white crystals of **(S)-(−)-α-N-(2-naphthyl)leucine (6)** (4.8 g, 25% yield after two crops) that pinken on exposure to air: mp 173 °C; ^{1}H NMR (acetone-d_6) δ 0.92–1.05 (dd, J = 3 Hz, 6 H), 1.7–1.8 (td, J = 3.8, 1 Hz, 2 H), 1.8–2.1 (m, 1 H), 2.5–3.3 (b, 1 H), 4.2 (t, J = 3.8 Hz, 1 H), (naphthyl assignments) 6.85 (d, J = 3 Hz, 1 H), 7.05–7.12 (dd, J = 9, 3 Hz, 1 H), 7.05–7.35 (dt, J = 7 Hz, 2 H), 7.58–7.68 (m, 3 H); ^{13}C NMR (acetone-d_6) δ 22.5, 23.6, 25.8, 42.5, 55.6, (naphthyl assignments) 104.9, 119.4, 122.7, 126.9, 127.1, 128.3, 128.4, 129.5, 136.2, 146.8; IR (Nujol) 3 (b), 3.3–3.8 (s), 6–6.5 (s), 7.4, 7.8 (m), 8.3 (d, m), 8.5 (w), 8.7 (m), 11.5 (m), 12 (s), 13.4 (s), 14.5 (s); UV/vis (CH_3OH) [λ_{max} (ε)] 345 nm (2.18 × 10^3), 289 (6.34 × 10^3), 280 (7.24 × 10^3), 270 (5.63 × 10^3), 245 (3.52 × 10^4); MS (10 eV), m/e (relative intensity) 257 (M$^+$, 100), 213 (71), 212 (100), 170 (80), 156 (99), 154 (93); $[\alpha]^{20}_D$ −127.5° (c 1.0, THF). Enantiomeric purity was determined to be greater than 98% by HPLC of the ethyl ester of **6** on CSP **3**. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; N, 5.44; H, 7.44. Found: C, 74.34; N, 5.26; H, 7.72.

Because of the similarity of structure for all the compounds reported in the following tabulation, only the ^{1}H NMR and ^{13}C NMR resonances that are not assigned to the naphthyl ring system are reported. Complete characterizations will be published in the Ph.D. thesis of T.C.P. In all cases in which rotations are reported, enantiomeric purities have been found to be greater than 98% by HPLC of the derived ester on CSP **3**.

(RS)-α-N-(2-Naphthyl)alanine (4): mp 170 °C; ^{1}H NMR (acetone-d_6) δ 1.51 (d, J = 7.5 Hz, 3 H), 4.23 (q, J = 7.5 Hz, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 18.0, 50.9, 175.7; MS (10 eV) m/e (relative intensity) 216 (M + 1, 20.5), 215 (M$^+$, 100), 171 (92), 170 (100), 156 (62), 128 (42.8), 127 (48.5). Anal. Calcd for $C_{13}H_{13}NO_2$: C 72.54; H, 6.09; N, 6.61. Found: C, 72.56;; H, 6.14; N, 6.42.

(R)-(+)-α-N-(2-Naphthyl)alanine (4a): mp 153 °C, $[\alpha]^{20}_D$ +187.2° (c 0.4, THF). Anal. Calcd for the ethyl ester of **4a** ($C_{15}H_{17}NO_2$): C, 74.05; H, 7.04; N 5.76. Found: C, 73.66; H, 6.83; N, 5.78.

(S)-(−)-α-N-(2-Naphthyl)serine (5): mp 125 °C dec; ^{1}H NMR acetone-d_6) δ 4.22 (d, J = 4 Hz, 2 H), 4.53 (t, J = 4 Hz, 1 H); MS (70 eV) m/e (relative intensity) 232 (M + 1, 8.4), 231 (M$^+$, 53.9), 200 (39.5), 186 (38.6), 168 (34.5), 154 (100), 143 (55), 127 (90); HRESMS for $C_{13}H_{13}NO_3$, calcd 231.0895885, found 231.0895885; $[\alpha]^{20}_D$ −25.7° (c 1.0, THF); ^{13}C NMR of ethyl ester of **5** ($CDCl_3$): δ 44.4, 47.9, 48.5, 91.8, 104.1, 108.5, 110.0, 112.2, 112.3, 113.5, 113.9, 115.1, 120.6, 129.9, 157.9. Anal. Calcd for the ethyl ester of **5** ($C_{15}H_{17}NO_3$): N, 5.40; C, 69.48; H, 6.61. Found: N, 5.29; C, 69.44; H, 6.65.

(S)-(−)-α-N-(2-Naphthyl)valine (7): mp 125 °C; ^{1}H NMR (acetone-d_6) δ 1.05–1.15 (dd, J = 3 Hz, 6 H), 2.13–2.32 (sept, J = 3 Hz, 1 H), 4.0 (d, J = 3 Hz, 1 H); ^{13}C NMR (acetone-d_6) δ 19.2, 19.5, 31.7, 62.8, 174.9; MS (70 eV) m/e (relative intensity) 244 (M + 1, 7.2), 243 (M$^+$, 43.7), 200 (35.8), 198 (95.9), 154 (100), 143 (34.3), 127 (85); HRESMS for $C_{15}H_{17}NO_2$, calcd 243.12551, found 243.12555 $[\alpha]^{20}_D$ −168.7° (c 1.0, THF) for free acid **7**. Anal. Calcd for the ethyl ester of **7** ($C_{17}H_{21}NO_2$): C, 75.25; H, 7.80; N, 5.16. Found: C, 75.33; H, 8.05; N, 4.90.

(S)-(+)-α-N-(2-Naphthyl)phenylalanine (8): mp 170 °C; ^{1}H NMR (acetone-d_6) δ 3.08–3.38 (dp, J = 8, 3 Hz, 2 H), 4.45 (t, J = 3 Hz, 1 H), 7.15–7.38 (m, 5 H); ^{13}C NMR (acetone-d_6) δ 38.8, 58.2, 126.6, 128.7, 129.2, 129.6, 130.2, 136.3, 174.6; MS (10 eV) m/e (relative intensity) 292 (M + 1, 6.3), 291 (M$^+$, 27.6), 201 (80), 200 (72.0), 154 (100), 127 (62.6)%; $[\alpha]^{20}_D$ +76.7° (c 1.0, THF). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.34; H, 5.90; N, 4.73.

(S)-(−)-α-N-(2-Naphthyl)methionine (9): mp 158 °C; ^{1}H NMR (acetone-d_6) δ 2.08 (s, 3 H), 2.03–2.30 (m, 2 H), 2.68–2.70 (t, J = 7 Hz, 2 H), 4.40 (dd, J = 5, 8 Hz, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 14.9, 30.0, 31.7, 54.5, 175.2; MS (10 eV) m/e (relative intensity) 277 (M + 2, 12.2), 276 (M + 1, 37.4), 275 (M$^+$, 100), 182 (100), 156 (42), 154 (82), 127 (50.4, 61 (100); $[\alpha]^{20}_D$ −31.0° (c 1.0, THF). Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09; S, 11.64. Found: C, 65.50; H, 6.23; N, 5.07; S, 11.59.

(R)-(−)-α-N-(2-Naphthyl)phenylglycine (10): mp 173 °C; ^{1}H NMR (acetone-d_6) 5.33 (s, 1 H), 7.20–7.41 (m, 4 H), 7.52 (d, 1 H), (naphthyl assignments) 6.81 (d, J = 3 Hz, 1 H), 7.13 (t, J = 7 Hz, 1 H), 7.22 (dd, J = 9 3 Hz, 1 H), 7.27 (t, J = 7 Hz, 1 H), 7.62–7.70 (m, 4 H); ^{13}C NMR (acetone-d_6) δ 53.6, 98.4, 112 .0, 115.2, 119.3, 119.5, 120.6, 120.8, 121.2, 122.0, 131.9, 138.0, 165.5; MS (10 eV) m/e (relative intensty) 278 (M + 1, 15.0), 277 (M$^+$, 74.0), 233 (70.8), 232 (100), 154 (13.8), 143 (12.9), 127 (47.4); $[\alpha]^{20}_D$ −238.0° (c 1.0, THF). Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.90; H, 5.50; N, 4.98.

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Stereoselectivity of the Reduction of Naltrexone Oxime with Borane

Mosad S. Mohamed and Philip S. Portoghese*

Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455

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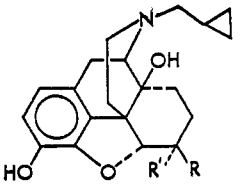
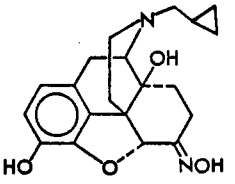
The opiate β-naltrexamine (**1b**)[1,2] is employed as an intermediate in the synthesis of the affinity label β-funaltrexamine (**2**),[3] which is employed widely as a tool in



1a: R = H, R′ = NH_2
1b: R = NH_2, R′ = H
2: R = NHCOHC=CHCOOMe, R′ = H

opioid research.[4] A highly stereoselective synthesis of **1b** has been reported,[2] but its time-consuming nature prompted us to examine a simple alternative approach. In this report, we describe a simple stereoselective method for preparing **1b**. Moreover, this method may have general application in altering the usual stereochemical course of reductive amination in vicinally substituted cyclohexanones.

The route to obtaining **1b** stereoselectively involved the borane reduction of oxime **3**.[5] The choice of borane as



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reducing agent[6] of the oxime group was based on previous studies[2] that suggested that the steric course of reduction at the C-6 center of the opiate is dependent on the conformation of ring C. We had proposed that pseudoallylic strain[7] arising from a disubstituted iminium intermediate (**4a**, **5a**) stabilizes the boat conformation (**5a**), which is more accessible to hydride attack from the α direction. This is in contrast to the unsubstituted iminium intermediate (**4b**, **5b**) that was presumed to be reduced pre-

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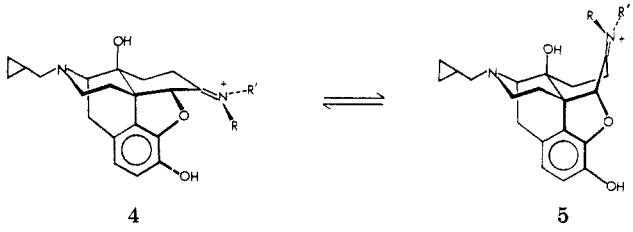
dominantly via β attack on a preferred chair conformation **4b**.



4 5

a: R = R' = $CH_2C_6H_5$
b: R = R' = H
c: R,R' = OB< and B<

In view of these results, we investigated a more direct synthetic procedure using pseudoallylic strain as the stereochemical determinant in the borane reduction of oxime **3** to the 6β isomer **1b**. We expected epimer **1b** to predominate in this reaction because, as a Lewis acid, the boron atom of borane should coordinate with the oxime nitrogen lone pair, thereby forming an intermediate (**5c**) analogous to a disubstituted iminium species (e.g., **5a**). Consistent with this expectation, we found that the epimeric products (**1a**:**1b**) of the reduction were in a ratio of about 1:9.

We conclude from these results that the steric course of reductive amination is determined by the substitution on the imine nitrogen when it is vicinal to a substutuent in a six-membered ring. Moreover, the facility with which an oxime can be prepared from a ketone gives this procedure a decided advantage over the generation of the more difficultly accessible iminium intermediate.

Experimental Section

General Procedure. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. IR spectra were obtained on a Perkin-Elmer 281 infrared spectrometer. NMR spectra were taken at ambient temperature with Me_4Si as internal standard on a Nicolet 300-MHz spectrometer. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. Mass spectra were obtained on an AEI MS-30 instrument. All TLC data were determined with Analtech silica gel chromatographic plates (EtOAc–MeOH–NH_4OH, 5:1:0.2). All reagents were reagent grade and were used without subsequent purification.

Naltrexone Oxime (3). A solution prepared from naltrexone[8] (6.8 g, 20 mmol), 2 g of NH_2OH·HCl (29 mmol), sodium acetate (4 g) dissolved in water (5 mL), and ethanol (100 mL) was refluxed for 3 h. The ethanol was removed in vacuo, rendered sufficiently acidic with HCl to dissolve all solid material, and made alkaline with aqueous sodium carbonate. The precipitate that formed was collected by filtration and washed with water, the mother liquor and washings were extracted with chloroform (3 × 100 mL), and the solvent was removed in vacuo. The combined crops (6.6 g, 93%) were crystallized from aqueous ethanol. Oxime **3**: mp 239–240 °C (lit.[5] mp 235–236 °C).

Borane Reduction of Naltrexone Oxime (3). A borane–tetrahydrofuran (THF) solution (400 mL, 1 M) was cooled to −5 °C and added with stirring to **3** under N_2. The mixture was heated under reflux for 48 h and cooled (25 °C), and the excess borane was destroyed by cautious addition of water (10 mL). The borane complex was hydrolyzed by gradual addition of aqueous KOH (10%, 150 mL) and heating under reflux for 3 h. The resultant mixture was rendered acidic (pH 2–3) with HCl and heated under reflux for an additional 2 h. The THF was removed in vacuo, and the aqueous solution was rendered alkaline (Na_2CO_3). After extraction with chloroform (3 × 200 mL) and drying (Na_2SO_4), the solvent was removed in vacuo to afford the crude product (3 g, 88%). Medium-pressure chromatography (175 g of silica gel 200–245 mesh, 25:5:1 MeCN–MeOH–NH_4OH) gave four fractions. The first (280 mg, 10%) displayed no aromatic proton or C_5-H absorptions in its NMR spectrum. The second fraction appeared to be boron-complexed oxime **3** (570 mg, 20%). The more polar fractions were identified as follows. **1b**: 1.75 g (58%); mp 229–230 °C; R_f 0.23; [α] 25D −156° (*c* 1, MeOH); NMR δ 4.50 (1 H, d, J = 7.5 Hz C_5-H). **1a**: 0.200 g (7%); mp 179–180 °C; R_f 0.18; [α] 25D −184° (*c* 0.5, MeOH); NMR δ 4.72 (1 H, d, J = 3.7 Hz, C_5-H). The identity of **1b** was confirmed by conversion of authentic **1b**·2HCl[1,2] to the free base, mp 231–233 °C, with an identical R_f and NMR spectrum.

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[1,2] Anionic Rearrangements of Substituted *N*-Hydroxy-2-azetidinones and Applications to the Synthesis of Bicyclic β-Lactams

Byung Hyun Lee, Atanu Biswas, and Marvin J. Miller*†

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

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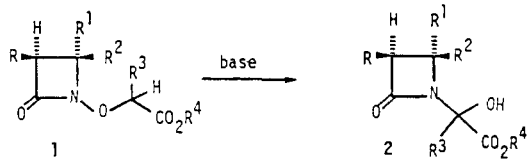
The Wittig ($R_2C^-OR^1\ M^+ \rightarrow R_2R^1CO^-M^+$) and related rearrangements have been thoroughly studied and frequently utilized synthetically.[1] However, only recently have analogous [1,2] anionic $NOC^- \rightarrow NCO^-$ rearrangements been reported.[2,3] Herein we describe a [1,2] anionic rearrangement of substituted *N*-hydroxy-2-azetidinones (eq 1) and demonstrate its utility for the synthesis of novel bicyclic β-lactams.



(1)

The first requirement was the synthesis of appropriate *N*-hydroxy β-lactam precursors. As usual, synthesis of β-lactams by our hydroxamate approach required preparation of the appropriate β-hydroxy acid precursor. Thus, treatment of the dianion of methyl acetoacetate[4] (**3**) with benzyl chloromethyl ether (**4**) gave the β-keto ester **5** in 60% yield (Scheme I). Reduction of **5** to the racemic[5] alcohol **6** with $NaBH_4$ (0 °C, CH_3OH, 30 min) proceeded in 90% yield. Saponification (1 N NaOH, THF/H_2O, room temperature, 1 h), of **6** provided the desired β-hydroxy acid **7** in 92% yield. Coupling of **7** and *O*-benzylhydroxylamine by the usual procedure[6] gave the hydroxamate **8** in 64% yield. Cyclization of **8** with diethyl azodicarboxylate/triphenylphosphine (DEAD/TPP)[6,7] provided the *N*-benzyloxy-substituted β-lactam **9** in 75–85% yields. Selective hydrogenation of **9** with a poisoned catalyst (5% Pd–C, 1 atm of H_2, 1 h, in ethanol containing quinoline) gave the desired *N*-hydroxy β-lactam **10** in 93% yield. Hydrogenation of **9** in the absence of quinoline resulted in formation of **11** by removal of both benzyl protecting groups. The structures of these β-lactams were

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