Unexpected Rearrangement of a Borneol-Derived *O*-Benzylated Hydroxamic Acid: Facile Synthesis of an Optically Active Multidentate Ligand

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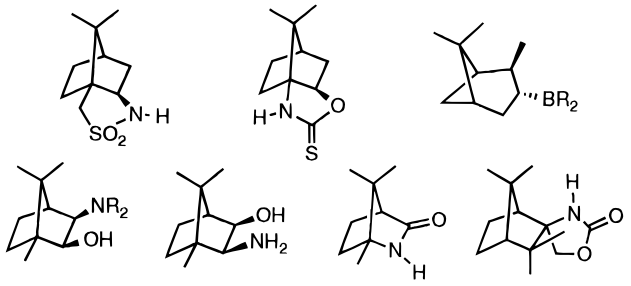
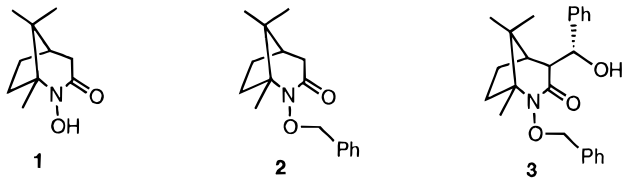
Introduction

The use of bicyclic optically active terpene derivatives as chiral auxiliaries and ligands has become a popular strategy in controlling the stereoenvironment in organic transformations. The effectiveness of this class of compounds is due to the conformational rigidity inherent in their bicyclic structures and the fixed orientation of one or more heteroatoms in a sterically well-defined space. A few representative examples include Oppolzer's chiral sultam[1] derived from camphorsulfonic acid, Yan's camphor-based oxazolidinethione,[2] Brown's pinene-derived boron reducing agents,[3] a number of 1,2 amino alcohol derivatives of camphor,[4,5] camphor lactams,[6] and camphene, pinol, and borneol-dervived oxazolidinones.[7] For many reactions employing these compounds, stereoinduction results from transition state geometries which are exquisitely controlled by bidentate chelation involving a second heteroatom.

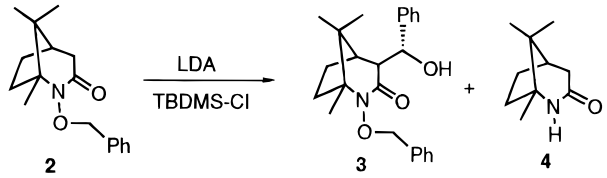


The cyclic hydroxamic acid **1** is readily available from photochemical rearrangement of the nitrite esters of borneol or isoborneol,[8] or from photolysis of 2-nitrobornane.[9] We were attracted to **1** as a conformationally rigid chiral scaffolding for stereochemical investigations of nitroxyl radicals. However, oxidation of the hydroxamic acid did not lead to the expected acyl nitroxyl radical, but instead promoted a disproportionation−dimerization reaction.[10] It was clear that the acyl nature of the nitroxyl radical was responsible for its instability. While trying to modify the hydroxamic acid carbonyl functionality, we attempted to prepare the corresponding silyl enol ether from the *O*-benzylated derivative **2**. Upon treatment with base, an unanticipated rearrangement occurred, resulting in a new compound bearing an additional heteroatom as a single diastereomer. Herein is detailed our studies on the formation and structure of this optically active potentially useful mulitidentate ligand.

Chart 1



Scheme 1



Results and Discussion

The initial investigations were carried out with racemic material derived from *d,l*-isoborneol. Benzylation of **1** with sodium hydride and benzyl bromide proceeded as expected. Treatment of the *O*-benzylated cyclic hydroxamic acid **2** at −78 °C with 2 equiv of LDA followed by 2 equiv of *tert*-butyldimethylsilyl chloride, warming to room temperature, aqueous workup, and column chromatography resulted in the isolation of a white crystalline product which contained no silyl group. Unexpectedly, the product had an exchangeable proton at δ 6.25 which disappeared upon addition of D_2O. Integration of the aromatic region indicated that there were two phenyl groups in the molecule as compared to one in the starting material. Further spectroscopic analysis revealed the structure to be that of alcohol **3**, in which 1 mol of the benzylated hydroxamic acid cannibalizes a second mole of itself (Scheme 1). It was clear that the benzyl alcohol could only be derived from the benzyl protecting group of the starting material. We postulate that benzaldehyde is initially formed and then trapped by the enolate of another molecule of intact starting material (Scheme 2). Extraction with ethyl acetate of the combined aqueous layers from the workup afforded the de-oxybenzylated amide side product **4.** When the reaction was repeated with LDA in the absence of silylating reagent, the same product was obtained. A brief survey utilizing several

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(2) Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613.

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(10) Braslau, R. *J. Org. Chem.* **1995**, *60*, 6191.

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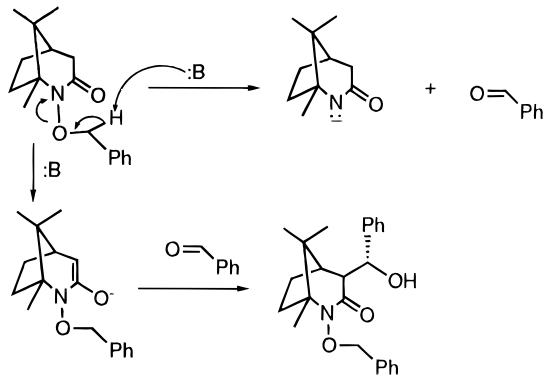
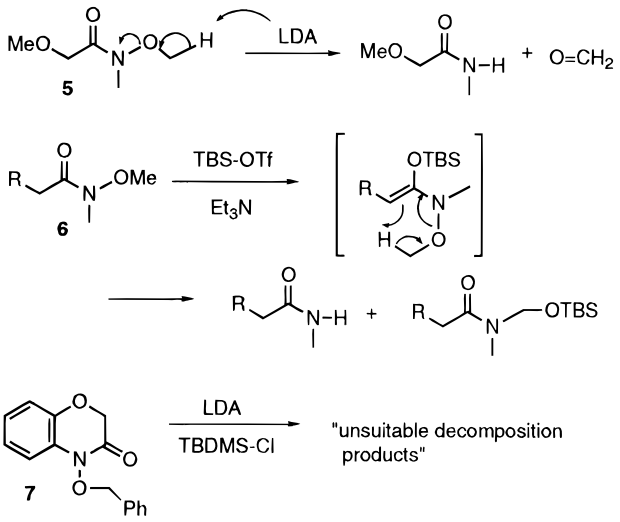
Scheme 2



Scheme 3



bases was carried out: each reaction was followed by aqueous workup and analyzed by ^{1}H NMR on the crude reaction mixture. Use of 2 equiv of either *n*-BuLi or *t*-BuLi effectively converted the starting material into the alcohol **3** and the amide **4**, with *n*-BuLi providing the cleanest transformation. However, sodium hydride in DMF or THF was completely ineffective: starting material was recovered intact.

Several Weinreb amide derivatives have been observed to undergo elimination of aldehyde upon treatment with base (Scheme 3). Graham and Scholz[11] observed loss of formaldehyde from Weinreb amide **5** upon treatment with LDA in a reaction that they determined to occur by E_2 elimination. Recently Keck[12] investigated a related reaction with substrate **6** using an amine base and silyl triflate, in which the parent amide as well as *N*-alkylated product was formed. Under these conditions, nonenolizable starting materials did not react, and a cyclic retro-ene fragmentation was postulated as a route to the final products. The cyclic benzylated hydroxamic acid **7** was reported to lead to "unsuitable decomposition products" upon attempted silylation.[13] In addition, several cases of photochemical cleavage of *O*-benzylated hydroxamic acid derivatives at the N−O bond have been reported.[14]

To confirm the feasibility of a free benzaldehyde intermediate as opposed to a concerted bimolecular

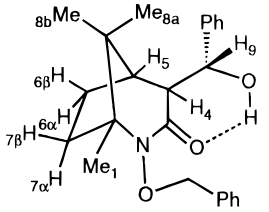
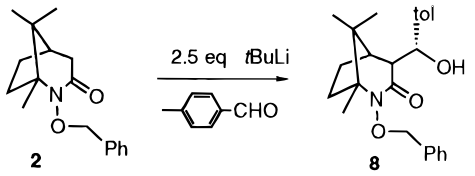


Figure 1.

Scheme 4



rearrangement, the reaction was carried out using *t*-BuLi in the presence of 3 equiv of *p*-tolualdehyde (Scheme 4). The expected trapping product **8** containing a tolyl group at C_9 was isolated in 65% yield following flash chromatography. Recrystallization gave analytically pure product in 40% yield. None of the amide **4** could be detected by ^{1}H NMR of the crude reaction mixture. The normal product **3** containing an unsubstituted phenyl group at C_9 was not isolated. The ^{1}H NMR spectra of **3** and **8** are nearly identical, except for the tolyl methyl group of **8**. Only ^{13}C NMR in the aromatic region shows a significant difference: most notably the ipso carbon of the benzyl alcohol in the all phenyl compound **3** has a peak at 141.7 ppm, whereas in tolyl derivative **8** the analogous peak is found at 138.6 ppm. Although no signal at 141.7 ppm was observed prior to recrystallization, a small amount of **3**, if formed, could have escaped detection.

It is particularly striking that **3** is produced as a single diastereomer, even though its formation involves the generation of two new stereogenic centers (Figure 1). Both ^{1}H−^{1}H COSY and HMQC were used to unambiguously assign each of the peaks in the ^{1}H and ^{13}C spectra. NOESY ^{1}H NMR at 500 MHz indicated that the stereochemistry of the phenylhydroxymethyl group adjacent to the carbonyl to be β from the following observations: a strong NOESY crosspeak was observed between H_4 at 2.59 ppm and $H_{6\alpha}$ at 1.27 ppm, whereas no such crosspeak was seen between H_4 and $H_{6\beta}$ at 1.93 ppm. In addition, none of the methyl groups gave a significant NOESY crosspeak with H_4, indicating that H_4 was α: on the *endo* face away from the *gem*-dimethyl bridge. However, a strong NOESY crosspeak was observed between Me_{8a} at 1.21 ppm and H_9 at 5.05 ppm. Interestingly, H_4 and H_5 (at 1.48 ppm) showed absolutely no coupling, indicating a dihedral angle of approximately 90° between them. We were unable to determine the stereochemistry at C_9 until an X-ray structure determination was carried out.[15] The X-ray structure did indeed confirm the stereoassignment at C_4 and revealed the benzyl alcohol to be oriented as shown in Figure 1. There is an intramolecular hydrogen bond between the hydroxy hydrogen and the hydroxamic acid carbonyl, with a bond distance of 1.87 Å. This is consistent with the downfield shift of the alcohol proton at δ 6.25 ppm.

(11) Graham, S. L.; Scholz, T. H. *Tetrahedron Lett.* **1990**, *31*, 6269.
(12) Keck, G. E.; McHardy, S. F.; Murry, J. A. *Tetrahedron Lett.* **1993**, *34*, 6215.
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(14) (a) Furrer, H. *Tetrahedron Lett.* **1974**, 2953. (b) Katritzky, A. R.; Brown, S. B. *Synthesis* **1978**, 619.

(15) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Scheme 5

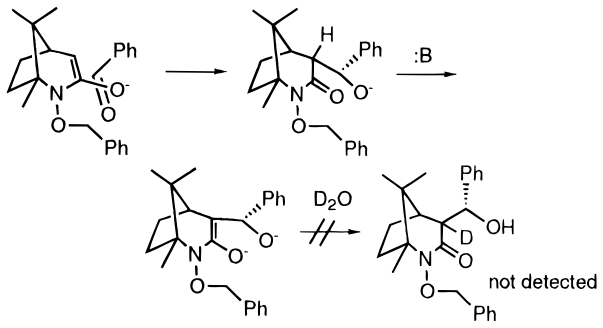
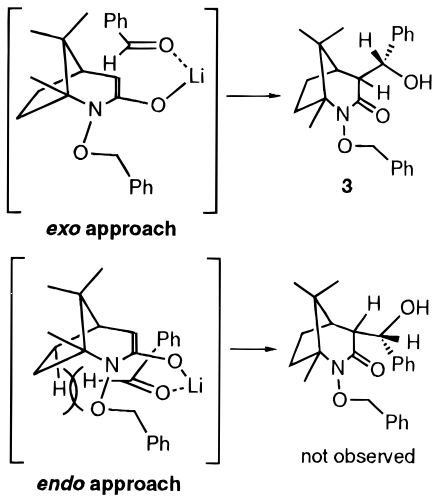


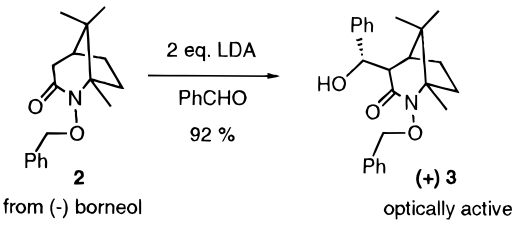
Chart 2



Initially we were surprised that the alkylation at C_4 had occurred from the *exo* face, as one would at first consideration expect a new bond to be formed on the *endo* face of the [3.2.1] system, distal from the methyl group Me_{8a}. One possibility is that the enolate adds to benzaldehyde from the *endo* face and that this initial product is deprotonated to form another enolate, which is ultimately protonated from the *endo* face upon workup. To test this hypothesis, the reaction was run using *n*-BuLi under the normal conditions and quenched with either D_2O or D_2O containing 2 equiv of acetyl chloride to provide *in situ* generation of DOAc and DCl. No deuterium incorporation was observed in either case (Scheme 5). Thus it appears that the benzaldehyde does indeed approach the enolate from the top face proximal to the methyl group on the one-carbon bridge.

A transition state model involving chelation of the aldehyde to the lithium enolate on the *exo* face of the molecule does predict formation of the observed product, in which both newly formed stereogenic centers are taken into account (Chart 2). It is noteworthy that the enolate is part of a [3.2.1] ring system, with the three-atom bridge consisting of a nitrogen and two sp^2-hybridized enolate carbons. Thus the angle between the one- and three-atom bridges is widened, making the interaction between the methyl group Me_{8a} on the one-atom bridge and the incoming electrophile much less severe than in a typical norbornane-based system. The lithium chelation between the enolate oxygen and the aldehyde is reminiscent of the intramolecular hydrogen bond observed in the X-ray structure of the alcohol product **3**. Approach of a chelated aldehyde from the *endo* face results in severe steric interactions between the aldehyde hydrogen and $H_{6\alpha}$.

Scheme 6



By starting with (−)-borneol, alcohol **3** can been prepared in enantiomerically pure form. Optically active alcohol **3** and its derivatives are attractive candidates to be used as chiral auxiliaries and ligands in asymmetric synthesis. The rigid bicyclic framework combined with several heteroatom functionalities oriented in the same local environment appears to satisfy the initial structural requirements for chiral control. The crystallinity of alcohol **3** as well as that of hydroxamic acid **1** and *O*-benzylated species **2** is an added attractive feature of this class of compounds. In order to consider their development as asymmetric control elements, a more efficient synthesis is required to avoid loss of half of the starting material. Enantiomerically pure alcohol **3** can now be prepared in good yield, completely suppressing the formation of amide side product **4**, by adding exogenous benzaldehyde *before* addition of the base (Scheme 6). The use of two full equivalents of LDA is required in order to ensure complete consumption of the starting material. Under these conditions, optically active alcohol **3** has been prepared on a several gram scale.

A few exploratory experiments utilizing alcohol **3** as a chiral ligand have been examined, showing modest but promising asymmetric induction. For example, under nonoptimized conditions, diethylzinc adds to benzaldehyde at 0 °C in the presence of 3 mol % of alcohol **3** to give 1-phenylpropanol in 23% ee. Further experiments probing the utility of alcohol **3** as well as the starting hydroxamic acid **1** as chiral ligands are under active investigation in our labs. The possibility of their development as chiral auxiliaries could also be explored. In addition, derivatives in which the *N*-hydroxy group is unprotected or which contain additional heteroatoms are now being prepared as potentially useful optically active species for asymmetric synthesis.

Experimental Section

General. All reactions were run under N_2. Solvents were dried as follows: THF and DME were distilled under N_2 from sodium−benzophenone. Methanol was distilled from Mg metal. Flash chromatography was performed using Universal Scientific Inc. silica gel 63−200. IR spectra were recorded in $CDCl_3$ solution. Mass spectra were obtained using Magic Bullet or fast atom bombardment (FAB). Elemental analysis was carried out by M-H-W Laboratories in Phoenix, AZ. The X-ray crystallographic structure was obtained from the facilities at the University of California Davis. Melting points are uncorrected.

***d,l*-1,8,8-Trimethyl-2-(benzyloxy)-2-azabicyclo[3.2.1]octan-3-one (2).** NaH (245 mg, 6.1 mmol, 60% dispersion in oil) was added to *d,l*-1,8,8-trimethyl-2-hydroxy-2-azabicyclo[3.2.1]octan-3-one (991.6 mg, 5.41 mmol) in 26 mL of DME at rt. Vigorous gas evolution was observed as a thick white suspension formed. Benzyl bromide (0.68 mL, 5.7 mmol) was added, and the reaction was allowed to stir overnight. The mixture was diluted with 60 mL of ether and washed with 50 mL of 10% aqueous HCl. The organic phase was washed with 20 mL of H_2O followed by 20 mL of saturated aqueous NaCl and dried over $MgSO_4$, and the solvent was removed *in vacuo* to yield 1.5131 g of a yellow oily solid. Flash chromatography using 3:1 hexanes:ethyl

acetate as eluent afforded 1.411 g (95% yield) of the title compound which crystallized upon standing to a white solid: mp 53.5−55.5 °C; IR 2959, 1666, 1354, 1030 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.34−7.27(m, 5H), 5.14 (d, 1H, J = 9.3 Hz), 4.70 (d, 1H, J = 9.3 Hz), 2.70−2.79 (m, 1H), 1.68−2.29 (m, 5H), 1.42−1.51 (m, 1H), 1.29 (s, 3H), 1.10 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.4, 135.4, 129.6, 128.6, 128.4, 77.9, 74.4, 45.5, 42.8, 39.7, 36.6, 27.7, 24.5, 18.3, 15.1. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.78; H. 8.41.

Rearrangement To Form *d,l*-1,8,8-Trimethyl-2-(benzyloxy)-4-(phenylhydroxymethyl)-2-azabicyclo[3.2.1]octan-3-one (3). A solution of **2** (52.6 mg, 0.19 mmol) dissolved in 0.49 mL of THF was cooled to −78 °C, and *n*-BuLi (2.5 M, 0.16 mL, 0.39 mmol) was added. The reaction mixture was allowed to warm slowly to rt. After a total of 3 h, the reaction was quenched by the addition of 15 mL of wet ether followed by 5 mL of water. The organic layer was washed with 5 mL of aqueous saturated NaCl and dried over $MgSO_4$. Volatiles were removed *in vacuo* to give 1.0499 g of viscous oil. Purification by flash chromatography using 6:1 hexanes:ethyl acetate afforded 23.2 mg (0.061 mmol, 63% based on 0.5 equiv of starting material) of the title compound as a white solid: mp 152−153 °C (hexanes/EtOAc); IR 3354 (br), 3033, 2966, 1614 (br), 1334, 1044 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50−7.52 (m, 2H), 7.31−7.42 (m, 8H), 6.25 (s, 1H, disappears upon addition of D_2O), 5.22 (d, 1H, J = 9.0 Hz), 5.05 (d, 1H, J = 10.2 Hz), 4.88 (d, 1H, J = 9.0 Hz), 2.59 (d, 1H, J = 10.2 Hz), 2.07−2.13 (m, 1H), 1.90−1.97 (m, 1H), 1.73−1.79 (m, 1H), 1.48 (d, 1H, J = 7.5 Hz), 1.36 (s, 3H), 1.24−1.30 (m, 1H), 1.21 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.0 (s), 141.7 (s), 134.9 (s), 129.6 (d), 128.9 (d), 128.7 (d), 128.1 (d), 127.7 (d), 78.0 (t), 75.5 (d), 74.6 (s), 57.8 (d), 45.6 (s), 44.1 (d), 37.7 (t), 31.0 (t), 24.9 (q), 20.3 (q), 15.1 (q); MS *m/e* 380 (M + 1, 100), 362 (56); HRMS calcd for $C_{24}H_{30}NO_3$ 380.2226, found 380.2221. Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69. Found: C, 75.64; H, 7.52; N, 3.65.

Also isolated by chromatography was 7.4 mg (14%) of recovered starting material **2**. Elution of the flash column with MeOH afforded 18.7 mg of the amide *d,l*-1,8,8-trimethyl-2-azabicyclo-[3.2.1]octan-3-one **(4)** (lit. ref 1b) mixed with silica gel: IR 3398, 2962, 1666,1267 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.78 (br s, 1H), 2.57−2.70 (m, 1H), 1.48−2.26 (m, 6H), 1.11 (s, 3H), 1.02 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.5, 77.2, 43.5, 42.8, 40.1, 39.4, 27.7, 23.4, 18.5, 17.9.

***d,l*-1,8,8-Trimethyl-2-(benzyloxy)-4-(*p*-tolylhydroxymethyl)-2-azabicyclo[3.2.1]octan-3-one (8).** A solution of **2** (105.1.6 mg, 0.39 mmol) and *p*-tolualdehyle (137 μL, 1.16 mmol) dissolved in 0.69 mL of THF was cooled to −78 °C, and *t*-BuLi (1.7 M in pentane, 0.60 mL, 0.97 mmol) was added. The reaction mixture became yellow. After allowing the mixture to slowly warm to rt overnight, the reaction was quenched by the addition of 20 mL of wet ether followed by 5 mL of saturated $NaHSO_3$ solution. The organic layer was washed with 5 mL of water followed by 5 mL of aqueous saturated NaCl and dried over $MgSO_4$. Volatiles were removed *in vacuo* to give 259.3 mg of oily yellow solid. ^1H NMR of the crude mixture did not show any methyl peaks from amide **4**. Purification by flash chromatography using a hexanes/ethyl acetate gradient afforded 98.9 mg of the title compound as white crystals. Recrystallization from hexanes/ethyl acetate afforded 61.0 mg of white crystals (40%): mp 172.5−174.5 °C; IR 3360 (br), 3034, 2966, 1627, 1394, 1047 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20−7.50 (m, 9H), 6.17 (s, 1H), 5.23 (d, 1H, J = 9.0 Hz), 5.03 (d, 1H, J = 10.1 Hz), 4.88 (d, 1H, J = 9.0 Hz), 2.58 (d, 1H, J = 10.1 Hz), 2.36 (s, 3H), 1.68−2.20 (m, 3H), 1.50 (d, 1H, J = 7.5 Hz), 1.35 (s, 3H), 1.20−1.35 (m, 1H), 1.20 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.1 (s), 138.6 (s), 137.8 (s), 134.9 (s), 130.2 (d), 129.6 (d), 129.4 (d), 129.2 (d), 128.9 (d), 128.6 (d), 127.6 (d), 127.1 (d), 78.0 (t), 75.3 (d), 74.6 (s), 57.7 (d), 45.6 (s), 44.1 (d), 37.8 (t), 31.0 (t), 24.9 (q), 21.3 (q), 20.3 (q), 15.1 (q). Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 75.91; H, 7.79; N, 3.57.

Preparation of Optically Active 1,8,8-Trimethyl-2-(benzyloxy)-4-(phenylhydroxymethyl)-2-azabicyclo[3.2.1]octan-3-one (3). A solution of optically active *O*-benzylhydroxamic acid **2** derived from [1*S*-endo] (−)-borneol (3.488 g, 12.76 mmol) and benzaldehyde (2.60 mL, 25.6 mmol) dissolved in 16.4 mL of THF was cooled to −78 °C, and LDA (1.0 M, 26.2 mL, 26.2 mmol) was added slowly over a period of 8 min. The reaction mixture became a deep gold-brown color and was allowed to warm slowly to rt. After stirring overnight, the reaction was quenched by the addition of 25 mL of a saturated $NaHSO_3$ solution. Volatiles were reduced *in vacuo*, followed by addition of 50 mL of ether. The aqueous layer was back-washed with 25 mL of ether. The combined organic layer was washed with 15 mL of water and 10 mL of an aqueous saturated NaCl solution and then dried over $MgSO_4$. Volatiles were removed *in vacuo* to give 6.6021 g of viscous yellow oil. Flash chromatography (8 cm column, 5:1 to 3:1 hexanes:ethyl acetate gradient) afforded 4.4572 g of the title compound as a yellow oil which was estimated to be approximately 95% pure by ^1H NMR (92% yield). Recrystallization from aqueous ethanol provided 2.6935 g of a white crystalline solid (56% yield): mp 57−95 °C. (A second recrystallization afforded a highly crystalline material with the same broad mp range.) $[\alpha]_D$ = +15.5 (c = 0.0347, EtOH). The NMR spectra were identical to that of the racemic analogue. Also recovered from flash chromatography were 392 mg of a fraction containing benzaldehyde and 465 mg of a fraction composed primarily of benzyl alcohol.

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Supporting Information Available: Copies of the ^1H NMR and ^{13}C NMR spectra of **1**, **2**, **3**, and **8**. For compound **3**, APT, $^1H-^1H$ COSY, $^1H-^{13}C$ COSY, HMQC, NOESY and spectra and details of the X-ray crystal structure data acquisition and thermal ellipsoid plot of the structure (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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