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Boranes in Synthesis. 3. Conversion of the Morpholine and Pyrrolidine Enamines of Symmetrical Dialkylketones to the Corresponding *threo*-β-Amino Alcohols via Hydroboration/Oxidation

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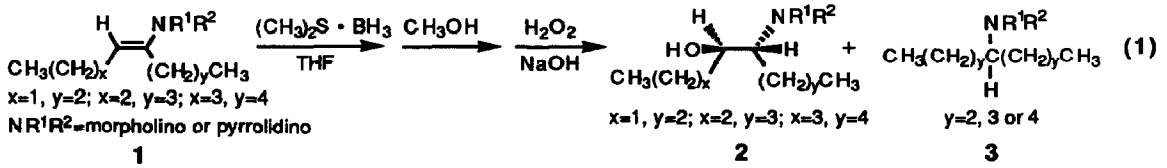
Summary: *The hydroboration of the morpholine and pyrrolidine enamines of symmetrical dialkylketones with BMS followed by methanolysis and oxidation with basic hydrogen peroxide gave the corresponding threo-β-amino alcohols in moderate yields.*

β-Amino alcohols are important as pharmacological agents,[1] and enantiomerically pure β-amino alcohols are becoming increasingly important as chiral auxiliaries in asymmetric organic synthesis.[2] The synthesis of β-amino alcohols by the hydroboration/oxidation of the enamines of cyclic ketones[3] and α-substituted aldehydes[4] has been described, and we recently reported the asymmetric synthesis of β-amino alcohols from aldehyde enamines.[5] We now report the preparation of otherwise inaccessible regiochemically and stereochemically defined β-amino alcohols *via* the hydroboration/oxidation of the enamines of symmetrical dialkylketones.

Morpholine and pyrrolidine reacted with 4-heptanone, 5-nonanone and 6-undecanone to give the corresponding enamines with the (*E*)-configuration (**1**, eq 1).[6] Hydroboration of these enamines with BMS followed by methanolysis and oxidation with basic hydrogen peroxide or Me_3NO afforded the corresponding *threo* amino alcohols (**2, Table 1**) in moderate yields (eq 1). The crude amino alcohols were shown to contain



(1)

Table 1. ***threo*-β-Amino Alcohols 2 from the Enamines of Symmetrical Dialkyl Ketones 1**

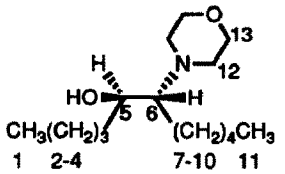
X	Y	NR^1R^2	Yield, %[a]	Bp, °C (Torr)
1	2	4-morpholino	64	b
2	3	4-morpholino	29	119-121 (1.4)
2	3	1-pyrrolidino	34	48-50 (0.02)
3	4	4-morpholino	45	125-127 (0.7)

[a]Isolated and distilled. [b]Crude product. Oxidation with Me_3NO.

small amounts (3-7%) of the reduction products **3**. When the reactions were quenched with CH_3OD no deuterium incorporation was observed in **3** by GC/MS suggesting that these products do not arise during the methanolysis step[7].

The structure of *threo*-6-(4-morpholino)-5-undecanol was determined by ^1H and ^{13}C NMR analyses (**Table 2**). Homonuclear decoupling (^1H) experiments determined the coupling constants of interest. The stereochemistry was determined by the magnitude of the coupling between the methine protons. The interpretation of the coupling was simplified by the presence of internal hydrogen bonding between the hydroxyl proton and the morpholine nitrogen. The possible rotational conformations which are highly populated are shown in **Scheme 1**. In the T-2, E-1, and E-2 conformations the methine protons are *gauche*.

Table 2. NMR Parameters ($CDCl_3$) of *threo*-6-(4-Morpholino)undecanol

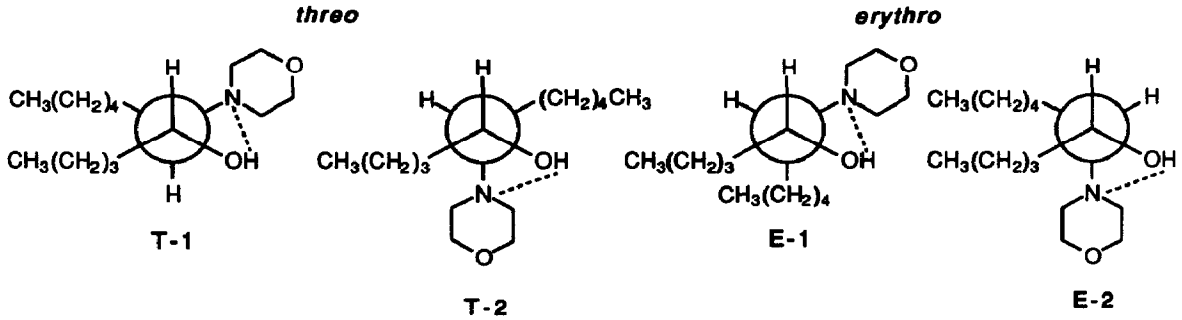


Position	^{13}C (∂ ppm)	^1H (∂ ppm)	$\lvert^nJ_{HH}\rvert$ (Hz)[a]
1	113.8 or 13.7	0.92 or 0.90	$^3J_{1,2} = {}^3J_{10,11}$=7.0
2	22.5	~1.30	
3	28.3	~1.38	
4,4*	33.4	~1.57	$^3J_{4,5}$=8.2; $^3J_{4*,5}$=2.0
5	69.1	3.26	$^3J_{5,6}$=9.5
6	69.3	2.20	$^3J_{6,7}$=7.0; $^3J_{6,7*}$=4.4
7,7*	27.9	~1.57	
8	25.9	~1.38	
9	32.0	~1.30	
10	22.4	~1.30	
11	13.7 or 13.8	0.90 or 0.92	
12,12*	48.8	2.77 and 2.53	
13	67.2	3.70	

[a]Absolute value of the coupling constant is presented; ±0.2 Hz. All other couplings are either zero or were not determined. The * designates the non-equivalent methylene proton with the smaller coupling to the methine proton.

The magnitudes of the gauche couplings were expected to be approximately 2.6 Hz.[8] In the *anti* conformation, T-1, the coupling would be expected to be approximately 10.3 Hz.[8] Analysis of the proton multiplets associated with the methine protons yielded a coupling of 9.5 Hz, in qualitative agreement with the *anti* conformation, T-1.

Scheme I



threo*-6-(4-Morpholino)-5-undecanol.** A previously dried and nitrogen flushed 100-mL, single-neck flask equipped with a magnetic stirrer and a Claisen adapter fitted with a rubber septum and a nitrogen bubbler was charged with 4.58 g (19.1 mmol) of (*E*)-6-(4-morpholino)-5-undecene and 13 mL of tetrahydrofuran. The solution was cooled with an ice bath and 2.0 mL (20 mmol) of borane methyl sulfide (10M) (BMS) was slowly added. The reaction was stirred with cooling for 10 min and then at room temperature for 2.0 h. The reaction was treated with 3.0 mL of methanol and stirred at room temperature for 1.5 h. The reaction was then treated with 1.20 g of solid sodium hydroxide followed by the slow addition of 2.5 mL of 30% hydrogen peroxide. The reaction was stirred at room temperature for 1.0 h. The organic layer was decanted away from a white, sticky solid which had formed. The solid was washed with three 30-mL portions of diethyl ether. The solvents were removed *in vacuo* from the combined organic layers leaving a nearly colorless oil. The oil was dissolved in 25 mL of methanol and the solution made acidic with concentrated hydrochloric acid. The solution was stirred at room temperature for 5 h. The methanol was removed *in vacuo* leaving a mixture of a gummy solid and a colorless oil. The gummy solid was washed with two 30-mL portions of diethyl ether. The residue was dried again on a rotary evaporator to give 4.28 g of gummy solid. The solid was dissolved in 25 mL of water and the solution mixed with 30 mL of diethyl ether. The aqueous solution was made strongly basic with 50% sodium hydroxide. The layers were separated and the aqueous layer was extracted with five 30-mL portions of diethyl ether. the combined ether extracts were dried over anhydrous magnesium sulfate. The magnesium sulfate was separated by filtration and washed with two 30-mL portions of diethyl ether. The ether was removed in vacuo from the filtrate leaving 2.48 g (50% yield) of the crude amino alcohol (7% reduced product by GC/MS) as a yellow oil. The crude amino alcohol was distilled at reduced pressure to give 2.21 g (45% yield) of *threo*-6-(4-morpholino)-5-undecanol as a colorless liquid, bp (125-127 °C (0.7 Torr). ***Analysis. Calc'd for $C_{15}H_{31}NO_2$: C, 69.98; H, 12.14; N, 5.44. Found: C, 69.51; H, 11.42; N, 5.73.[9]

***threo*-5-(4-Morpholino)-4-nonanol.** An identical reaction using 5.42 g (25.6 mmol) of (*E*)-5-(4-morpholino)-4-nonene and 2.6 mL (26 mmol) of BMS (10M) gave 2.19 g (37% yield) of crude amino alcohol (3% reduced product by GC/MS) as a yellow oil. The crude amino alcohol was distilled at reduced pressure to give a 0.19 g forecut as a colorless liquid, bp 70-74 °C (1.4 Torr) and 1.71 g (29% yield) of *threo*-5-(4-morpholino)-4-nonanol as a colorless liquid, bp 119-121 °C (1.4 Torr).[10]

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7. Reduction products have been reported as biproducts and, in some instances, as the major product of the hydroboration/oxidation of enamines. See: (a) Munk, M.E.; Kim, Y.K. *J. Org. Chem.* **1965**, *30*, 3705. (b) Gore, J.; Barieux, J.-J. *Tetrahedron Lett.* **1970**, 2849. (c) Barieux, J.-J.; Gore, J. *Tetrahedron* **1972**, *28*, 1537. Deuterated reduction products have been observed in other hydroboration/methanolysis/oxidation reactions of enamines when CH_3OD was employed (Ref. 3e). A more detailed study of this phenomenon has been conducted, and the results will be presented separately.

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9. This material was analyzed by HPLC using a chiral stationary phase (250 mm x 4.6 mm Chiralpak-AD column from Chiral Technologies Inc.) using 5% methanol in pentane as the mobile phase. This system gave a separation of the enantiomers with a k' of 0.66 and an α of 1.09. Nicholson, L.W.; Goralski, C.T.; Singaram, B.; Fisher, G.B. *Abstracts of Papers*, Fourth International Symposium on Chiral Discrimination, Montreal, Quebec, Canada, **1993**, Abstract 161.

10. Using the same conditions described above (Ref. 9) a separation of the enantiomers was achieved with a k' of 0.46 and an α of 1.22.

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