PREPARATION OF A NEW CHIRAL 5,6-DIHYDROPYRIDINIUM SYNTHON

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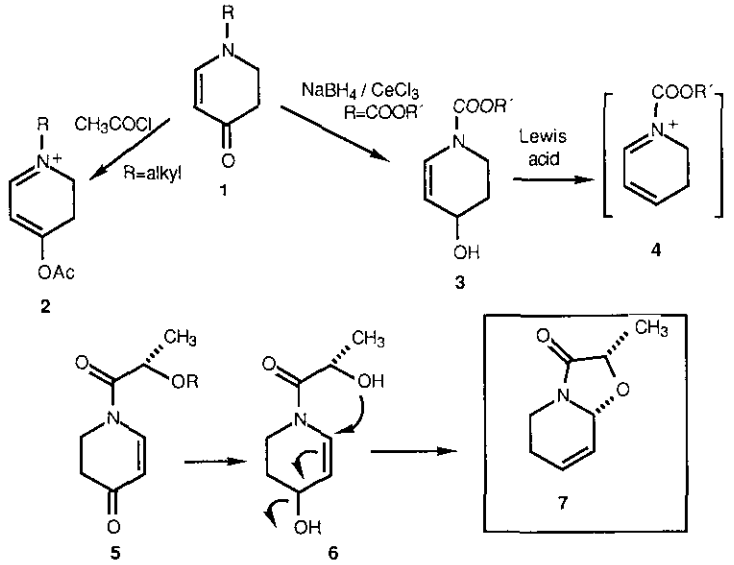
Abstract – A new chiral synthon, oxazolidinonepiperidine **7**, is prepared from intermediate **5**, derived from (S)-(-)-ethyl lactate, by chemoselective reduction of the piperideinone carbonyl group followed by oxazolidinone ring closure.

Two efficient routes have now been established for the preparation of synthetically useful 5,6-dihydropyridinium salts or their equivalent forms from Δ^2-piperidones **1** (Scheme 1). The first one involves O-acetylation of the piperidone carbonyl to give 4-acetoxy-5,6-dihydropyridinium salts **2** (or the corresponding alkylation of Δ^2-thiopiperidones),[1] and the second involves chemoselective reduction of the carbonyl group using sodium borohydride in the presence of cerium salts giving the γ-hydroxy ene carbamates.[2]



Scheme 1

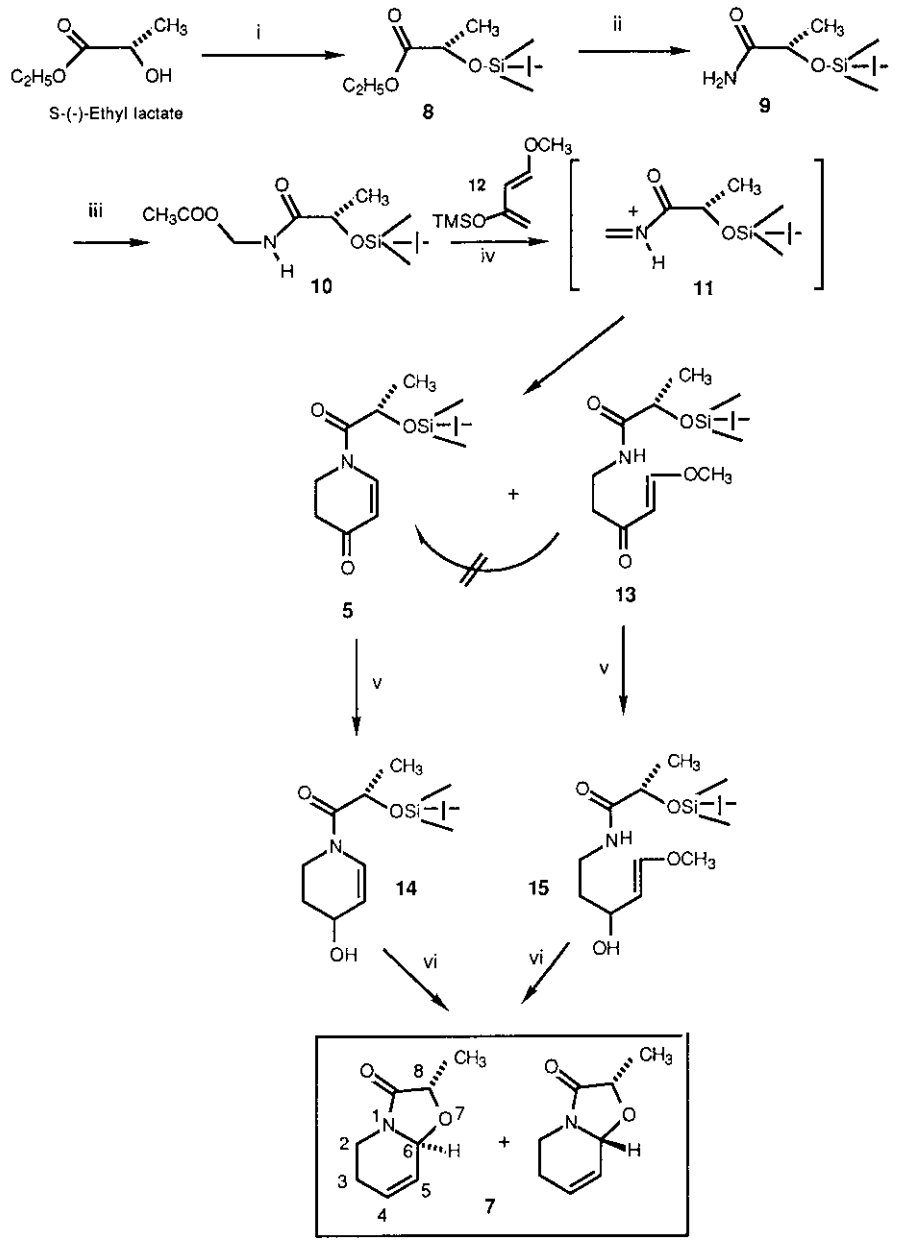
In the former approach it is necessary to both generate the dihydropyridinium species and carry out its reaction with nucleophiles at low temperature, whereas in the latter approach the reactive dihydropyridinium intermediates **4** are generated in situ from the relatively stable piperideines **3** on reaction with a nucleophile in the presence of a Lewis acid.

Although compounds **3** are highly attractive synthons for the synthesis of alkaloids, one important limitation inherent to their use is that the products obtained are racemic. In a study directed towards finding a new chiral synthon of this type we describe in this report the preparation of the $\Delta^{3,4}$-unsaturated oxazolidinonepiperidine **7**. A projected key transformation in this synthesis was the spontaneous intramolecular S_N2' displacement of the γ-hydroxy group in the intermediate **6** by the hydroxyl oxygen of the lactic acid derived carbamate appendage.[3]

The initial objective was the preparation of intermediate **5**. The strategy chosen was to construct the Δ^2-piperidone ring about the nitrogen atom of lactamide via a Diels-Alder reaction between Danishefsky's diene **12**[4] and the acyl imine **11**, generated under thermal conditions from acetoxymethyllactamide **10**.[5] O-tert-Butyldimethylsilyl lactamide **9** was prepared in two steps and 85% overall yield from S-(-)-ethyl lactate (Scheme 2),[6] and converted into intermediate **10** in 78% yield according to the procedure described by Weinreb and coworkers.[7] Unfortunately, and despite numerous attempts in which heat or Lewis acid catalysis under a variety of conditions were screened, the Diels-Alder reaction[8] between **10** and **12** did not proceed cleanly, producing a mixture of products from which the desired Δ^2-piperidone **5** (yield 10%) and the partial condensation product **13** (yield~30%) could be isolated pure. The low product yields obtained in this reaction result from the fact that two column chromatographies were necessary to separate the silica sensitive compounds **5** and **13** from minor impurities. Combined yields of 60% were typically observed after the first chromatographic purification.

Selective reduction of the keto group in the minor component **5** was achieved in nearly quantitative yield on treatment with sodium borohydride in methanol containing cerium chloride (0 ºC, 20 min).[9] Immediate treatment of the crude product **14** with 3M aqueous hydrochloric acid in acetonitrile effected cleavage of the O-silyl protecting group and promoted cyclization to the desired bicyclic system **7**, obtained as a mixture of epimers at C-2 (yield 72% from **5**).

Fortunately, the major compound **13** could also be carried through to compound **7** on sequential reaction with sodium borohydride and cerium chloride in acid conditions. A probable mechanism for this transformation involves initial formation of the piperidine ring by S_N2'displacement of the



Reagents and conditions: i) TBDMSCl, imidazole, DMF, 40 °C, 20 h. (Y=96%); ii) NH_3 gas , CH_3OH, 4 days, r.t., (Y=89%); iii) (1) (HCHO)n, anh. Cs_2CO_3 , r.t., 17 h; (2) 6:1 Ac_2O- Pyr, r.t., 5 h, (Y=78%); iv) Diels-Alder reaction, o-DCB, 180 °C , 20 h (Y=5% of **5** and 28% of **13**) ; v) $NaBH_4$, $CeCl_3.7H_2O$, CH_3OH; vi) HCl 3M, CH_3CN, [Y=72% from **5** and 47% from **13**].

Scheme 2

hydroxyl group in **15** by the nitrogen lone pair followed by O-deprotection and closure of the oxazolidinone ring with loss of a molecule of methanol.

Although it is unnecessary in terms of the acyl iminium ion reactivity of compound **7** to separate the two epimers, this was achieved by column chromatography on silica gel using 6:4 hexane-ethyl acetate as the eluent. Compounds **7a** and **7b**, obtained as colorless oils, were fully characterized spectroscopically and by elemental analysis.

The reactivity of this new synthon vis-à-vis the condensation with nucleophiles is currently being investigated as are means to improve formation of intermediate **5** in the Diels-Alder step.

EXPERIMENTAL

General Methods. ^{1}H And ^{13}C-nmr spectra were recorded in $CDCl_3$ (unless otherwise indicated) on a Bruker WP-200 spectrometer using TMS as an internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS. Ir spectra were taken with an Infracord Perkin-Elmer spectrophotometer and only noteworthy absorptions (reciprocal centimeters) are listed. Mass spectra were determined on an AEI MS-50 mass spectrometer. Optical rotation measurements were obtained with a Perkin-Elmer 241 polarimeter. Tlc was carried out on SiO_2 (silica gel 60, Merck 0.0063-0.200 mm), and the spots were located with uv light or phosphomolibdate reagent. Flash column chromatography was carried out on SiO_2 (silica gel 60, 0.040-0.063 mm, Merck). Drying of organic extracts during the workup of reactions was performed over anhydrous sodium sulfate. Microanalyses were performed on a Carlo-Erba 1106 analyzer .

(S)-Ethyl 2-(tert-butyldimethylsilyloxy)propanoate (**8**). A solution of S-(-)ethyl lactate (10 ml, 0.08 mmol), TBDMSCl (15.9 g, 0.10 mmol) and imidazole (11.9 g, 0.17 mmol) in freshly distilled dry DMF (20 ml) was stirred overnight at 40°C, under argon atmosphere. The reaction mixture was poured on water-ice and extracted with Et_2O. The organic layer was washed with brine, dried and evaporated. The resulting oil was purified by distillation (40°C, 0.2 mmHg) to give pure **8** as a colorless oil (17.91 g, 96%). $[\alpha]_D$= -21.4° (c=1, MeOH); ir (NaCl) 1765 (C=O), 1040 (SiO); ^{1}H-nmr 0.06 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.89 (s, 9H, $SiCCH_3$), 1.26 (t, J= 7 Hz, 3H, CH_3CH_2), 1.38 (d, J= 6.7 Hz, 3H, $CHCH_3$), 4.15 and 4.17 (2 m, 1H each, CH_3CH_2O), 4.29 (q, J= 6.7 Hz, 1H, CH_3CH); ^{13}C-nmr -5.3 (CH_3Si), -4.9 (CH_3Si), 14.1 (CH_3CH_2O), 18.2 ($C(CH_3)_3$), 21.2 ($CHCH_3$), 25.7 ($C(CH_3)_3$), 60.6 (CH_3CH_2O), 68.4 (CH_3CH); ms (m/z, %) 232 (M^+, 3), 217 (2), 175 (39),

159 (20), 147 (100), 119 (39), 103 (39), 75 (57), 73 (59), 68 (81). Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.40. Found: C, 56.58; H, 10.17.

(S)-2-(tert-Butyldimethylsilyloxy)propanamide (**9**). To a stirred solution of **8** (17.91 g, 77.2 mmol) in dry methanol (500 ml) cooled at 0°C dry gaseous ammonia was bubbled for 2 h. The reaction mixture was stirred at room temperature until the reaction was complete (4 days). Methanol was evaporated under vacuum at room temperature to yield **9** as an oil (14.3 g, 89 %): $[\alpha]_D$= -13.2° (c=1, MeOH); ir (NaCl) 3500 (NH_2), 1670 and 1570 (C=O), 1120 (SiO); ^{1}H-nmr 0.03 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si), 0.85 (s, 9H, $SiCCH_3$), 1.33 (d, J=6.7 Hz, 3H, CH_3CH), 4.16 (q, J=6.7 Hz, 1H, CH_3CH), 6.63 (br s, $W_{1/2}$=18 Hz, 1H, NH), 6.78 (br s, $W_{1/2}$=18 Hz, 1H, NH); ^{13}C-nmr -5.3 ($SiCH_3$), -4.7 ($SiCH_3$), 17.9 ($C(CH_3)_3$), 21.7 (CH_3CH), 25.7 ($C(CH_3)_3$), 69.9 (CH_3CH), 178.1 (C=O); ms (m/z, %) 203 (M^+, 0.1), 188 (6), 159 (12), 146 (100), 128 (9), 118 (12), 101 (6), 74 (40). Anal. Calcd for $C_9H_{21}NO_2Si$: C, 53.15; H, 10.40; N, 6.88. Found: C, 53.13; H, 10.12; N, 6.72.

(S)-N-Acetoxymethyl-(2-(tert-butyldimethylsilyloxy)propanamide (**10**) A mixture of powdered paraformaldehyde (2.04 g), anhydrous Cs_2CO_3 (11.09 g, 34 mmol) and amide **9** (13.8 g, 68 mmol) in dry THF (300 ml) was stirred under argon at room temperature for 15 h. The reaction mixture was filtered and the solvent was evaporated under vacuum at room temperature. A solution of dry pyridine (32 ml) in acetic anhydride (188 ml) was added and the mixture was stirred for 5 h under argon. The solvent was removed by evaporation and the residue was purified by flash chromathography (hexane-ethyl acetate, 9:1) to give pure **10** as a colorless oil (14.5 g, 78 %): $[\alpha]_D$=-38.3° (c=1, MeOH); ir (NaCl) 3450 (NH), 1740 (COO), 1700 (CONH), 1120 (SiO); ^{1}H-nmr 0.02 (s, 3H, CH_3Si), 0.03 (s, 3H, CH_3Si), 0.84 (s, 9H, CCH_3), 1.30 (d, J= 6.7 Hz, 3H, CH_3CH), 2.00 (s, 3H, CH_3COO), 4.22 (q, J= 6.7 Hz, 1H, CH_3CH), 5.24 and 5.29 (2d, J_{AB} = 10.8 Hz, 1H each, NCH_2O), 7.70-7.80 (br s, $W_{1/2}$= 16 Hz, 1H, NH); ^{13}C-nmr -5.5 (CH_3Si), -4.9 (CH_3Si), 17.8 ($C(CH_3)_3$), 20.5 (CH_3CO), 21.5 (CH_3CH), 25.5 ($C(CH_3)_3$), 63.5 (OCH_2), 69.8 ($CHCH_3$), 171.1 (COO), 174.7 (CONH); ms (m/z, %) 275 (M^+, 0.05), 260 (1), 218 (61), 216 (21), 200 (17), 158 (100), 146 (34), 129 (90), 115 (25), 103 (34), 73 (74), 59 (19). Anal. Calcd for $C_{12}H_{25}NO_4Si$: C, 52.34; H, 9.15; N, 5.08. Found: C, 52.07; H, 8.99; N, 5.10.

(S)-1-[2-(tert-Butyldimethylsilyloxy)propanoyl]-4-piperideinone (**5**). To a 0.4 M solution of acetate **10** (3.98 g, 14.5 mmol) in dry o-dichlorobenzene (36 ml) under argon atmosphere at room

temperature, Danishefsky's diene **12** (Aldrich, 5 g, 29 mmol) was added . The reaction mixture was refluxed for 8 h and stirred at 125 °C for 15 h. The solvent was removed in vacuo (80°C, 0.2 mmHg) and saturated aqueous $NaHCO_3$ (10 ml) was poured on the residue and extracted with Et_2O. The organic layers were washed with brine, dried and evaporated, to give 4.5 g of a (1:3) mixture of **5** and (S)-2-(tert-butyldimethylsilyloxy)-N-(5-methoxy-3-oxo-4-pentenyl)propanamide (**13**) which was separated by flash chromatography (6:4 hexane-ethyl acetate). Compound **5** (830 mg) was further purified by column chromatography (hexane-ethyl acetate gradient) under atmospheric pressure (400 mg, 10%): $[\alpha]_D$= +21.4° (c=0.04, MeOH); uv λ_{max} (C_2H_5OH) 289 and 204 nm; ir (NaCl) 1660 (C=O), 1620 (NC=O), 1600 (C=C); ^{1}H-nmr 0.08 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.85 (s, 9H, $C(CH_3)_3$), 1.44 (d, J= 7.0 Hz, CH_3CH), 2.47 (t, J= 7.5 Hz, 5-H), 4.03 (t, J= 7.5 Hz, 6-H), 4.62 (q, J=7.0 Hz, CH_3CH), 5.30 (d, J=8.0 Hz, 3-H), 8.14 (d, J= 8.0 Hz, 2-H); ^{13}C-nmr -4.8 and -4.9 ($SiCH_3$), 18.0 ($C(CH_3)_3$), 21.31 (CH_3CH), 25.7 ($C(CH_3)_3$), 36.1 (C-5), 42.0 (C-6), 75.1 (CH_3CH), 108.0 (C-3), 143.5 (C-2), 172.2 (NC=O), 193.3 (C=O); ms (m/z,%) 283 (M^+, 27), 239 (11), 227 (11), 212 (7), 187 (2), 160 (38), 129 (9), 119 (16), 115 (14), 110 (4), 96 (34), 75 (34), 73 (100), 59 (16). Anal. Calcd for $C_{14}H_{25}NO_3Si$: C, 59.32; H, 8.89; N, 4.96. Found: C, 59.19; H, 8.94; N, 4.92. The major product **13** was purified by flash chromatography (hexane-ethyl acetate, 4:6) (1.29 g, 28 %): ir (NaCl) 3425 (NHCO), 1670 (CO), 1620 (NHCO), 1600 (C=C), 1250 (SiO); ^{1}H-nmr 0.02 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.87 (s, 9H, $SiCCH_3$), 1.27 (d, J= 6.8 Hz, 3H, CH_3CH), 2.80 (t, J= 6 Hz, 2H, CH_2CO), 3.42 (dt, J= 19 and 6 Hz, NCH_A), 3.53 (dt, J= 19 and 6 Hz, 1H, NCH_B), 3.65 (s, 3H, OCH_3), 4.10 (q, J= 6.8 Hz, 1H, CH_3CH), 5.52 (d, J= 12.5 Hz, 1H, COCH=), 7.15 (br s, 1H, NHCO), 7.57 (d, J= 12.5 Hz, 1H, CH_3OCH=); ^{13}C-nmr -5.16 ($SiCH_3$), -4.66 ($SiCH_3$), 18.2 ($C(CH_3)_3$), 21.9 (CH_3CH), 25.9 ($C(CH_3)_3$), 34.8 (CH_2CO), 40.5 (NCH_2), 57.7 (OCH_3), 70.3 (CH_3CH), 105.9 (COCH=C), 163.1 (CH_3OCH=C), 174.5 (NCO), 197.2 (CO); ms (m/z, %) 318 (M^+, 0.1), 218 (60), 216 (21), 200 (15), 171 (6), 159 (97), 158 (100), 146 (30), 129 (98), 117 (25), 115 (13), 103 (16). Anal. Calcd for $C_{15}H_{29}NO_4Si$: C, 57.10; H, 9.29; N, 4.44. Found: C, 56.79; H, 9.25; N, 4.71.

8-Methyl-7-oxa-1-azabicyclo[4.3.0]non-4-en-9-one (**7**). Method A. To a stirred solution of piperideinone **5** (2.35 g, 8.29 mmol) and $CeCl_3.7H_2O$ (3.08 g, 8.28 mmol) in methanol (21 ml) sodium borohydride (313 mg, 8.28 mmol) was added at 0°C portionwise. After stirring at 0°C for 20 min (tlc control), water (20 ml) was added, the methanol was evaporated, and the resulting residue was extracted with Et_2O. The organic layers were dried and evaporated to afford alcohol

14 (2.28 g, 96 %) as a colorless oil. Crude **14** was dissolved in a 3M aqueous (1:4) HCl-CH_3CN mixture (44 ml) and stirred at 40 °C for 6 h. After neutralization with saturated aqueous $NaHCO_3$ and extraction with Et_2O, the organic layer was dried and evaporated (r.t., 18 mmHg) to give a 1:2 epimeric mixture of **7** (913 mg, 72 %) which was separated by flash chromatography (hexane-ethyl acetate, 6:4). The minor (6R,8S) epimer (higher Rf, 64% ee) : $[\alpha]_D$= -22.7° (c= 5.2, CH_3OH); ir (NaCl) 1690 (CO), 1650 (C=C); ^{1}H-nmr 1.43 (d, J= 6 Hz, 3H, CH_3CH), 2.03 (dt, J= 18 and 5 Hz, 1H, 3-Hα), 2.20-2.50 (m, 1H, 3-Hβ), 3.06 (ddd, J= 14, 11, and 5 Hz, 1H, 2-Hα), 4.16 (dd, J= 14 and 7 Hz, 1H, 2-Hβ), 4.41 (qd, J= 7 and 2 Hz, 1H, 8-H), 5.60 (br s, $W_{1/2}$= 6 Hz, 1H, 6-Hβ), 5.80 (ddd, J= 10, 2, and 1 Hz, 1H, 5-H), 5.90 (dd, J=10 and 5 Hz, 1H, 4-H); ^{13}C-nmr 16.9 (CH_3), 23.7 (C-3), 36.2 (C-2), 74.6 (C-6), 83.5 (C-8), 126.4 (C-4), 128.8 (C-5), 168.7 (C=O); ms (m/z, %) 153 (M^+, 100), 152 (77), 124 (9), 98 (14), 81 (22), 80 (31).

The major (6S,8S) epimer (lower Rf, 71% ee) : $[\alpha]_D$= +117.8° (c=0.2, MeOH); uv λ_{max} (EtOH) 209 nm; ir (NaCl) 1680 (CO), 1650 (C=C); ^{1}H-nmr 1.36 (d, J= 7 Hz, 3H, CH_3), 2.00-2.10 (m, 1H, 3-Hα), 2.20-2.50 (m, 1H, 3-Hβ), 3.05 (ddd, J= 14, 12, and 5 Hz, 1H, 2-Hα), 4.16 (dd, J=14 and 7 Hz, 1H, 2-Hβ), 4.40 (qd, J= 7 and 1.5 Hz, 1H, 8-H), 5.53 (br s, $W_{1/2}$= 6 Hz, 1H, 6-Hα), 5.80 (ddd, J= 10, 2, and 1 Hz, 1H, 5-H), 5.95 (dd, J=10 and 5 Hz, 1H, 4-H); ^{13}C-nmr 17.2 (CH_3), 24.0 (C-3), 35.8 (C-2), 74.7 (C-6), 82.6 (C-8), 125.9 (C-4), 128.4 (C-5), 170.6 (C=O). High resolution ms, m/z: 153.0790 [M^+] ($C_8H_{11}NO_2$ requires: 153.0789). Anal. Calcd for $C_8H_{11}NO_2$.2/3 H_2O: C, 58.16 ; H, 7.11 ; N, 8.47. Found: C, 58.01; H, 6.90; N, 7.99.

Method B. Operating as above, from **13** (1.14 g, 3.6 mmol), $CeCl_3.7H_2O$ (1.35 g, 3.6 mmol), methanol (23 ml) and $NaBH_4$ (136 mg, 3.6 mmol), a mixture of the diastereomeric alcohols **15** was obtained (1.04 g, 91 %) as a colorless oil: ir (NaCl) 3450-3300 (OH and NH), 1650 (CONH), 1520 (C=C and NHCO), 1250 (NHCO), 1120 (SiO); ms (m/z, %) 317 (M^+, 25), 302 (24), 286 (10), 242 (91), 228 (16), 159 (58), 158 (100), 129 (50), 115 (33), 103 (26), 97 (54), 75 (47), 73 (57). Operating as above, from crude alcohols **15** (1.04 g, 3.2 mmol), 3M HCl (3 ml) and CH_3CN (14 ml), a 1:2 mixture of C-6 epimers of **7** was obtained (152 mg, 47 %) after purification by column chromatography (6:4 hexane-ethyl acetate).

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REFERENCES

1. (a) A. I. Meyers and S. Singh, Tetrahedron Lett., 1967, 5319. (b) A. I. Meyers, D. A. Dickman, and M. Boes, Tetrahedron, 1987, **43**, 5095. (c) F. Tubéry, D. S. Grierson, and H.-P. Husson, Tetrahedron Lett., 1987, **28**, 6457. (d) F. Tubéry, D. S. Grierson, and H.-P. Husson, Tetrahedron Lett., 1987, **28**, 6461.
2. (a) A. P. Kozikowski and P. Park, J. Am. Chem. Soc., 1985, **107**, 1763. (b) D. L. Comins and R. M. A. Foley, Tetrahedron Lett., 1988, **29**, 6711. (c) S. Torii, T. Inokuchi, F. Akahosi, and M. Kubota, Synthesis, 1987, 242. (d) S. Torii, T. Inokuchi, S. Takagishi, F. Akahoshi, and K. Uneyama, Chemistry Lett., 1987, 639.
3. (a) R. M. Magid, Tetrahedron, 1980, **36**, 1901, and references cited therein. (b) C. B. Chapleo, M. A. W. Finch, S. M. Roberts, G. T. Woolley, R. F. Newton, and D. W. Selby, J. Chem. Soc., Perkin Trans I, 1980, 1847.
4. (a) S. Danishefsky, T. Kitahara, C. F. Yan, and J. Morris, J. Am. Chem. Soc., 1979, **101**, 6996. (b) S. Danishefsky and T. Kitahara, J. Am. Chem. Soc., 1974, **96**, 7807. (c) J. F. Kerwin, Jr. and S. Danishefsky, Tetrahedron Lett, 1982, **23**, 3739. (d) M. L. Bremmer and S. M. Weinreb, Tetrahedron Lett., 1983, **24**, 261.
5. (a) W. N. Speckamp and H. Hiemstra, Tetrahedron, 1985, **41**, 4367. (b) H. E. Zaugg, Synthesis, 1984, 85.
6. E. J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., 1972, **94**, 6190.
7. R. A. Gobao, M. L. Bremmer, and S. M. Weinreb, J. Am. Chem. Soc., 1982, **104**, 7065.
8. (a) S. M. Weinreb and J. I. Levin, Heterocycles, 1979, **12**, 949. (b) M. E. Jung, K. Shishido, L. Light, and L. Davis, Tetrahedron Lett., 1981, **22**, 4607. (c) P. Hartmann and J.-P. Obrecht, Syn. Comm., 1988, **18**, 553.
9. (a) J.-L. Luche, J. Am. Chem. Soc., 1978, **100**, 2226; (b) Ref. 2a.

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