Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of (R)- and (S)-Oxymethylmorpholine Derivatives

Chi-Wan Lee [a] & Seok Jong Lee [a]
[a] Department of Chemistry, Center for Superfunctional Materials , Pohang University of Science and Technology , San 31, Hyoja-dong, Namgu, Pohang, 790--784, Korea
Published online: 04 Dec 2007.

To cite this article: Chi-Wan Lee & Seok Jong Lee (2000) Synthesis of (R)- and (S)-Oxymethylmorpholine Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 30:3, 559-563, DOI: 10.1080/00397910008087353

To link to this article: http://dx.doi.org/10.1080/00397910008087353

SYNTHETIC COMMUNICATIONS, 30(3), 559–563 (2000)

SYNTHESIS OF (R)- AND (S)-OXYMETHYLMORPHOLINE DERIVATIVES

Chi-Wan Lee* and Seok Jong Lee

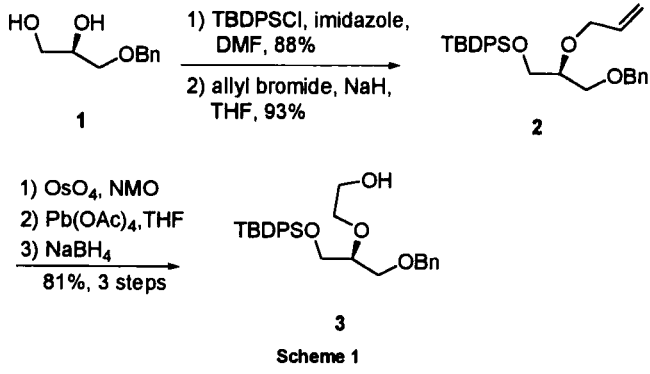
Department of Chemistry, Center for Superfunctional Materials, Pohang University of Science and Technology, San 31, Hyoja-dong, Namgu, Pohang 790-784, KOREA

ABSTRACT: (S)-*N*-benzyl-3-*tert*-butyldiphenylsilyloxymethylmorpholine and (R)-*N*-benzyl-3-benzyloxymethylmorpholine are synthesized starting from (R)-1-benzylglycerol.

Many morpholine derivatives are important compounds for medicinal agents.[1] Very few examples are known of optically pure derivatives.[2] As optically pure enantiomers, (R)- and (S)-oxymethylmorpholine derivatives have been prepared by optical resolution of racemate.[3] Herein we describe a synthetic route to both (R)- and (S)-oxymethylmorpholine derivatives using commercially available (R)-1-benzylglycerol **1** as the starting material.

The primary hydroxyl group in diol **1** was selectively protected from the

secondary hydroxyl group with TBDPSCl and imidazole in DMF in 88% yield. Treatment of the corresponding secondary alcohol with allyl bromide in the presence of NaH in THF produced the fully protected glycerol **2** in 93% yield. Conversion of the allyl group in **2** to hydroxyethyl group was carried out in two stages: (i) dihydroxylation with OsO_4-NMO and (ii) diol cleavage with $Pb(OAc)_4$ followed by *in situ* reduction with $NaBH_4$, producing alcohol **3** in overall 81% yield (**Scheme 1**).



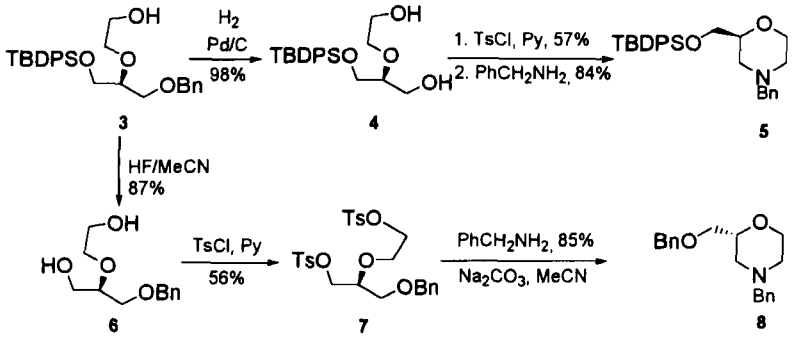
1 **2** **3**

Scheme 1

In **Scheme 2**, debenzylation of the benzyloxy group in **3** and tosylation of the corresponding diol **4** gave ditosylate in 56% for two steps. Finally the cyclization of ditosylate and benzylamine with Na_2CO_3 in refluxing acetonitrile afforded homochiral protected (S)-*N*-benzyl-3-tert-butyldiphenylsilyloxymethyl-morpholine **5** in 84% yield.

The synthesis of (R)-oxymethylmorpholine derivatives is described as follows. Deprotection of the TBDPS group in key intermediate **3** and subsequent tosylation gave ditosylate **7** in overall 49% yield for two steps. Cyclization of

ditosylate and benzylamine with Na_2CO_3 in refluxing acetonitrile afforded (R)-*N*-benzyl-3-benzyloxymethylmorpholine **8** in 85% yield.



Scheme 2

In summary, the presently described synthetic routes allow preparation of optically pure (R)- and (S)-oxymethylmorpholine derivatives. Moreover, depending on the selective deprotection of their different protective groups, these (R)- and (S)-oxymethylmorpholine derivatives can serve as a versatile compound for organic synthesis.

References

1. (a) Wagle, D. R.; Monteleone, M. G.; Krishnan, L.; Manhas, M. S.; Bose, A. K. *J. Chem. Soc., Chem. Commun.* **1993**, 915. (b) Gandour R. D.; Blackwell, N. L.; Colucci, W. J.; Chung, C.; Bieber, L. L.; Ramsay, R. R.; Brass, E. P.; Fronczek, F. R. *J. Org. Chem.* **1992**, *57*, 3426-3431.
2. Bennis, K.; Calinaud, P.; Gelas, J. Ghobsi, M. *Carbohydr. Res.* **1994**, *264*, 33-44 and references cited therein.

3. (a) Howe, R.; Leigh, T.; Rao, B. S.; Tood, A. H. *J. Med. Chem.* **1976**, *19*, 1074-1076. (b) Jinbo, Y.; Kondo, H.; Taguchi, M.; Inoue, Y.; Sakamoto, F.; Tsukamoto, G. *J. Med. Chem.* **1994**, *37*, 2791-2796.

4. **Procedure for the synthesis of (R)- and (S)-oxymethylmorpholine derivatives:** A suspension of ditosylate (1 mmol), benzylamine (1 mmol) and anhydrous Na_2CO_3 (3 mmol) in MeCN (12 mL) was refluxed for 40 h with vigorous stirring. The reaction mixture, cooled at room temperature, was filtered, and the filtered solution was dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (4:1, hexanes-ethyl acetate) afforded the desired product.

5. **Spectral data for compound (2)**: $[\alpha]^{23}_D$ –7.65 (*c* 10.09, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9H), 3.43-3.75 (m, 5H), 4.08 (s, 1H), 4.09 (s, 1H), 4.54 (s, 2H), 5.11-5.27 (m, 2H), 5.84-5.88 (m, 1H), 7.26-7.42 (m, 11H), 7.65-7.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.1, 26.7, 63.4, 70.1, 71.2, 73.3, 78.6, 116.5, 127.4, 127.5, 127.6, 128.2, 129.6, 133.3, 133.4, 135.1, 135.5, 138.3; FAB-MS m/z 461.2 ([M + H]$^+$, calcd 461.2); **for compound (3):** $[\alpha]^{23}_D$ –10.94 (*c* 10.05: $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H), 3.60-3.74 (m, 9H), 4.55 (s, 2H), 7.33-7.45 (m, 11H), 7.66-7.70 (m, 4H); ^{13}CNMR ($CDCl_3$) δ 19.1, 26.7, 62.0, 63.7, 70.3, 71.9, 73.4, 80.0, 127.6, 127.7, 128.3, 129.7, 133.1, 133.2, 135.5, 137.7; FAB-MS m/z 465.1 ([M + H]$^+$, calcd 465.2); **for compound (4):** $[\alpha]^{23}_D$ –17.6 (*c* 2.10 : $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 9H), 3.57-3.81 (m, 11H), 7.39-7.46 (m, 6H), 7.69-7.72 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.1, 26.7, 61.9, 62.7, 63.5, 71.6, 81.2, 127.7, 129.7, 133.05, 133.13, 135.5; FAB-MS m/z 375.12 ([M + H]$^+$, calcd 375.20); **for (S)-*N*-benzyl-3-tert-**

butyldiphenylsilyloxymethylmorpholine (5): $[\alpha]^{23}_{D}$ +2.2 (*c* 5.2 : $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.14 (s, 9H), 1.99-2.06 (m, 1H), 2.19-2.28 (m, 1H), 2.70-2.74 (m, 1H), 2.99-3.03 (m, 1H),3.60 (s, 2H), 3.68-3.93 (m, 5H), 7.40-7.49 (m, 11H), 7.73-7.77 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.8, 53.1, 55.9, 63.4, 65.2, 66.6, 76.0, 127.0, 127.6, 128.2, 129.1, 129.6, 133.4, 135.49, 135.53, 137.6; FAB-MS m/z 446.25 ($[M + H]^+$, calcd 446.01); **for compound (6):** $[\alpha]^{23}_{D}$ +6.23 (*c* 1.61 : $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.52-3.79 (m, 11H), 4.54 (s, 2H), 7.25-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 61.8, 62.5, 70.0, 71.6, 73.4, 79.6, 127.6, 127.8, 128.3, 137.7; **for compound (7):** $[\alpha]^{23}_{D}$ +3.45 (*c* 5.56 : $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.40 (s, 6H), 3.40-3.42 (m, 2H), 3.65-3.70 (m, 3H), 3.96-4.12 (m, 4H), 4.41 (s, 2H), 7.21-7.33 (m, 9H), 7.73-7.76 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 22.0, 68.5, 69.1, 69.7, 69.9, 73.8, 78.0, 128.0, 128.2, 128.3, 130.3, 130.4, 133.0, 133.3, 1385.1, 145.3, 145.5; **for (R)-*N*-benzyl-3-benzyloxymethylmorpholine (8):** $[\alpha]^{23}_{D}$ −11.5 (*c* 2.5 : $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.99-2.06 (m, 1H), 2.19-2.28 (m, 1H), 2.68-2.82 (m, 2H), 3.43-3.56 (m, 4H), 3.70-3.95 (m, 3H), 4.54-4.64 (m, 2H), 7.28-7.40 (m, 10H), ; ^{13}C NMR ($CDCl_3$) δ 52.9, 55.3, 63.2, 66.7, 71.4, 73.3, 74.8, 127.1, 127.5, 127.6, 128.2, 128.3, 129.1, 137.6, 138.0; FAB-MS m/z 298.12 ($[M + H]^+$, calcd 298.18).

(Received in Japan 19 April 1999)