted with toluene (1.5 mL). *p*-Toluenesulfonic acid (20 mg, 0.105 mmol) was added, and the mixture was warmed to reflux for 4 h. The reaction mixture was evaporated directly onto 60–200-mesh silica gel and then chromatographed, to give **15** (62 mg, 0.185 mmol, 70% yield based on **14**) as a colorless oil: R_f (30% EtOAc/hexanes) = 0.55; ^{1}H NMR δ 7.28–7.15 (m, 8 H), 6.81 (d, J = 8.9 Hz, 2 H), 6.08 (d, J = 10.3 Hz, 1 H), 4.33 (s, 2 H), 3.75 (s, 3 H), 3.37 (t, J = 6.6 Hz, 2 H), 2.40–2.10 (m, 6 H); ^{13}C NMR δ 199.4 (u), 158.3 (u), 156.1 (d), 138.1 (u), 134.9 (u), 129.0 (d), 128.4 (d), 127.7 (d), 127.60 (d), 127.56 (d), 114.0 (d) × 2, 73.1 (u), 66.9 (u), 55.2 (d)8 42.7 (u), 41.2 (u), 36.4 (u), 34.5 (u); IR 3068, 2951, 2927, 1732, 1609, 1580, 1551, 1515, 1454, 1254, 1190, 1101, 1043, 1009, 979; MS 336 (M^+) (37), 245 (12), 202 (40), 201 (100), 187 (11), 173 (17), 159 (10), 158 (11), 129 (11), 121 (12), 115 (10); exact mass found 336.1723, calcd for $C_{22}H_{24}O_3$ 336.17253; $[\alpha]^{25}_D = +49.5°$ ($c = 0.040$, $CHCl_3$).

(+)-*O*-Methyljoubertiamine (1). A flame-dried 1-mL reactivial under an N_2 atmosphere was charged with enone **15** (32.5 mg, 0.097 mmol) in CH_3CN (0.15 mL). Sodium iodide (72 mg, 0.48 mmol, 5 equiv) was added, and the reaction was heated for 10 s with a heat gun to dissolve the sodium iodide. The reactivial was cooled to room temperature, and chlorotrimethylsilane (0.06 mL, 0.481 mmol, 5 equiv) was added. The reaction was stirred for 1.75 h and then quenched with saturated aqueous sodium bisulfite solution (0.5 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate. All organic layers were combined, dried ($MgSO_4$), and concentrated under a stream of nitrogen. Dimethylamine (0.1 mL of a 40% aqueous solution of the amine) was added, and the solution was stirred for 30 min and then concentrated under a stream of nitrogen. The residual oil was concentrated in vacuo and chromatographed to give **1** (11.1 mg, 0.040 mmol, 42% yield based on **15**) as a yellow oil: R_f (ether/pH 10 buffer/diethylamine, 80:10:10) = 0.15. The ^{1}H NMR and MS data are identical with the literature values for synthetic[8b] and natural material,[8a] respectively. Because literature data for **1** is sketchy, full characterization is reported: ^{1}H NMR δ 7.20 (d, J = 8.9 Hz, 2 H), 7.12 (d, J = 10.3 Hz, 1 H), 6.87 (d, J = 8.9 Hz, 2 H), 6.14 (d, J = 10.2 Hz, 1 H), 3.79 (s, 3 H), 2.40–1.90 (m, 14 H); ^{13}C NMR δ 199.5 (u), 158.2 (u), 155.5 (d), 135.0 (u), 129.3 (d), 127.6 (d) × 2, 114.0 (d) × 2, 55.2 (d), 55.1 (u), 45.5 (d), 42.7 (u), 39.3 (u), 36.4 (u), 34.4 (u); IR 3386 (br), 2981, 2943, 1686, 1553, 1513, 1462, 1251, 1191, 1119, 1051; MS 273 (M^+) (22), 71 (13), 59 (10), 58 (100); exact mass found 273.1729, calcd for $C_{17}H_{23}NO_2$ 273.1729; $[\alpha]^{25}_D = +50.3°$ ($c = 0.003$, $CHCl_3$).

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Supplementary Material Available: Tables of bond distances and angles for the X-ray structure of **9** (3 pages). Ordering information is given on any current masthead page.

Stereochemistry of Reduction and Methylation of 5-(Trimethylsilyl)adamantan-2-one and 5-(Trimethylstannyl)adamantan-2-one[1]

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It is reported that the title compounds are reduced with sodium borohydride to give both the *E* and *Z* alcohols with the latter in small excess; the tin compound can also be treated with methyllithium to furnish the tertiary *E* and *Z* alcohols, with the latter again predominant. These findings lend further support to the conjecture that the stereochemistry of addition is controlled by transition-state hyperconjugation if steric and/or conformational factors are absent.

The reduction and alkylation of cyclohexanones are among the most thoroughly studied reactions of organic chemistry. One of the factors contributing to this development was Winstein's fruitful insight[2] that large groups such as phenyl and *tert*-butyl effectively lock cyclohexane rings in one of the two possible chair conformations; this feature enables chemists to study the question whether nucleophiles approach the carbonyl group of cyclohexanones preferably from the equatorial or the axial direction. The result, namely that attack from the more hindered axial side is strongly favored, drew much attention.[3] In time, it was realized that this preference must reflect an electronic factor, but while a number of proposals have been made, the nature of this factor remains controversial to this day.[4]

There is one problem associated with the use of locked cyclohexanones beside the fact that the two carbonyl faces

(1) This work was done by M.X. in partial fulfillment of the requirement for the M.S. degree.

(2) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562.

(3) Dauben, W. G.; Fonken, G. J.; Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2579.

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