Pergamon

Tetrahedron Letters, Vol. 37, No. 29, pp. 5209-5212, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01053-2

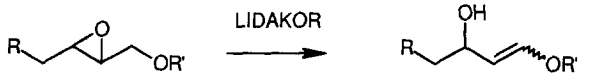
A Stereoselective Approach to The Synthesis of Aminoalcohols

Alessandro Mordini *, Michela Valacchi, Sabina Pecchi, Alessandro Degl'Innocenti, Gianna Reginato

Centro CNR Composti Eterociclici, Dipartimento di Chimica Organica "U. Schiff", via G. Capponi 9, I-50121 Firenze, Italy, e-mail: mordini@chimorg.unifi.it

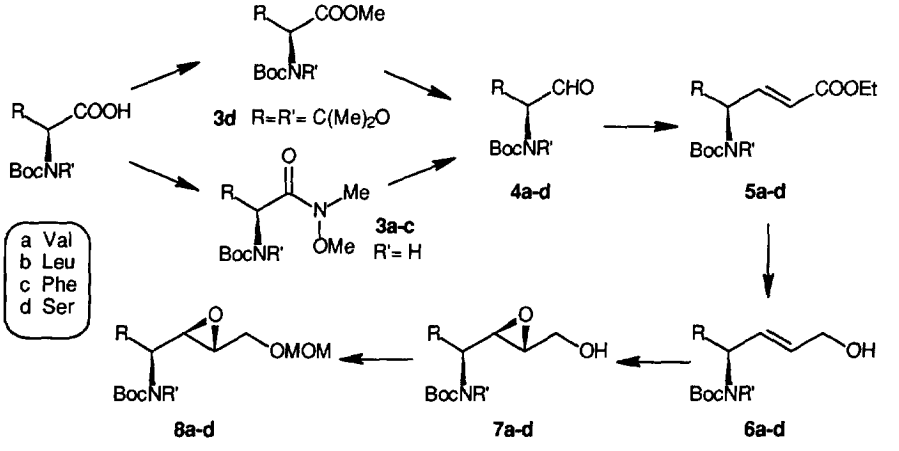
Abstract: *Amino alkoxy oxiranes have been isomerized to stereochemically pure amino alcohols, useful precursors for dipeptides isosteres, by treatment with the superbasic mixture butyllithium/ diisopropylamine/ potassium tert-butoxide.* Copyright © 1996 Elsevier Science Ltd

The stereoselective synthesis of hydroxyethylene dipeptide isosteres[1] is still a very important target, due to the active interest in the enzyme inhibition properties[2] of these substances. Any reaction sequence able to produce amino alcohols in an easy and highly stereoselective manner, is therefore appealing. For this reason we wish to report our recent findings on the base-promoted isomerization of amino alkoxy oxiranes derived from natural aminoacids, leading to aminoalcohols.



1 **2**

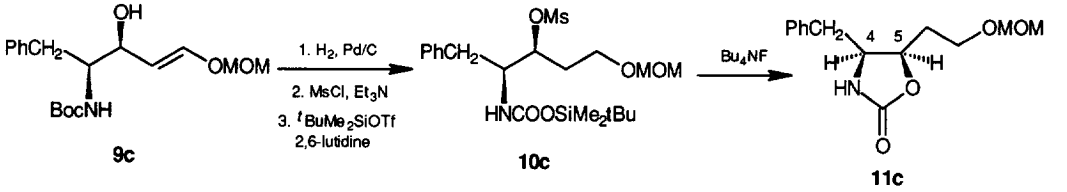
We have recently reported[3] that alkoxy oxiranes **1** can be easily and selectively isomerized to hydroxy enol ethers **2** by simple treatment with the equimolar mixture butyllithium/ diisopropilamine/ potassium *tert*-butoxide (LIDAKOR).[4] Starting from this observation we envisaged to apply the same reaction sequence to substrates **8** derived from natural aminoacids.



Starting materials can be prepared with known procedures[5,6] from aminoacids, via the N-methoxy-N-methyl amide **3**[7,8] followed by reduction with lithium aluminum hydride to the aldehyde **4**. The amino aldehyde **4** can also be prepared via esterification of the corresponding amino acid and reduction with diisobutyl aluminum hydride,[13] as in the case of serine (**4d**). The desired epoxy ethers **8** were obtained by way of Horner-Emmons olefination[9,10] to the α,β-unsaturated ester **5**, reduction with diisobutyl aluminum hydride and boron trifluoride[5] etherate to the allylic alcohol **6**, epoxidation with *meta*-chloroperbenzoic acid[11,12] and protection of the free hydroxyl group. The key step in the sequence outlined above is the epoxidation of the allylic alcohol. Treatment of the *trans*-alkenols **6a-c** with *m*-CPBA, afforded the *syn*-epoxides **7a-c** as the sole products. In the case of substrate **6d** derived from serine, however, the synthesis of *cis*-isomeric alkenol was required in order to achieve good selectivities in the oxidation step.[6]

8a-d **9a-d**

The resulting amino alkoxy oxiranes **8** were then submitted to the isomerization procedure with LIDAKOR in tetrahydrofuran at -50 °C. In all the cases examined, the corresponding amino alcohols were obtained in good yields. The stereochemistry of the newly formed double bond was the one expected on the basis of our previous results[3] in the isomerization of disubstituted oxiranes. *trans*-Epoxyalcohols **8a-c**, after treatment with LIDAKOR, were converted into a mixture of *Z* and *E*-hydroxy enethers **9a-c** (**9a**, 25:75; **9b**, 20:80; **9c**, 18:82) whereas the *Z*-oxirane **8d** gave exclusively the *E*-alkenol.



9c **10c** **11c**

The relative stereochemistry of the hydroxy and amino groups in compounds **9a-d** is always *syn* and it is obviously related to the configuration of the starting amino oxiranes **8a-d**. This has been proven by measuring[14] the coupling constants between hydrogens on carbon 4 and 5 of the cyclic carbamate derivative **11c** ($J_{4,5}$= 7.2 Hz)[15], obtained by reduction of the double bond in **9c** with hydrogen and Pd/C, mesylation of the free hydroxyl group and fluoride ion induced ring closure of the N-silyloxycarbonylated amino diol **10c**.[16] In conclusion, the LIDAKOR induced isomerization of oxiranyl ethers **8a-d** provided a highly stereoselective route to amino hydroxy enethers **9a-d**, valuable precursors for the synthesis of dipeptide isosteres.

EXPERIMENTAL PART

1. Typical procedure

Compound **6a** was obtained by reduction of the corresponding α,β-unsaturated ester. The ester **5a**[5] (16.5 mmol) was dissolved in dry CH_2Cl_2 (65 mL) and cooled to -78 °C. $BF_3{\cdot}Et_2O$ (2.0 eq) was added and after 30 min DIBAH (1.5 M solution in toluene, 3.0 eq) was slowly transferred to the solution. After 45 min the reaction was quenched with CH_3COOH (5.0 M solution in CH_2Cl_2, 30 mL), washed with 10% citric acid (100 mL), sat. $NaHCO_3$ (100 mL), brine (100 mL), and dried (Na_2SO_4). The resulting allylic alcohol **6a** was used in the next step without any further purification. It was dissolved in CH_2Cl_2 (20 mL) and

cooled to 0 °C; *m*-CPBA (2.0 eq) also dissolved in CH_2Cl_2 (60 mL) was slowly added. The reaction mixture was then warmed up to room temperature, allowed to react overnight and then quenched with 10% $Na_2S_2O_3$ (40 mL), washed with sat. $NaHCO_3$ (2x50 mL), brine (2x50 mL) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave the crude epoxide **7a** as a light yellow oil (92 %) which was purified by flash column chromatography (petroleum ether/ethyl acetate 1:2). Oxirane **7a** (1.7 mmol) was dissolved in dry CH_2Cl_2 (5.0 mL) under N_2 and the solution was cooled to 0 °C. Diisopropylethylamine (2.0 eq) and methoxymethyl chloride (1.5 eq) were added. The reaction mixture was warmed up to room temperature and allowed to react overnight. The mixture was then washed with 10% HCl (2x10 mL), sat $NaHCO_3$ (2x10 mL), brine (2x10 mL) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification by flash column chromatography (petroleum ether/ethyl acetate 3:2) afforded pure **8a** (77%).

Isomerization of the oxirane. The same techniques or principles were applied as previously described.[3b] Hexane was stripped off from a solution of BuLi (3.0 eq) and precooled THF (1.5 mL) was added at -78 °C under N_2, followed by diisopropylamine (3.0 eq) and potassium *tert*-butoxide (3.0 eq). The mixture was stirred at -78 °C for 45 min. Compound **8a** (0.6 mmol, dissolved in 0.5 mL of dry THF) was added and allowed to react for 18 h at -50°C. The reaction mixture was then warmed up to room temperature, quenched with H_2O (2 mL) and extracted with Et_2O (2x5 mL). The organic layers were combined, washed with brine (10 mL) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave 166 mg of the desired product as an orange oil, which upon purification by flash column chromatography (petroleum ether/ethyl acetate 1:1), yielded pure **9a** (60%).

2. Products[17]

7a: (25%). ^{1}H-NMR ($CDCl_3$, 200 MHz): 4.6 (1H, bd, *J*= 9.2); 3.92 (1H, dd, *J*= 12.4, 1.8); 3.72 (1H, m); 3.62 (1H, dd, *J*= 12.4, 4.4); 3.09 (1H, m); 2.94 (1H, m); 2.23 (1H, bs); 1.89 (1H, m); 1.42 (9H, s); 0.99 (3H, d, *J*= 4.4); 0.96 (3H, d, *J*= 4.4). ^{13} C-NMR ($CDCl_3$, 50.3 MHz) 155.9; 79.4; 61.1; 55.4; 55.0; 53.4; 32.8; 28.5; 19.1; 18.4. MS *m/z* (%): 202 (50, M^+-C_3H_7); 146 (20); 102 (65); 57 (100, $C_4H_9^+$). $[\alpha]_D^{21}$= +13.08° (c= 1; $CHCl_3$). **8a**: (77%). ^{1}H-NMR ($CDCl_3$, 200 MHz): 4.62 (2H, s); 3.78 (1H, dd, *J*= 11.8, 2.6); 3.75 (1H, m); 3.52 (1H, dd, *J*= 11.9, 5.0); 3.35 (3H, s); 2.97 (2H, m); 1.95 (1H, m); 1.41 (9H, s); 0.99 (3H, d, *J*= 4.8); 0.96 (3H, d, *J*= 4.8).^{13} C-NMR ($CDCl_3$, 75.45 MHz): 155.7; 96.3; 79.1; 66.87; 57.6; 55.4; 55.1; 53.0; 32.1; 28.1; 18.9; 18.2. MS *m/z* (%): 246 (10, M^+-43); 202 (38); 190 (30); 146 (28); 72 (90); 57 (100, $C_4H_9^+$). **9a**: (60%). ^{1}H-NMR ($CDCl_3$, 200 MHz): 6.47 (1H, d, *J*= 12.4); 5.13 (1H, dd, *J*= 12.4, 8.4); 4.79 (2H, s); 4.13 (1H, dd, *J*= 8.2, 4.4); 3.37 (3H, s); 2.25 (1H, m); 1.88 (1H, m); 1.42 (9H, s); 0.95 (3H, d, *J*= 6.6); 0.88 (3H, d, *J*= 6.6). ^{13} C-NMR ($CDCl_3$, 50.3 MHz): 156.7; 146.5; 108.6; 95.6; 79.1; 70.0; 60.8; 55.8; 29.6; 28.3; 20.0. MS *m/z* (%): 198 (4); 154 (8); 116 (70); 72 (100); 57 (86, $C_4H_9^+$). **7b**: (28%). ^{1}H-NMR ($CDCl_3$, 200 MHz): 4.45 (1H, bd, *J*= 9.1); 3.98 (1H, m); 3.92 (1H, dd, *J*= 12.4, 1.4); 3.63 (1H, dd, *J*= 12.4, 3.3); 3.01 (2H, bs); 2.12 (1H, m); 1.68 (1H, m); 1.3-1.5 (2H, m); 1.41 (9H, s); 0.97 (3H, s); 0.93 (3H, s). MS *m/z* (%): 259 (5, M^+); 202 (3, M^+-C_4H_7); 146 (10); 102 (22); 86 (50); 57 (95, $C_4H_9^+$). $[\alpha]_D^{21}$= -2.83° (c= 1.05, $CHCl_3$). **8b**: (25%). ^{1}H-NMR ($CDCl_3$, 200 MHz): 4.63 (2H, s); 4.38 (1H, bd, *J*= 5.3); 4.11 (1H, m); 3.81 (1H, dd, *J*= 11.8, 2.6); 3.52 (1H, dd, *J*= 11.8, 5.6); 3.38 (3H, s); 3.05 (1H, m); 2.94 (1H, m); 1.85 (1H, m); 1.3-1.5 (2H,m); 1.42 (9H, s); 0.98 (3H, s); 0.93 (3H, s).^{13} C-NMR ($CDCl_3$, 50.3 MHz): 155.5; 96.5; 79.4; 67.0; 57.5; 55.3; 54.1; 46.7; 42.4; 28.3; 24.6; 22.9; 22.1. MS *m/z* (%): 246 (10, M^+-C_4H_9); 190 (16); 146 (15); 130 (32); 57 (100, $C_4H_9^+$). $[\alpha]_D^{21}$= +0.17° (c= 1.32, $CHCl_3$). **9b**: (40%) ^{1}H-NMR ($CDCl_3$, 200 MHz): 6.47 (1H, d, *J*= 12.6); 5.12 (1H, dd, *J*= 12.6, 8.6); 4.82 (2H, s); 3.95 (1H, m); 3.63 (1H, m); 3.38 (3H, s); 1.89 (1H, m); 1.44 (9H, s); 1.25 (2H, m); 0.93 (3H, m); 0.91 (3H, m). MS *m/z* (%): 303 (1, M^+); 247 (2); 191 (7); 147 (6); 57 (100, $C_4H_9^+$). **7c**: (82%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.28 (5H, m); 4.62 (1H, bd, *J*= 9.6); 4.10 (1H, bs); 3.85 (1H, dd, *J*= 12.6, 2.6); 3.55 (1H, dd, *J*= 12.6, 4.0); 3.05 (1H, m); 2.97 (1H, m); 2.87 (2H, AB); 1.79 (1H, m); 1.41 (9H, s). ^{13} C-NMR ($CDCl_3$, 75.45 MHz): 155.3; 137.1; 129.4; 128.6; 126.6; 79.6; 61.0; 56.2, 56.1; 50.5; 39.7; 28.2. MS *m/z* (%): 202 (31, M^+-C_7H_7); 176 (10); 146 (64); 102 (86); 91 (89); 57 (100 $C_4H_9^+$). $[\alpha]_D^{21}$= +3.72° (c= 1.1, $CHCl_3$). **8c**: (16%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.27 (5H, m); 4.61 (2H, AB); 4.55 (1H, m); 4.12 (1H, m); 3.74 (1H, dd, *J*= 11.8, 3.0); 3.46 (1H, dd, *J*= 11.8, 6.0); 3.17 (3H, s); 3.02 (1H, m); 2.97 (1H, m); 2.86 (2H, dd, *J*= 11.4, 8.4), 1.38 (9H, s). ^{13} C -NMR ($CDCl_3$, 75.45 MHz): 155.2; 137.1; 129.4; 129.1; 126.6; 96.3, 79.4; 66.8; 56.0; 55.1, 54.4; 50.3; 39.6; 28.1. MS *m/z* (%): 246 (27, M^+-C_7H_7); 190 (48); 176 (16); 158 (10); 146 (76); 91 (97); 57 (100, $C_4H_9^+$). $[\alpha]_D^{21}$= +4.1° (c= 1.06, $CHCl_3$). **9c**: (28%) ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.26 (5H, m); 6.43 (1H, d, *J*= 12.4); 5.17 (1H, dd, *J*= 12.4, 8.4); 4.79 (2H, s); 4.76 (1H, m); 4.02 (1H, dd, *J*= 8.4, 2.8); 3.38 (3H, s); 2.90 (2H, AB); 1.38 (9H, s). ^{13} C-NMR ($CDCl_3$, 200 MHz): 156.0; 147.8; 138.3; 129.4; 128.4; 126.6; 107.8; 95.7; 79.4; 70.3; 56.7; 55.9; 37.9; 28.3. MS *m/z* (%): 220 (8); 164 (37); 120 (72); 91 (60); 57 (100, $C_4H_9^+$). **11c**: ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.2-7.4

(6H, m); 4.87 (1H, m); 4.65 (2H, s); 4.00 (1H, ddd, *J*= 11.0, 7.2, 3.4); 3.75 (2H, m); 3.38 (3H, s); 2.92 (1H, dd, *J*= 13.2, 3.4); 2.65 (1H, dd, *J*= 13.2, 11.0); 2.05 (2H, m). **7d**: (86%). ^{1}H-NMR ($CDCl_3$, 200 MHz): 4.02 (2H, m,); 3.85 (3H, m); 3.11 (2H, m); 1.61 (3H, s); 1.48 (12H, s). ^{13} C-NMR ($CDCl_3$, 50.3 MHz): 151.6; 94.1; 80.6; 66.0; 59.8; 59.5; 56.4; 55.5; 28.3; 27.3; 24.5. MS *m/z* (%): 258 (15, M^+-CH_3); 202 (11); 186 (5); 158 (80); 57 (100, $C_4H_9^+$). $[\alpha]_D^{17}$= +7.4° (c= 0.9 $CHCl_3$). **8d**: (60%) ^{1}H-NMR ($CDCl_3$, 500 Mhz, 323 K): 4.64 (2H, q AB, *J*=6.5); 4.02 (1H, dd, *J*= 9.2, 2.6); 3.88 (2H, m); 3.56 (1H, dd, *J*= 9.2,4.6); 3.65 (1H, m); 3.39 (3H, s); 3.14 (2H, m); 1.64 (9H, s); 1.52 (9H, s); 1.49 (3H, s). ^{13}C-NMR ($CDCl_3$, 50.3 Mhz): 151.7; 96.9; 94.3; 80.7; 65.8; 58.9; 56.9; 55.6; 53.6; 52.6; 29.8; 28.1. MS *m/z* (%): 302 (8, M^+-CH_3); 202 (60); 57 (100, $C_4H_9^+$).$[\alpha]_D^{25}$= +21.3° (c= 0.8, $CHCl_3$). **9d**: (43%). ^{1}H-NMR ($CDCl_3$, 500 MHz): 6.41 (1H, d, *J*= 12.4); 5.00 (1H, app t, *J*= 12.2); 4.76 (2H, s); 4.21 (1H, m); 3.96(1H, m); 3.91 (2H,m); 3.30 (3H, s); 1.56 (3H, s); 1.54 (3H, s); 1.41 (9H, s). ^{13}C-NMR ($CDCl_3$, 75.45 MHz): 156.5; 147.5; 107.7; 95.0; 81.5; 73.4; 64.8; 56.0; 55.8; 28.4; 27.2. MS *m/z* (%): 317 (1, M^+); 240 (5); 164 (32); 140 (60); 57 (100, $C_4H_9^+$). $[\alpha]_D^{21}$= -44.3° (c= 0.65, $CHCl_3$).

Acknowledgement: Financial support by the Consiglio Nazionale delle Ricerche, Roma, is much appreciated.

REFERENCES AND NOTES

1. Green, B. E.; Chen, X.; Norbeck, D. W.; Kempf, D. J. *Synlett* **1995**, 613; Ng, J. S.; Przybyla, C. A.; Liu, C.; Yen, J. C.; Muellner, F. W.; Weyker, C. L. *Tetrahedron* **1995**, *51*, 6397; Beaulieu, P. L.; Wernic, D.; Duceppe, J. S.; Guindon, Y. *Tetrahedron Lett.* **1995**, *36*, 3317.
2. Greenlee, W. *J. Med. Res. Rev.* **1990**, *10*, 173; Rich, D. H. "Peptidase Inhibitors" in *Comprehensive Medicinal Chemistry*, Sammes P. G. Ed.; Pergamon Press: Oxford, 1990, Vol. 2, pp. 391-441.
3. a) Degl'Innocenti, A.; Mordini, A.; Pecchi, S.; Pinzani, D.; Reginato, G.; Ricci, A. *Synlett* **1992**, 803; b) Mordini, A.; Pecchi, S.; Capozzi, G.; Capperucci, A.; Degl'Innocenti, A.; Reginato, G.; Ricci, A. *J. Org. Chem.* **1994**, *59*, 4784.
4. Reviews: Mordini, A. in *Advances in Carbanion Chemistry*, Snieckus, V. Ed.; JAI Press: Greenwich CT, 1992; Vol. 1, p. 1; Schlosser, M. in *Modern Synthetic Methods*, Scheffold, R. Ed.; Verlag Helvetica Chimica Acta: Basel, 1992, Vol. 6, p. 227; Mordini, A. in *Comprehensive Organometallic Chemistry II*, Abel, E. W.; Stone, F. G. A.; Wilkinson G. Eds.; Pergamon Press: Oxford, 1995, Vol. 11, p. 93.
5. Moriwake, T.; Hamano, S.; Miki, D.; Saito, S.; Torii, S. *Chem. Lett.* **1986**, 815.
6. Sakai, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1992**, *114*, 998.
7. Feherentz, *J.* A.; Castro, B. *Synthesis* **1987**, 676.
8. Saari, W. S.; Fisher, T. E. *Synthesis* **1990**, 453.
9. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
10. Reetz, M. T.; Lauterbach, E. H. *Tetrahedron Lett.* **1991**, *32*, 4477.
11. Asensio, G.; Mello, R.; Boix-Bernardini, C.; González-Núñez, M. E.; Castellano, G. *J. Org. Chem.* **1995**, *60*, 3692.
12. Kocovsky, P.; Stary, I. *J. Org. Chem.* **1990**, *55*, 3236.
13. McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31.
14. The *J* values were obtained by selective ^{1}H-NMR homonuclear decoupling experiments.
15. The *J* values are consistent with a *syn* relationship between the two hydrogens in position 4 and 5 on the oxazolidinone **11c**; for a similar example see Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.*, **1990**, *55*, 1493.
16. Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150.
17. The identity and purity of all new products has been confirmed by spectral data and elemental analyses.

(*Received in UK* 24 *April* 1996; *revised* 28 *May* 1996; *accepted* 31 *May* 1996)