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Boranes in Synthesis. 4. Hydroboration of Enamines Derived from 2-Norbornanone. Synthesis of *endo*-3-(Dialkylamino)-*exo*-2-norbornanols and *endo*-2-(Dialkylamino)norbornanes

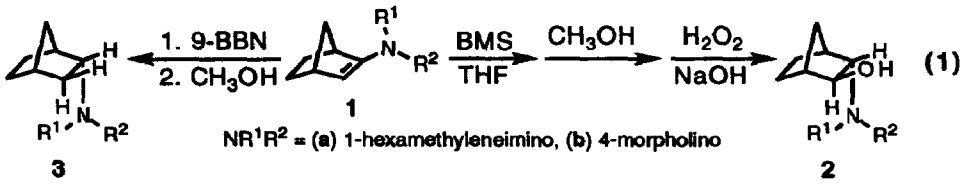
Christian T. Goralski*§, Dennis L. Hasha‡, Lawrence W. Nicholson‡, and Bakthan Singaram*†

§*Pharmaceuticals Process Research and* ‡*Analytical Sciences, Core R&D, The Dow Chemical Company, Midland, Michigan 48674 and* †*Department of Chemistry and Biochemistry, University of California, Santa Cruz, Santa Cruz, CA 95064*

Summary. *The hydroboration of the enamines derived from 2-norbornanone with BMS followed by methanolysis and oxidation with basic hydrogen peroxide afforded moderate yields of the corresponding endo-3-(dialkylamino)-exo-2-norbornanols. Hydroboration with 9-BBN followed by methanolysis gave excellent yields of the corresponding endo-2-(dialkylamino)norbornanes.*

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] α-substituted aldehydes,[4] and symmetrical dialkyl ketones has been described,[5] and we recently reported the asymmetric synthesis of β-amino alcohols from aldehyde enamines.[6] We now report the preparation of *endo*-3-(dialkylamino)-*exo*-2-norbornanols[7] and *endo*-2-(dialkylamino)norbornanes *via* the hydroboration of the enamines of 2-norbornanone.

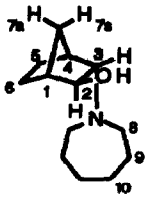
The reaction of morpholine or hexamethyleneimine with 2-norboranone in toluene gave the corresponding enamines **1**.[8] Hydroboration of **1** with BMS followed by methanolysis and oxidation with basic hydrogen peroxide afforded the corresponding *endo*-3-(dialkylamino)-*exo*-2-norbornanols **2** in moderate yields (eq 1). The



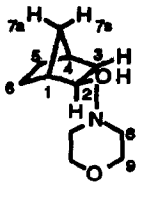
3 **1** **2** (1)

structures of **2** were determined by detailed analysis of their ^{1}H and ^{13}C NMR spectra, and the data are summarized in **Table 1.** The structural assignment for **2b** was based on the results of the following 2D experiments: ^{1}H-COSY, ^{1}H-^{13}C chemical shift correlation, and ^{13}C-^{13}C INADEQUATE. The resonances associated with H2 and H3 were broadened singlets with unresolved couplings, indicating that the coupling between H2 and H3 was small (<2 Hz), and suggested an *endo-exo* coupling.[9,10] For model norbornanes[11] and norbornenes[11,12] examination of the non-equivalent protons (H5 and H6) revealed that the *exo*-proton was located downfield from the corresponding *endo*-proton. The stereochemistry of **2b** was determined by the addition of Europium FOD (Eu(fod)$_3$), which was associated with the hydroxyl group. The *endo*-protons at positions 5 and 6 did not shift with the addition of Eu(fod)$_3$, while H7s and H3 were shifted downfield, indicating that the hydroxyl group was *exo* and the morpholine ring was *endo*. The structure of **2a** was assigned by spectral analogy. Hydroboration of **1** with 9-BBN followed by treatment with methanol gave the corresponding *endo*-2-(dialkylamino)norbornanes **3**, instead of norbornene.[13] The structures of **3a,b** were also established by NMR analysis using the 2D INADEQUATE (^{13}C-^{13}C) and 2D heteronuclear (^{1}H-^{13}C) shift

Table 1. ^{1}H and ^{13}C NMR Data ($CDCl_3$) for *endo*-3-(Dialkylamino)-*exo*-2-norbornanols, **2.**



2a



2b

Compound	2a		2b	
Position	^{1}H (δ ppm)	^{13}C (δ ppm)	^{1}H (δ ppm)	^{13}C (δ ppm)
1	2.07	45.3	2.11	44.8
2	3.32	80.3	3.38	78.5
3	2.34	77.9	2.02	78.6
4	2.29	39.8	2.35	37.8
5 (*endo, exo*)	1.19, 1.60	20.4	1.23, 1.52	20.0
6 (*endo, exo*)	1.15, 1.51	25.9	1.20, 1.48	25.5
7 (*syn, anti*)[a]	1.68, 1.24	34.6	1.68, 1.26	34.2
8	2.62	53.8	2.45	52.7
9	~1.65	28.4	3.71	66.5
10	~1.57	27.3		

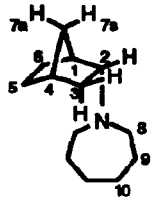
[a]*Syn* = s; *Anti* = a.

correlation spectra to assign the carbon and proton resonances, respectively, and the data are summarized in **Table 2.** The ^{1}H-^{13}C 2D heteronuclear correlation clearly indicated a single chemical shift for the methylene protons 7*syn* and 7*anti* in **3a,b**, a situation consistent only with the single substituent on the norbornane ring in the *endo*-position.[10]

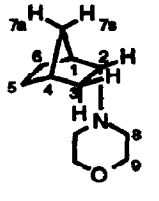
***endo*-3-(1-Hexamethyleneimino)-*exo*-2-norbornanol (2a).** A previously dried and nitrogen flushed 100-mL, single-neck flask equipped with a magnetic stirring bar and a Claisen adapter fitted with a rubber septum and a nitrogen bubbler was charged with 2-(1-hexamethyleneimino)norbornene (**1a**, 6.00 g, 31 mmol) and 21 mL of THF. The resulting solution was cooled with an ice bath for 0.5 h. To the cold solution, 10M BMS (3.10 mL, 31 mmol) was slowly added. The reaction was stirred with cooling for 10 min and then at room temperature for 2 h. The reaction mixture was treated with 5.0 mL of methanol (vigorous foaming and hydrogen evolution) and stirred at room temperature for 1.5 h. The reaction was then treated with solid sodium hydroxide (1.60 g, 40 mmol) and 4.0 mL of 30% hydrogen peroxide was slowly added (exothermic reaction). The reaction was stirred at room temperature over night. The organic layer was decanted away from a sticky, white solid which formed. The solid was washed with diethyl ether (3 x 30 mL). The solvents were removed *in vacuo* from the combined organic layers leaving a clear oil. The oil was dissolved in 50 mL of methanol and the solution

made acidic with concentrated hydrochloric acid. The acidified solution was stirred at room temperature for 0.5 h. The methanol was removed *in vacuo* leaving a white solid. The solid was washed with diethyl ether (3 x 30 mL) and vacuum dried at 40 °C (7.23 g). The solid was dissolved in 25 mL of water and the solution mixed with

Table 2. ^{1}H and ^{13}C NMR Data ($CDCl_3$) for *endo*-2-(dialkylamino)norbornanes, **3**.



3a



3b

Compound	3a		3b	
Position	^{1}H (δ ppm)	^{13}C (δ ppm)	^{1}H (δ ppm)	^{13}C (δ ppm)
1	2.24	39.7	2.27	38.4
2	2.61	65.5	2.34	67.7
3 (*endo*, *exo*)	0.90, 1.74	36.6	0.89, 1.68	35.2
4	2.14	36.8	2.18	36.5
5 (*endo*, *exo*)	1.28, 1.50	30.6	1.31, 1.44	30.3
6 (*endo*, *exo*)	1.27, 1.81	20.8	1.27, 1.75	20.7
7 (*syn*, *anti*)[a]	1.38	37.8	1.34	37.7
8	2.57	53.8	2.38	53.0
9	~1.65	28.0	3.76	66.7
10	~1.59	27.1		

[a]*Syn* = s; *Anti* = a.

25 mL of diethyl ether. The aqueous layer was made basic with 50% sodium hydroxide. The layers were separated, and the aqueous layer was extracted with diethyl ether (4 x 30 mL). The combined ether extracts were dried over anhydrous magnesium sulfate. The magnesium sulfate was separated by filtration and washed with diethyl ether (2 x 25 mL). The ether was removed *in vacuo* from the filtrate leaving 6.31 g (97% yield) of crude **2a**. The crude **2a** was recrystallized from approximately 15 mL of hexane to give 2.33 g (11.1 mmol) of **2a** as a white crystalline solid, mp 70.5- 72.5 °C.[14] ***Analytical.*** Calc'd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.42; H, 10.95; N, 6.56. A 1.61 g (7.7 mmol) second crop of **2a** was obtained, mp 68-71 °C (61% total yield).

endo*-3-(4-Morpholino)-*exo*-2-norbornanol (2b).** Using the above procedure, **1b** (7.59 g, 42.3 mmol) gave 6.34 g (76% yield) of crude **2b**. The crude **2b** was distilled to give a 0.10 g forecut, bp 115-120 °C (0.6 Torr), and 5.60 g (28.4 mmol; 67% yield) of **2b** as a colorless, viscous, liquid, bp 120-123 °C (0.6 Torr). ***Analytical. Calc'd for $C_{11}H_{19}NO_2$: C, 66.96; H, 9.71; N, 7.10. Found: C, 67.08; H, 9.46; N, 7.09.

References and Notes

1. Grayson, M., Ed. *Kirk-Othmer Encyclopedia of Chemical Technology* **1982**, *17*, p. 311-345.

2. (a) Imamoto, T.; Mukaiyama, T. *Chem. Lett.* **1980**, 45. (b) Leyendecker, F.; Laucher, D. *Tetrahedron Lett.* **1983**, *24*, 3513. (c) Corey, E.J.; Naef, R.; Hannon, F.J. *J. Am. Chem. Soc.* **1986**, *108*, 7114. (d) Soai, K.; Ookawa, A.; Kaba, T. *J. Am. Chem. Soc.* **1987**, *109*, 7111. (e) Oguni, N.; Matsumoto, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877. (f) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 6071. (g) Noyori, R.; Kitamura, M. *J. Organometallic Chem.* **1990**, *382*, 19. (h) Tomioka, K. *Synthesis* **1990**, 541. (i) Noyori, R.; Kitamura, M. *Angew. Chem. Intl. Ed. Engl.* **1991**, *30*, 49. (j) Mathre, D.J.; Jones, T.K.; Xavier, L.C.; Blacklock, T.J.; Reamer, R.A.; Mohan, J.J. Jones, E.T.T.; Hoogsteen, K.; Baum, M.W.; Grabowski, E.J.J. *J. Org. Chem.* **1991**, *56*, 751.

3. (a) Borowitz, I.J.; Williams, G.J. *J. Org. Chem.* **1967**, *32*, 4157. (b) Gore, J.; Drouet, J.-P.; Barieux, J.-J. *Tetrahedron Lett.* **1969**, 9. (c) Barieux, J.-J.; Gore, J. *Bull. Soc. Chim. Fr.* **1971**, 1649. (d) Barieux, J.-J.; Gore, J. *Bull Soc. Chim. Fr.* **1971**, 3978. (e) Mueller, R.H.; Thompson, M.E. *Tetrahedron Lett.* **1980**, *21*, 1093. (f) Goralski, C.T.; Singaram, B.; Brown, H.C. *J. Org. Chem.* **1987**, *52*, 4014. (g) Goralski, C.T.; Hasha, D.L.; Nicholson, L.W.; Rudolf, P.R.; Singaram, B. *Abstracts of Papers*, Eighth International Meeting on Boron Chemistry, Knoxville, Tennessee; The University of Tennessee, Knoxvillle, Tenn., **1993**; Abstract Number CB-4. (h) Goralski, C.T.; Hasha, D.L.; Nicholson, L.W.; Rudolf, P.R.; Singaram, B. *Current Topics in the Chemistry of Boron*, in press.

4. Singaram, B.; Goralski, C.T.; Fisher, G.B. *J. Org. Chem.* **1991**, *56*, 5691.

5. Goralski, C.T.; Hasha, D.L.; Nicholson, L.W.; Zakett, D.; Fisher, G.B.; Singaram, B. *Tetrahedron Lett.* **1994**, *35*, in press.

6. Fisher, G.B.; Goralski, C.T.; Nicholson, L.W.; Singaram, B. *Tetrahedron Lett.* **1993**, *34*, 7693.

7. Dobler, C.; Kreuzfeld, H.-J.; Pracejus, H. *J. Organomet. Chem.* **1988**, *344*, 89.

8. (a) Cook, A.G. *J. Am. Chem. Soc.* **1963**, *85*, 648. (b) Cook, A.G.; Meyer, W.C.; Ungrodt, K.E.; Mueller, R.H. *J. Org. Chem.* **1966**, *31*, 14. (c) Cook, A.G.; Schulz, C.R. *J. Org. Chem.* **1967**, *32*, 473. (d) Stephen, J.F.; Marcus, E. *J. Org. Chem.* **1969**, *34*, 2535.

9. Anett, F.A.L. *Can. J. Chem.* **1961**, *39*, 789.

10. Marshall, J.L.; Walton, S.R.; Barfield, M; Marchaud, A.P.; Marchaud, N.W.; Serge, A.L. *Tetrahedron* **1976**, *32*, 537.

11. Brugel, W. *Handbook of NMR Spectral Parameters*, Heyden & Son, Ltd, 1976, pp11-112.

12. Davis, Jr., J.C.; VanAiken, T.V. *J. Am. Chem. Soc.* **1965**, *87*, 3900.

13. (a) Singaram, B.; Goralski, C.T.; Rangaishenvi, M.V.; Brown, H.C. *J. Am. Chem. Soc.* **1989**, *111*, 384. (b) Singaram, B.; Rangaishenvi, M.V.; Brown, H.C.; Goralski, C.T.; Hasha, D.L. *J. Org. Chem.* **1991**, *56*, 1543. (c) Goralski, C.T.; Singaram, B.; Brown, H.C. U.S. Patent 4 895 996, 1990.

14. 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 enantiomers with a k' of 1.39 and an R_S of 0.86. 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.

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