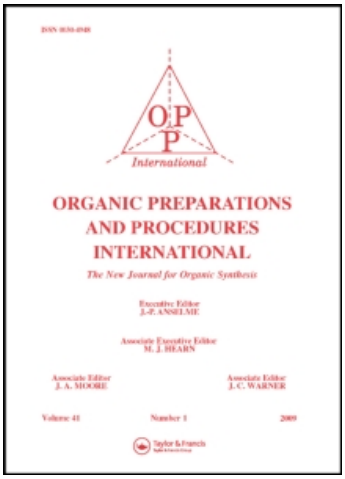

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A CONCISE SYNTHESIS OF CHIRAL 3-HYDROXYMETHYL-5-ISOPROPYL MORPHOLINES FROM VALINOL

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(11/14/01)

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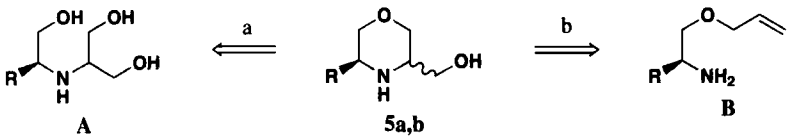
The morpholine substructure is quite common in nature and has many pharmacological attributes including antiviral (moroxydine, morazine), analgesic (morpheridine), antitussive (pholcodine), muscle relaxant (flumetramide), antiolytic (molindine), and antiparasitic (minorazole) applications. Additional examples include Largorce's report that morpholines and iodine form charge-transfer complexes with applications in novel thyroid-targeting drugs[1] and Bianchi's report that morpholine-based fungicides control *Helminthosporium teres* with excellent selectivity.[2] Morpholines can also play a significant role in modern organic synthesis. For example, Enders *et al.* recently reported that (*S,S*)-3,5-dimethylmorpholine imparts good to excellent diastereoselectivity when employed as a C2-symmetric auxiliary in Diels-Alder reactions.[3] In light of these valuable biological and synthetic uses, we undertook a study targeting optically active 3-hydroxymethyl-5-alkylmorpholines from amino acids and report here a concise route to **5** (*Scheme 1*).



A **5a,b** **B**

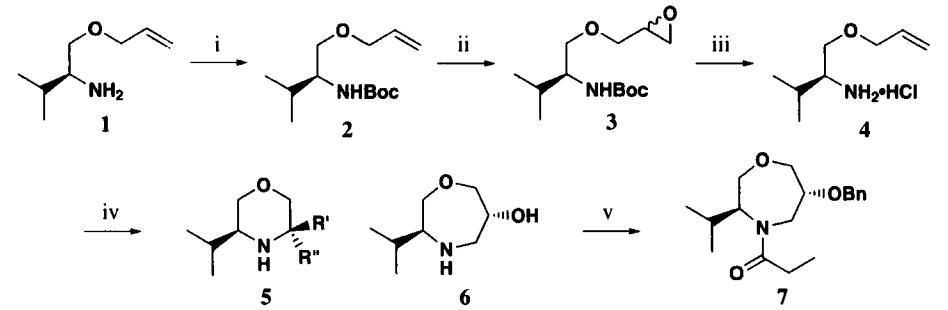
(R = isopropyl)

Routes investigated for the preparation of morpholine **5**

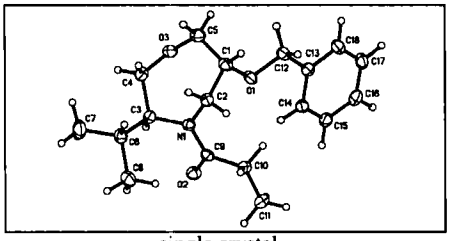
Scheme 1

Our efforts began with two unsuccessful routes to **5**. The first route (a), paralleled Enders approach to (*S,S*)-3,5-dimethylmorpholine where we envisioned heterocycle formation *via* a dehydrative cyclization of **A**. Unfortunately, the rigorous conditions required for dehydration (H_2SO_4, 180°)[3] led to extensive decomposition and **5** was obtained in very low yield. Our second unsuccessful approach [route (b)], relied on heterocycle formation *via* electrophilic cyclization of **B** and was based on the earlier studies of Wilson and Sawicki.[4] Again, only complex reaction mixtures, containing at best trace amounts of the desired 3-(halomethyl)morpholine, were obtained from bromine- or iodine-mediated electrophilic cyclizations of **B**. Protection of the nitrogen as the Boc derivative reduced the nucleophilicity of the nitrogen to the point where the major product was simple bromine addition across the C=C-double bond; attempts at base-mediated [$NaOCH_3$ in CH_3OH or $(Me_3Si)_2NLi$ in THF] morpholine formation from this dibromourethane resulted in dehydrohalogenation to the corresponding vinyl bromide.

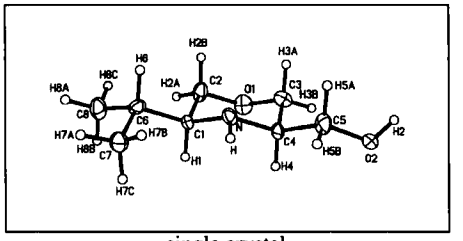
Our successful approach to morpholine **5** is outlined in *Scheme 2*. *O*-Allylation of L-valinol (NaH, THF; allyl bromide) gave *O*-allyl-L-valinol (**1**) in 85% yield.[5] Boc-Protection of the amino group delivered carbamate **2** in quantitative yield and was followed by epoxidation with *m*-CPBA to



a) R' = H, R" = CH_2OH (54%)
b) R' = CH_2OH, R" = H (14%)



single crystal
x-ray structure of **7**



single crystal
x-ray structure of **5b**

i) $(Boc)_2O$, CH_2Cl_2 ii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2 iii) HCl, MeOH. iv) KOH, MeOH.
v) a) NaH, THF; BnBr b) $CH_3CH_2C(O)Cl$, Et_3N, CH_2Cl_2.

Stereoselective route to morpholine **5a**.

Scheme 2

give an isolable but unresolved mixture of epoxide diastereomers (**3**). After work-up, this crude reaction mixture was dissolved in ice-cold methanolic HCl (AcCl added to MeOH) and TLC analysis [hexanes:EtOAc (3:1)] indicated that Boc deprotection was completed in 30 min. Addition of methanolic KOH to make the reaction mixture slightly basic resulted in intramolecular epoxide opening by the free amine (**3** → **4**). Standard work-up and flash column chromatography [SiO_2/$CHCl_3$: MeOH::85:15] delivered **5** (68% overall yield from **1**) as a 3.8:1 mixture of **5a** and **5b**,[6] along with a small amount of the *trans*-7-membered heterocycle **6** (5% yield from **1**). Unambiguous structural assignments for **5** and **6** were made by single crystal x-ray analyses of crystalline **5b** ($P2_1$ space group) and of **7**[7] ($P2_12_12_1$ space group). It is worth noting that conversion of **1** to **5** was accomplished as a two-pot procedure.

A more direct route to 3-hydroxymethyl-5-isopropylmorpholine (**5a** and **5b**) from **1**, patterned from Asensio *et al.*,[8] was to temporarily protect the 1°-amine of **1** from *N*-oxidation in the epoxidation step by simply forming the corresponding tosylate salt. Subsequent olefin epoxidation with *m*-CPBA delivered **4** as its tosylate salt which was dissolved in methanolic potassium hydroxide.

Neutralization to the free amine was accompanied by concomitant intramolecular epoxide opening to give **5** (75% yield) as a nearly 1:1 mixture of diastereomers along with small amounts of heterocycle **6**. However, while more direct than the path outlined in *Scheme 2*, the lack of stereoselectivity makes this route less attractive.

EXPERIMENTAL SECTION

All chemicals were purchased from Aldrich. Prior to use, CH_2Cl_2 was distilled from CaH_2 and THF was distilled from sodium benzophenone ketyl. NMR spectra were recorded with a Varian 300 spectrometer (^1H at 300 MHz, ^{13}C at 75 MHz). Infrared spectra were recorded on a Mattson Genesis II FTIR 3000 spectrometer. The elemental analyses were preformed by Midwest Microlabs (Indianapolis, IN).

***O*-Allyl-L-valinol (1).**- Into a flame-dried 500 mL three-neck flask fitted with a mechanical stirrer was placed NaH (60% dispersion in mineral oil; 4.64 g, 116 mmol) under argon. The NaH was triturated with dry toluene (2 x 10 mL) and dry THF (250 mL) was added followed by the dropwise addition of a THF solution (20 mL) of L-valinol (11.3 g, 110 mmol) at room temperature. After 3 h, the reaction mixture was cooled to -10°, allyl bromide (13.3 g, 110 mmol) was added dropwise, and the reaction mixture was stirred for an additional 3 h. After removal of the THF by rotary evaporation, the residue was dissolved in Et_2O (200 mL) and this solution was washed with brine (100 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined ethereal phases were dried over anhydrous magnesium sulfate and concentrated. The product was distilled under vacuum to provide 13.3 g (85%) of a colorless liquid, bp. 62-65°/0.1 mmHg [^1H-NMR (300 MHz, $CDCl_3$) δ 0.90 (d, 6H, J = 7.0 Hz), 1.30 (br, 2H), 1.61 (octet, 1H, J = 7.0 Hz), 2.72 (m, 1H), 3.22 (dd, 1H, J = 9.0, 9.0 Hz), 3.47 (dd, 1H, J = 9.0, 3.0 Hz), 3.97 (d, 2H, J = 7.0 Hz), 5.20 (m, 2H), 5.90 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 18.1, 19.4, 31.0, 56.3, 72.1, 74.0, 116.8, 134.9].

Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 66.97; H, 11.99; N, 9.59

[(3*S*,5*S*)-5-(Methylethyl)morpholin-3-yl]methan-1-ol (5).- A CH_2Cl_2 (200 mL) solution of di-*tert*-butyl dicarbonate (20.1 g, 92 mmol) was added dropwise to a CH_2Cl_2 (60 mL) solution of *O*-allyl L-valinol (13 g, 90.7 mmol). Carbon dioxide evolved from the mildly exothermic reaction which was maintained under N_2 at room temperature of 3 h (work-up of a 1 mL portion of this reaction mixture involved removing CH_2Cl_2 by rotary evaporation to give **2** as a yellow oil [^1H-NMR (300 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 7 Hz), 0.93 (d, 3H, J = 7 Hz), 1.44 (s, 9H), 1.88 (octet, 1H, J = 7 Hz), 3.42 (m, 1H), 3.50 (m, 2H), 3.97 (m, 2H), 4.7 (br, 1H), 5.18 (m, 1H), 5.27 (dt, 1H, J = 17, 1.5), 5.89 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 18.5, 19.5, 28.3, 31.1, 48.8, 55.4, 70.3, 72.0, 116.7, 134.6, 155.8]).

The resulting CH_2Cl_2 solution of **2** was treated with sodium bicarbonate (19.5 g, 230 mmol) and 70% *m*-CPBA (70%; 49.3 g, 200 mmol) and the reaction was stirred at room temperature for 2 days [monitored by ^1H-NMR (disappearance of C,C-double bond) and additional *m*-CPBA was added

as required]. Work-up involve extraction of the CH_2Cl_2 solution with 10% aq. sodium sulfite (100 mL) followed by 10% aq. potassium carbonate (100 mL). The resulting CH_2Cl_2 solution was dried over anhydrous magnesium sulfate and concentrated by rotary evaporation to give crude **3** as a yellow oil.

Next, methanol (100 mL) was cooled to 0° and acetyl chloride (15 mL) was carefully added in small portions. The resulting HCl•MeOH•MeOAc was added to the residue from above (crude **3**) and the mixture was stirred at room temperature for 30 min. The reaction mixture was neutralized (pH paper) by addition of methanolic KOH and the precipitate removed by filtration. After washing the precipitate with methanol (2 x 15 mL), the combined methanol solutions were concentrated by rotary evaporation to yield a slurry which was dissolved with ethyl acetate (200 mL), filtered, and concentrated to yield the crude product. Flash column chromatography (85:15::chloroform:methanol) gave **5a** (7.91 g, 54% from **1**) [^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 7 Hz), 0.95 (d, 3H, J = 7 Hz), 1.68 (octet, 1H, J = 7 Hz), 2.57 (dt, 1H, J = 8, 3 Hz), 2.72 (br, 2H), 2.98 (m, 1H), 3.35 (dd, 1H, J = 11, 8 Hz), 3.55 (m, 2H), 3.66 (dd, 1H, J = 11, 4 Hz), 3.78 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 18.9, 19.1, 28.9, 52.1, 54.8. 60.5, 67.5, 70.3; IR (film) 3397.97, 3324.67 cm^{-1}].

Anal. Calcd for $C_8H_{17}NO_2$: C, 60.35; H, 10.76; N, 8.80. Found: C, 60.44; H, 10.57; N, 8.63

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6. Compound **4**: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.90 (d, 3H, J = 7 Hz), 0.96 (d, 3H, J = 7 Hz), 1.56 (octet, 1H, J = 7 Hz), 2.11 (br, 2H), 2.60 (m, 1H), 3.04 (m, 1H), 3.13 (dd, 1H, J = 10, 11 Hz), 3.24 (dd, 1H, J = 10, 11 Hz), 3.47 (dd, 1H, J = 6, 11 Hz), 3.63 (dd, 1H, J = 4, 11 Hz), 3.78 (dd, 1H, J = 3, 10 Hz), 3.88 (dd, 1H, J = 3, 10 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 18.8, 18.9, 30.4, 56.2, 60.1, 63.2, 68.8, 70.5.

7. Compound **6** was prepared from **5** by *O*-benzylation (NaH, THF; BnBr) and *N*-acylation (propionyl chloride, Et_3N, CH_2Cl_2).

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