# Asymmetric Allylation and Reduction on an Ephedrine-Derived Template: Stereoselective Synthesis of α-Hydroxy Acids and Derivatives

Sunil V. Pansare,* R. Gnana Ravi, and Rajendra P. Jain

*Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411 008, India*

*Received December 16, 1997*

The asymmetric synthesis of α-hydroxy acids continues to be an area of active interest due to their utility as chiral building blocks.[1] Among the several synthetic approaches to α-hydroxy acids, the stereoselective addition of carbon nucleophiles to chiral α-keto acid derivatives has been extensively investigated.[2] We describe here a stereoselective synthesis of α-alkyl α-allyl α-hydroxy amides, α-alkyl α-hydroxy acids, and α-*H* α-hydroxy acids. The procedure involves prefunctionalization of the precursor α-keto acid by intramolecular hemiacetalization followed by (a) stereoselective allylation or (b) dehydration and hydrogenation of the chiral hemiacetal.

Stereoselective allylation of ketones has been a challenging task, and an efficient method has been described only recently.[3] Similarly, the development of an efficient procedure for asymmetric allylation of α-keto acid derivatives has been difficult, although their stereoselective reactions with other carbon nucleophiles are well established.[2] Stereoselective carbonyl ene reactions have been examined mainly with glyoxylates and, in a few instances, with pyruvates.[4] Menthyl esters of α-keto acids have been allylated[5] with low diastereoselectivity, whereas the diastereoselectivity for allylation of proline-derived α-keto amides is not uniformly high and the allylated intermediates have been converted to α-hydroxy ketones and not α-hydroxy acids.[6] Enzymatic resolution[7a] of a few α-allyl α-hydroxy esters and allylation of dioxolanone enolates[7b,c] have been examined as alternative routes to α-alkyl α-allyl hydroxy acids, but these do not employ α-keto acids as starting materials.

Our interest in chiral amino alcohol-based hemiacetals of α-keto acids as pecursors to α-hydroxy acids[8] led us to investigate (1*R*,2*S*)-ephedrine as a chiral controller in such systems. Acylation of (1*R*,2*S*)-ephedrine hydrochloride with aliphatic α-keto acid chlorides generates the corresponding hemiacetals **1b-e** in 65−71% yield. Hemiacetal **1a** is obtained by ester hydrolysis in the amido ester obtained by bis-acylation of ephedrine with benzoylformyl chloride (Scheme 1). The absolute configuration of the hemiacetal stereocenter was established as *S* by X-ray crystallographic analysis[9] of **1d** and **1e** and by analogy in the $^1$H NMR spectra of **1a**−**e**.

Initial experiments were conducted with **1a** (R = Ph). Contrary to expectation, **1a** proved to be unreactive toward a variety of carbon nucleophiles. Thus, treatment of **1a** with several alkyl Grignard reagents at ambient temperature or with MeLi or $MeTiCl_3$ at lower temperature did not generate any carbonyl addition products. The lack of reactivity of **1a** with alkylmetal reagents is in contrast to the facile reactions of lactols with carbon nucleophiles[10] and may be explained by formation of a stable metal chelate involving the amide oxygen and the hemiacetal alkoxide. Although the alkyl analogues **1b**−**e** were also unreactive toward Grignard reagents, all hemiacetals proved to be excellent substrates for allylation (Scheme 2).

Treatment of **1d** with allyltrimethylsilane/$TiCl_4$ at 0 °C generated a 1/2.5 mixture of the allylated product **2d** and the elimination product **3d**. As expected, the elimination process could be subdued by lowering the reaction temperature. Although the reaction was prohibitively slow at −78 °C, **1a**−**e** could be allylated with allyltrimethylsilane/$TiCl_4$ at −40 °C to produce **2a**−**e** as single diastereomers in 67−92% yield.[11] Small amounts (<5%) of the elimination products **3b**−**e** were also obtained (Scheme 2). The olefins **3c** and **3d** have been assigned the *Z* geometry on the basis of the chemical shift of the olefinic methine proton ($\delta$ 6.12 in **3c**) as compared to the upfield shift[12] in the *E* isomer ($\delta$ 5.75), which was obtained by irradiation of **3c** at 254 nm.

Liberation of the hydroxy acids from the ephedrine template[13] in **2** proved to be challenging. The benzylic C−O bond is resistant to cleavage under a variety of

* To whom correspondence should be addressed. Tel./Fax: 091-212-335153. E-mail: pansare@ems.ncl.res.in.

(1) (a) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: New York, 1983; Chapter 2. (b) Seuring, B.; Seebach, D. *Helv. Chim. Acta* **1977**, *60*, 1175−1181.

(2) (a) Akiyama, T.; Ishikawa, K.; Ozaki, S. *Synlett* **1994**, 275−276. (b) Kim, Y. H.; Byun, I. S.; Choi, J. Y. *Tetrahedron: Asymmetry* **1995**, *6*, 1025−1026. (c) Basavaiah, D.; Pandiaraju, S.; Bakthadoss, M.; Muthukumaran, K. *Tetrahedron: Asymmetry* **1996**, *7*, 997−1000. (d) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893−7894.

(3) Tietze, L. F.; Schiemann, K.; Wegner, C. *J. Am. Chem. Soc.* **1995**, *117*, 5851−5852.

(4) Asymmetric ene reactions of glyoxylates: a) Whitesell, J. K.; Bhattacharya, A.; Buchanan, C. M.; Chen, H. H.; Deyo, D.; James, D.; Liu, C.-L.; Minton, M. A. *Tetrahedron* **1986**, *42*, 2993−3001. (b) Mikami, K. *Pure Appl. Chem.* **1996**, *68*, 639 and references therein. Ene reactions of pyruvates: (c) Whitesell, J. K.; Nabona, K.; Deyo, D. *J. Org. Chem.* **1989**, *54*, 2258−2260. (d) Gladysz, J. A.; Yu, Y. S. *Chem. Commun.* **1978**, 599−600. (e) Spencer, H. K.; Hill, R. K. *J. Org. Chem.* **1975**, *40*, 217−220.

(5) Ojima, I.; Miyazawa, Y.; Kumagai, M. *Chem. Commun.* **1976**, 927−928.

(6) (a) Waldmann, H. *Synlett* **1990**, 627−628. (b) Soai, K.; Ishizaki, M. *J. Org. Chem.* **1986**, *51*, 3290−3295.

(7) (a) Moorlag, H.; Kellogg, R. M.; Kloosterman, M.; Kaptein, B.; Kamphuis, J.; Schoemaker, H. E. *J. Org. Chem.* **1990**, *55*, 5878−5881. (b) Fráter, Gy.; Müller, U.; Günther, W. *Tetrahedron Lett.* **1981**, *22*, 4221−4224. (c) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313−1324.

(8) For a stereodivergent reduction of prolinol based hemiacetals of α-keto acids see: Pansare, S. V.; Ravi, R. G. *Tetrahedron Lett.* **1995**, *36*, 5959−5962.

(9) Hemiacetal **1d:** colorless, orthorhombic crystals; space group *P*212121; unit cell parameters, $a$ = 8.083(2) Å, $b$ = 9.135(4) Å, $c$ = 40.635(5) Å; α = 90°, $\beta$ = 90°, $\gamma$ = 90°; $Z$ = 8, $R$ ($I > 2\sigma(I)$) = 0.0495, GOF = 1.119. Hemiacetal **1e:** colorless, orthorhombic crystals; space group *P*212121; unit cell parameters, $a$ = 8.256(5) Å, $b$ = 9.522(2) Å, $c$ = 18.836(4) Å; α = 90°, $\beta$ = 90°, $\gamma$ = 90°; $Z$ = 4, $R$ ($I > 2\sigma(I)$) = 0.0365, GOF = 1.071.

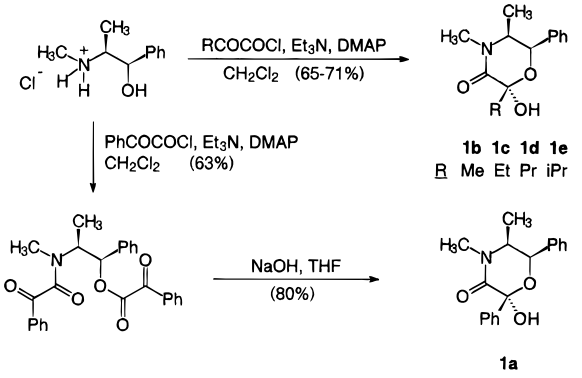
(10) (a) Tomooka, K.; Okinaga, T.; Suzuki, K. Tsuchihashi, G. *Tetrahedron Lett.* **1989**, *30*, 1563−1566. (b) Tomooka, K.; Okinaga, T.; Suzuki, K. Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 6335−6338. (c) Tomooka, K.; Matsuzawa, K.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 6339−6342.

(11) All crude products were analyzed for isomer composition by 200 MHz $^1$H NMR and/or $^{13}$C NMR.

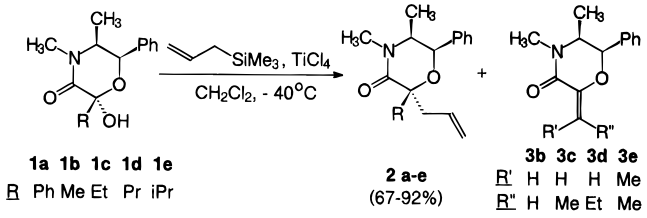
(12) The stereochemical assignment is based on the reported trend in chemical shifts for the olefinic methine protons in (*E*) and (*Z*)-benzylidenecamphor derivatives, see: Kossanyi, J.; Furth, B.; Morizur, J. P. *Tetrahedron* **1970**, *26*, 395−409.

S0022-3263(97)02282-2 CCC: $15.00 
Published on Web 05/15/1998

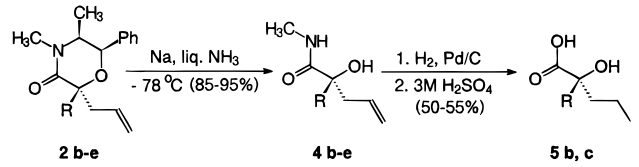
**Scheme 1**




**Scheme 2**




**Scheme 3**




hydrogenolytic conditions and is also inert under mild ether cleavage conditions (NBS/$CCl_4$, followed by NaOH). However, treatment of **2b**−**e** with Na in liquid $NH_3$ at −78 °C cleanly generates the hydroxy amides **4b**−**e** in 85−95% yield.[14] Presumably, the intermediate benzylic anion derived from **2** undergoes facile *β*-elimination of the *N*-acyl moiety at low temperature. Amides **4b** and **4c** were hydrogenated in quantitative yield ($H_2$, Pd/C, 1 atm) and hydrolyzed (3 M $H_2SO_4$, 120 °C) to the free α-alkyl α-hydroxy acids (Scheme 3).

Thus, **5b** and **5c** were obtained with the *R* configuration[15] (Scheme 3), which is assigned by comparison of the sign of the optical rotation with literature values.[15] The enantiomeric excess (>95%) of the α-alkyl α-hydroxy acids is based on the obtainment of precursors **2** as single diastereomers by $^1H$ and $^{13}C$ NMR (epimerization of the newly generated stereocenter during conversion of **2** to **4** and **4** to **5** is unlikely) and was confirmed by $^1H$ NMR analysis of the corresponding Mosher ester of **5b**. The *R* configuration establishes that the allylsilane adds to the *re* face of an oxocarbenium ion derived from **1**. The hydrogenation product of amide **4e** is resistant to hydrolysis, presumably due to steric hindrance by the isopropyl group, and undergoes decomposition. Conversion of **4d** to **5d** was not examined since **5d** is achiral.

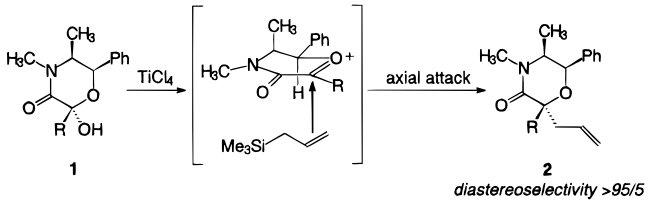
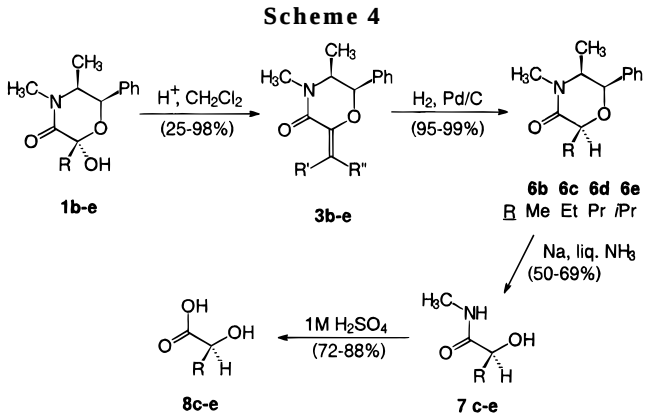



**Figure 1.** Stereoselective allylation of hemiacetals **1**.

**Scheme 4**




The configuration of the allylated product **2**, with respect to the hemiacetals **1** (Figure 1), is strongly suggestive of an $S_N1$-like mechanism[16] for the allylation process. The stereoselectivity of the allylation may be due to a stereoelectronic effect.[17] Considering a pseudoequatorial orientation of the phenyl group in the hemiacetal derived oxocarbenium ion, axial attack of the allylsilane would generate the product with the observed stereochemistry (Figure 1). Thus, the origin of stereocontrol in the allylation of oxocarbenium ions in the ephedrine template is similar to that proposed for the stereoselective addition of nucleophiles to chiral iminium ions[17a] and chiral imines[17b] in morpholin-2-one templates employed in the asymmetric synthesis of α-amino acids.

Hemiacetals **1** can also be employed in a stereoselective synthesis of α-*H* α-hydroxy acids by conversion to the elimination products **3**, which are admirable precursors of α-hydroxy acids. Dehydration of **1c**−**e** with trifluoroacetic acid in refluxing dichloromethane (78 h) affords the olefins **3c**−**e** in 92−98% yield. **1b** is inert under these conditions but affords **3b** in low yield (25%, 34% recovery of **1b**) by treatment with catalytic sulfuric acid in dichloromethane (0 °C, 20 min).[18] Hydrogenation of **3b**−**e** ($H_2$, Pd/C, 50 psi) generates **6b**−**e** as single diastereomers[11] in quantitative yield (Scheme 4).

Alternatively, **1** can be reduced to **6** directly[19] ($TiCl_4$/$Et_3SiH$, $CH_2Cl_2$, −40 °C), but with low stereoselectivity

(13) The alkylation of an ephedrine-based glycolic acid derivative has been briefly described. However, removal of the ephedrine portion was not investigated due to potential difficulties; see: Ludwig, J. W.; Newcomb, M.; Bergbreiter, D. E. *Tetrahedron Lett.* **1986**, *27*, 2731−2734.

(14) Dissolving metal reduction of **2a** generated a mixture of products arising from cleavage of both the benzylic C−O bonds and other side reactions. Other methods for regioselective cleavage of **2a** are being examined.

(15) (a) Ohta, H.; Kimura, Y.; Sugano, Y.; Sugai, T. *Tetrahedron* **1989**, *45*, 5469−5476. (b) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2943−2948.

(16) (a) Denmark, S. E.; Almstead, N. G.; *J. Am. Chem. Soc.* **1991**, *113*, 8089−8110. (b) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107−6115.

(17) (a) Chiral glycine derivatives: Vigneron J. P.; Kagan, H.; Horeau, A. *Tetrahedron Lett.* **1968**, 5681−5683. Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103−1104. Williams, R. M. *Aldrichim. Acta* **1992**, *25*, 11−25. (b) Chiral morpholin-2-ones derived from phenylglycinol: Cox, G. G.; Harwood, L. M. *Tetrahedron: Asymmetry* **1994**, *9*, 1669−1672.

(18) Extended reaction times lead to the exclusive formation of a dimeric product that probably arises from reaction of the enol ether in **3b** with the oxocarbenium ion derived from **1b**.

(19) Nishiyama, Y.; Tujino, T.; Yamano, T.; Hayashishita, M.; Itoh, K. *Chem. Lett.* **1997**, 165−166.

**Table 1. Allylation, Dehydration, and Reduction of Morpholinones 1−3, and 6 and Hydrolysis of Amides 4 and 7 to Acids 5 and 8**

| | % yield | | | | | | | % ee | |
|---|---|---|---|---|---|---|---|---|---|
| | **2**[a] | **3**[a,b] | **4** | **5** | **6**[a] | **7** | **8** | **5** | **8**[c] |
| **b** | 75 | 25 | 85 | 55 | 96 | 50 | | >95[c] | |
| **c** | 80 | 96 | 84 | 50 | 95 | 68 | 87 | >95[d] | 92[c] |
| **d** | 83 | 92 | 89 | | 99 | 59 | 88 | | 92[c] |
| **e** | 92 | 98 | 96 | | 99 | 51 | 72 | | 96[e] |

[a]Single diastereomers by $^1$H NMR. [b]Obtained by acid-catalyzed dehydration of **1**. [c]Based on $^1$H NMR analysis of Mosher esters. [d]Based on the de of **2**. [e]HPLC analysis of Mosher ester.

(88% yield of **6b**, ds = 5/1). The stereochemistry of the new stereocenter in **6e** is assigned as *S* by NOE measurements, which indicated a cis relationship of the hydrogens at C2, C5, and C6 in the morpholinone ring. Dissolving metal reduction ($Na/NH_3$, 20 s) of morpholinones **6** yields the α-hydroxy amides **7**[20] (51−68%). It is noteworthy that this reduction is extremely rapid at −78 °C, and prolonged reaction times (>30 s) result in significantly lower yields of **7**. Hydrolysis of **7c**−**e** (1 M $H_2SO_4$, reflux) generates the α-hydroxy acids **8c**−**e**[21] (72−88% yield, 92−96% ee by $^1$H NMR or HPLC analysis of Mosher derivatives of the methyl esters) with the *S* configuration, which confirms the stereochemistry of **6**. The high stereoselectivity for hydrogenation emphasizes the strong, intrinsic stereochemical bias for reagent approach in the ephedrine-derived template (Scheme 4).

The results of the allylation and dehydration of **1**, conversion of **2** to the free α-alkyl α-hydroxy acids **5**; hydrogenation of **3** to **6**, and subsequent conversion to α-*H* α-hydroxy acids **8** have been summarized in Table 1.

In conclusion, we have demonstrated high stereoselectivity in asymmetric carbon−carbon and carbon−hydrogen bond construction with chiral hemiacetals derived from α-keto acids and ephedrine. The methodology has been applied to the stereoselective synthesis of several α-*H* α-hydroxy acids, α-alkyl α-hydroxy acids, and α-allyl α-hydroxy amides, which are potential precursors of α-substituted butyrolactams and lactones.[22] Since (1*S*,2*R*)-ephedrine is also commercially available, the enantiomeric series of α-hydroxy acids should also be readily available by this methodology. Current efforts focus on the reactivity of **3** and acetals derived from **1**.

## Experimental Section

**General Methods.** All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (120 °C) that was cooled under argon. THF was distilled from sodium benzophenone ketyl, and dichloromethane and triethylamine were distilled from $CaH_2$. Commercially available titanium tetrachloride ($TiCl_4$) was used as such. Petroleum ether refers to the fraction boiling in the range 60−80 °C. Commercial precoated silica gel (Merck 60F-254) plates were used for TLC. Silica gel for column chromatography was 60−120 or 230−400 mesh. All melting points are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker MSL-300 or Bruker AC-200 instruments. Coupling constants (*J*) are given in Hz. Optical rotations were measured at the sodium D line on a JASCO-181 digital polarimeter at ambient temperature. Elemental analyses were performed by the Microanalysis facility at NCL, Pune.

**General Procedure for the Preparation of Hemiacetals 1b−e.** To a suspension of the sodium salt of the α-keto acid in $CH_2Cl_2$ or to the neat α-keto acid was added $Cl_2CHOMe$ at ambient temperature, and the mixture was stirred for 20 min. The resulting suspension or solution was heated at 50−55 °C for 30 min, after which time it was cooled to ambient temperature and diluted with anhydrous $CH_2Cl_2$, and the solution was added to a suspension of (1*R*,2*S*)-ephedrine hydrochloride, triethylamine, and DMAP in anhydrous $CH_2Cl_2$ dropwise with cooling (ice bath). The mixture was then stirred at ambient temperature for 6 h. The reaction mixture was diluted with $CH_2Cl_2$ and the solution washed with 5% HCl, saturated aqueous sodium bicarbonate, and brine, dried ($Na_2SO_4$), and concentrated to provide the crude product, which was purified by flash chromatography on silica gel.

**(2*S*,5*S*,6*R*)-2,4,5-Trimethyl-2-hydroxy-6-phenylmorpholin-3-one (1b).** Reaction of pyruvoyl chloride (prepared from pyruvic acid (2.06 mL, 30 mmol) and $Cl_2CHOCH_3$ (3.2 mL, 35 mmol)) and (1*R*,2*S*)-ephedrine hydrochloride (3 g, 15 mmol) in the presence of triethylamine (8.4 mL, 60 mmol) and DMAP (183 mg, 1.5 mmol) in $CH_2Cl_2$ (45 mL) afforded 4.03 g of crude product, which on purification by flash chromatography on silica gel (3/7 petroleum ether/ethyl acetate) furnished 2.48 g (71%) of **1b**. An analytical sample was obtained by crystallization from ethyl acetate: mp 110 °C; IR ($CHCl_3$) 3340, 3000, 2940, 1635, 1490, 1450, 1380, 1220, 1130, 1010, 940, 890, 750 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.36−7.23 (m, 5H), 5.47 (d, 1H, $J$ = 2.9), 4.4 (br s, 1H), 3.43 (dq, 1H, $J$ = 2.9, 6.5), 2.99 (s, 3H), 1.69 (s, 3H), 0.93 (d, 3H, $J$ = 6.5); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 168.7, 137.4, 128.1, 127.4, 125.6, 95.9, 71.2, 59.2, 33.5, 26.3, 11.9; MS (70 eV) *m*/*z* 58 (100), 77 (12), 91 (8), 100 (28), 105 (71), 118 (32), 146 (2), 235 (<1, $M^+$); $[\alpha]^{24}_D$ = −107.4 (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.39; H, 7.43; N, 5.99.

**General Procedure for the Allylation of Hemiacetals 1a−e to Morpholinones 2a−e.** To a solution of **1** in $CH_2Cl_2$ was added allyltrimethylsilane at −40 °C followed by $TiCl_4$, and the solution was stirred for 6−10 h at −40 °C (−20 °C for **1a**). Saturated aqueous $NH_4Cl$ was added to the reaction mixture, and it was warmed to ambient temperature. Water was added to dissolve precipitated solids, and the solution was extracted with $CH_2Cl_2$, dried ($Na_2SO_4$), and concentrated to furnish the crude product, which was purified by flash chromatography on silica gel.

**(2*R*,5*S*,6*R*)-2,4,5-Trimethyl-6-phenyl-2-(1-propenyl)morpholin-3-one (2b).** Reaction of **1b** (0.29 g, 1.2 mmol) and allyltrimethylsilane (1 mL, 6.3 mmol) in the presence of $TiCl_4$ (0.68 mL, 6.2 mmol) in $CH_2Cl_2$ (10 mL) afforded 0.32 g of a gum, which on purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) furnished 0.24 g (75%) of **2b** as a gum: IR ($CHCl_3$) 3000, 1630, 1430, 1210, 750 cm$^{-1}$; $^1$H NMR (200

(20) Dobashi, Y.; Nakamura, K.; Saeki, T.; Matsuo, M.; Hara, S.; Dobashi, A. *J. Org. Chem.* **1991**, *56*, 3299−3305.

(21) (a) Kim, M.-J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1988**, *110*, 2959−2964. (b) Li, W.-R.; Ewing, W. R.; Harris, B. D.; Joullié, M. M. *J. Am. Chem. Soc.* **1990**, *112*, 7659−7672. (c) Chenault, H. K.; Kim, M.-J.; Akiyama, A.; Miyazawa, T.; Simon, E. S.; Whitesides, G. M. *J. Org. Chem.* **1987**, *52*, 2608−2611.

(22) (a) Chung, S.-K.; Jeong, T.-H.; Kang, D.-H. *Tetrahedron: Asymmetry* **1997**, *8*, 5−9. (b) Kitagawa, O.; Sato, T.; Taguchi, T. *Chem. Lett.* **1991**, 177−180.

Hz, $CDCl_3$) $\delta$ 7.45−7.20 (m, 5H), 5.98−5.75 (m, 1H), 5.2 (d, 1H, $J$ = 2.7), 5.18−5.03 (m, 2H), 3.5 (dq, 1H, $J$ = 6.5, 2.7), 3.04 (s, 3H), 2.83 (dd, 1H, $J$ = 14.4, 5.9), 2.53 (dd, 1H, $J$ = 14.4, 8.7), 1.50 (s, 3H), 0.98 (d, 3H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 171.4, 137.7, 132.6, 127.8, 127.0, 125.1, 117.6, 78.8, 71.7, 58.7, 40.2, 33.2, 24.8, 12.1; MS (70 eV) *m/z* 58 (53), 67 (22), 77 (19), 91 (27), 105 (18), 117 (40), 148 (100), 174 (6), 190 (27), 218 (69), 259 (8, $M^+$); HRMS (FAB$^+$) for $C_{16}H_{22}NO_2$ $[M + H]^+$ calcd 260.1651, found 260.1645; $[\alpha]^{24}_D = -67.1$ (*c* 2.1, $CHCl_3$).

**General Procedure for Dissolving Metal Reduction of Morpholinones 2b−2e to Amides 4b−e.** To anhydrous liquid ammonia (distilled over sodium) was added Na (10 equiv) at −78 °C and the mixture stirred for 15 min. To the resulting blue solution was added a solution of **2** (1 equiv) in anhydrous THF, and the mixture was stirred for 2−3 min. Methanol (3 mL) was added followed by water (3 mL), and the mixture was warmed to ambient temperature and extracted with ethyl acetate after removal of ammonia. The combined extracts were dried over $Na_2SO_4$ and concentrated to provide the crude product, which was purified by flash chromatography on silica gel.

**(2*R*)-2-Hydroxy-2-methylpent-4-enoic Acid *N*-methylamide (4b)** was prepared from **2b** (0.18 g, 0.7 mmol) in THF (2 mL) and Na (0.16 g, 7 mmol) in ammonia (8 mL) to furnish 0.105 g of crude product, which on purification by flash chromatography on silica gel (6/4 petroleum ether/ethyl acetate) furnished 85 mg (85%) of product. IR ($CHCl_3$) 3366, 3078, 2936, 1651, 1545, 1456, 1412, 1369, 1240, 1165, 1070, 1033, 918 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 6.80 (br s, 1H), 5.88−5.65 (m, 1H), 5.25−5.10 (m, 2H), 2.81 (d, 3H, $J$ = 5), 2.7 (dd, 1H, $J$ = 13.7, 6.0), 2.3 (dd, 1H, $J$ = 13.7, 8.7), 1.4 (s, 3H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 176, 132.7, 119.8, 74.9, 44.5, 26.0, 25.9; HRMS (FAB$^+$) for $C_7H_{14}NO_2$ $[M + H]^+$ calcd 144.1025, found 144.1021; $[\alpha]^{25}_D = +45.8$ (*c* 0.6, $CHCl_3$).

**General Procedure for Hydrogenation of Amides.** Amides **4b,c,e** were dissolved in ethyl acetate and hydrogenated over 5% Pd/C (5 wt %) at ambient temperature and atmospheric pressure for 2−3 h. The catalyst was removed by filtration through Celite. The filtrate upon concentration furnished the hydrogenated amides in quantitative yield. These were pure by $^1$H NMR and were hydrolyzed to the acids without purification.

**(2*R*)-2-Hydroxy-2-methylpentanoic Acid (5b).** Hydrolysis (3 M $H_2SO_4$, 120 °C, 30 h) of the hydrogenation product of **4b** (0.04 g, 0.28 mmol) gave 0.02 g (55%) of **5b**: IR ($CHCl_3$) 3019, 2964, 1713,1216, 759, 669 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 6.6 (br s, 1H), 1.9−1.1 (m, 4H), 1.47 (s, 3H), 0.93 (t, 3H, $J$ = 7.2); MS (70 eV) *m/z* 69 (20), 71 (12), 87 (100), 133 (1, M + 1); $[\alpha]^{24}_D = -11.2$ (c 0.4, $CHCl_3$), ee >95% (based on de of **2b**) (lit.[15a] $[\alpha]^{24}_D = +9.53$ (*c* 2.1, $CHCl_3$) for the *S* enantiomer, >95% ee).

**General Procedure for Dehydration of Hemiacetals 1 to Alkylidenemorpholinones 3.** A solution of the hemiacetal **1** in dichloromethane was either treated with concentrated sulfuric acid at 0 °C for 20 min or heated to reflux with trifluoroacetic acid for 78 h. The reaction mixture was then washed with saturated aqueous sodium bicarbonate solution followed by brine. The organic layer was separated and dried over anhydrous sodium sulfate. Concentration of the organic phase under reduced pressure gave the crude product, which was purified by column chromatography over silica gel. The purified products decompose gradually at room temperature. Storage at −20 °C under Ar is beneficial. However, solutions in common solvents are stable at ambient temperatures.

**(5*S*,6*R*)-2-(2-Propylidene)-4,5-dimethyl-6-phenylmorpholine-3-one (3e)** was prepared from hemiacetal **1e** (108 mg, 0.41 mmol) and trifluoroacetic acid (0.5 mL) in anhydrous dichloromethane (8 mL). Purification of the crude product by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) gave 99 mg (98%) of **3e** as a pale yellow oil: IR (neat) 2922, 1660, 1626, 1449, 1378, 1291, 1174, 1067, 757 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.5−7.3 (m, 5H), 5.12 (d, $J$ = 2.5, 1H), 3.55 (dq, $J$ = 2.5, 7, 1H), 3.05 (s, 3H), 2.25 (s, 3H), 1.9 (s, 3H), 0.95 (d, $J$ = 7, 3H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 160.4, 138.2, 137.3, 128.1, 127.4, 126.3, 125.1, 76.5, 58.5, 33.0, 19.8, 11.6; MS (70 eV) *m/z* 56 (43), 67 (33), 77 (24), 82 (40), 91 (47), 96 (22), 105 (19), 110 (7), 118 (100), 128 (21), 140 (6), 146 (25), 154 (15), 228 (16), 245 ($M^+$, 67); $[\alpha]^{23}_D = -177.1$ (*c* 0.7, $CHCl_3$).

**General Procedure for Reduction of Alkylidenemorpholinones 3 to Morpholinones 6.** A solution of alkylidene morpholinones **3** in ethyl acetate was shaken with 5% Pd/C in a Parr hydrogenator under 50 psi of hydrogen at room temperature for 1.5−2.5 h. The catalyst was removed by filtration through a pad of Celite, and the solvent was removed under reduced pressure to give pure morpholinones **6** as colorless oils.

**(2*S*,5*S*,6*R*)-2-(2-Propyl)-4,5-dimethyl-6-phenylmorpholin-3-one (6e)** was prepared from **3e** (150 mg, 0.61 mmol) in ethyl acetate (15 mL) and Pd/C (5%, 30 mg): reaction time 2.5 h; yield 150 mg (99%); IR (neat) 2966, 1735, 1648, 1451, 1253, 1151, 1042, 705 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.37−7.24 (m, 5H), 4.93 (d, $J$ = 2.8, 1H), 4.16 (d, $J$ = 2.4, 1H), 3.45 (dq, $J$ = 2.8, 6.4, 1H), 3.00 (s, 3H), 2.52 (dseptet, $J$ = 6.9, 2.4, 1H), 1.12 (d, $J$ = 6.9, 3H), 0.96 (d, $J$ = 6.9, 3H), 0.92 (d, $J$ = 6.4, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 168.7, 137.9, 128, 127.2, 125.1, 82, 75.7, 58.3, 33, 30.4, 19, 16.3, 12.8; MS (70 eV) *m/z* 58 (92), 69 (43), 77 (24), 84 (20), 91 (34), 98 (31), 105 (22), 113 (71), 118 (100), 126 (21), 132 (7), 141 (86), 148 (12), 205 (11), 247 ($M^+$, 29); HRMS calcd for $C_{15}H_{21}NO_2$ 247.1573, found 247.1565; $[\alpha]^{24}_D = -158.7$ (*c* 1.8, $CHCl_3$).

**(*S*)-2-Hydroxy 3-methyl butanoic acid *N*-methylamide (7e)**[20] was prepared from **6e** (0.488 g, 1.98 mmol) in THF (2 mL) and Na (0.453 g, 19.7 mmol) in ammonia (40 mL). Purification by flash chromatography on silica gel (ethyl acetate) furnished 0.132 g (51%) of **7e**: IR ($CHCl_3$) 3365, 2958, 1632, 1577, 1409, 1021, 616 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 6.59 (bs, 1H), 3.98 (bs, 1H), 2.96 (bs, 1H), 2.85 (d, $J$ = 4.9, 3H), 2.17 (dsept, $J$ = 3.1, 6.9, 1H), 1.02 (d, $J$ = 6.9, 3H), 0.84 (d, $J$ = 6.9, 3H). MS (70 eV): *m/z* 55 (87), 58 (74), 60 (64), 73 (86), 83 (17), 89 (100), 98 (3), 113 (11), 131($M^+$, 5); $[\alpha]^{25}_D = -57.0$ (*c* 2.6, $CHCl_3$).

**(2*S*)-2-Hydroxy-3-methylbutanoic Acid (8e).**[21b] **7e** (130 mg, 0.99 mmol) in 1 M $H_2SO_4$ (18 mL) was heated to reflux for 36 h to yield 85 mg (72%) of **8e**: IR 2967, 1728, 1467, 1215, 1136, 1028, 895, 759 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.8 (bs, 2H), 4.16 (d, $J$ = 3.4, 1H), 2.30−2.05 (m, 1H), 1.07 (d, $J$ = 6.9, 3H), 0.93 (d, $J$ = 6.9, 3H); MS (70 eV) *m/z* 55 (53), 58 (38), 73 (85), 76 (100), 87 (5), 102 (5), 118 ($M^+$, 2). Ee of the methyl ester of **8e** (obtained by treatment with $CH_2N_2$): 96% (HPLC analysis of the Mosher derivative with (*S*)-MTPA; Macherey-

Nagel Nucleosil 5 $C_8$ (reversed phase) column, 250 × 4 mm, acetonitrile/water 6/4, flow rate 1.2 mL/min; $t_R$ (major) 3.81 min; $t_R$ (minor) 5.11 min).

**Acknowledgment.** We are grateful to Professor Scott E. Denmark for valuable comments. We thank Professor S. Kanemasa, Kyushu University, for HRMS of some of the intermediates, the Department of Science and Technology (Grant No. SP/S1/G-11/96), and the Council of Scientific and Industrial Research (fellowships to R.G.R. and R.P.J.) for financial support. This is NCL Communication No: 6420.

**Supporting Information Available:** Experimental methods and spectroscopic data with assignments for all compounds (**1**−**8**) and copies of $^1$H and/or $^{13}$C NMR spectra for **1a**, **2a**−**e**, **3b**−**e**, **4b**,**d**,**e**, **6b**−**e**, and **7b**−**e** (45 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.

JO9722820