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

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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 TBDPSCI and imidazole in DMF in 88% yield. Treatment of the corresponding secondary alcohol with ally! 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 NaBH₄, producing alcohol 3 in overall 81% yield (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 Na₂CO₃ 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.



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.

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- 4. Procedure for the synthesis of (R)- and (S)-oxymethylmorpholine derivatives: A suspension of ditosylate (1 mmol), benzylamine (1 mmol) and anhydrous Na₂CO₃ (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 MgSO₄ 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, CHCl₃); ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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: CHCl₃); ¹H NMR (CDCl₃) 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); ¹³CNMR (CDCl₃) 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 : CHCl₃); ¹H NMR (CDCl₃) δ 1.09 (s, 9H), 3.57-3.81 (m, 11H), 7.39-7.46 (m, 6H), 7.69-7.72 (m, 4H); ¹³C NMR (CDCl₃) 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*-benzyI-3-tert-

butyldiphenylsilyloxymethylmorpholine (5): $[\alpha]_{D}^{23}$ +2.2 (c 5.2 : CHCl₃); ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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): $[\alpha]_{D}^{23}$ +6.23 (c 1.61 : CHCl₃); ¹H NMR (CDCl₃) δ 3.52-3.79 (m, 11H), 4.54 (s, 2H), 7.25-7.36 (m, 5H); ¹³C NMR (CDCl₃) δ 61.8, 62.5, 70.0, 71.6, 73.4, 79.6, 127.6, 127.8, 128.3, 137.7; for compound (7): $[\alpha]_{D}^{23} + 3.45$ (c 5.56 : CHCl₂); ¹H NMR (CDCl₂) 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); ¹³C NMR (CDCl₃) 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)-Nbenzyl-3-benzyloxymethylmorpholine (8): $\left[\alpha\right]_{D}^{23} - 11.5$ (c 2.5 : CHCl₃); ¹H NMR (CDCl₃) 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), ; ¹³C NMR (CDCl₃) & 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).

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