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Facile Route to 3,5-Disubstituted Morpholines: Enantioselective Synthesis of O-Protected *trans*-3,5-Bis(hydroxymethyl)morpholines

Rajesh Dave and N. André Sasaki*

Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France

andre.sasaki@icsn.cnrs-gif.fr

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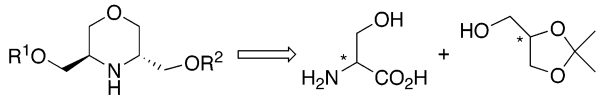
ABSTRACT



(**3*R*,5*R*)-1** R^1 & R^2 = TBDPS
(**3*S*,5*R*)-2** R^1 = Bn, R^2 = TBDPS
(**3*S*,5*S*)-3** R^1 & R^2 = Bn

***trans*-3,5-Bis(benzyl/*tert*-butyldiphenylsilyloxymethyl)morpholines, promising candidates for the C_2-symmetric class of chiral reagents, were prepared with excellent optical purity. A key step in the synthesis is the coupling of a serinol derivative with 2,3-*O*-isopropylideneglycerol triflate or its equivalent. This methodology was extended to the synthesis of chiral *trans*-3-(benzyloxymethyl)-5-(*tert*-butyldiphenylsilyloxymethyl)-morpholine, a potentially useful chiral building block.**

C_2-symmetric *trans*-α,α′-bis(alkyl/silyloxymethyl)-azacycloalkanes of different ring sizes are emerging as efficient chiral auxiliaries/ligand catalysts in asymmetric transformations.[1] The presence of a C_2 symmetry axis in the chiral directors often offers unique advantages in achieving asymmetric induction by reducing the number of competing undesired diastereomeric transition states.[2] However, there is little information on the synthesis and application profile of C_2-symmetric trans-α,α′-disubstituted cyclic amines bearing a heteroatom such as the oxygen of morpholines. The presence of such an atom might influence the chirality induction and the ligand catalytic properties. It has been reported that a morpholine amide can be cleaved with nucleophiles such as hydride and various alkyl/alkynyl carbanions to give chiral aldehydes, ketones, and ynones, respectively.[3] Recently, Jacobsen and Goodman used a morpholine amide in an acyl transfer reaction to synthesize a HMG-CoA reductase inhibitor intermediate.[4]

To the best of our knowledge, there exist only two enantioselective synthetic routes to trans-3,5-disubstituted morpholines: the first by Enders et al.[5] provides *trans*-3,5-dimethylmorpholine, while the other by Takahata et al.[6] gives *trans*-3,5-bis(*tert*-butyldiphenylsilyloxymethyl)morpholine **1**.

(1) (a) Tanner, D.; Birgersson, C.; Gogoll, A.; Luthman, K. *Tetrahedron* **1994**, *50*, 9797. (b) Tanner, D.; Korno, H. T.; Guijarro, D.; Andersson, P. G. *Tetrahedron* **1998**, *54*, 14213. (c) Shi, M.; Jiang, J.-K.; Feng, Y.-S. *Tetrahedron: Asymmetry* **2000**, *11*, 4923. (d) Shi, M.; Jiang, J.-K. *Tetrahedron: Asymmetry* **1999**, *10*, 1673. (e) Hoshino, J.; Hiraoka, J.; Hata, Y.; Sawada, S.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 693. (f) Donohoe, T. J.; Guillermin, J.-B.; Frampton, C.; Walter, D. S. *Chem. Commun.* **2000**, 465. (g) Najdi, S.; Reichlin, D.; Kurth, M. J. *J. Org. Chem.* **1990**, *55*, 6241.

(2) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

(3) (a) Douat, C.; Heitz, A.; Martinez, J.; Fehrentz, J.-A. *Tetrahedron Lett.* **2000**, *41*, 37. (b) Anderson, J. C.; Flaherty, A.; Swarbrick, M. E. *J. Org. Chem.* **2000**, *65*, 9152. (c) Sengupta, S.; Mondal, S.; Das, D. *Tetrahedron Lett.* **1999**, *40*, 4107. (d) Badioli, M.; Ballini, R.; Bartolacci, M.; Bosica, G, Torregiani, E.; Marcantoni, E. *J. Org. Chem.* **2002**, *67*, 8938. (e) Jackson, M. M.; Leverett, C.; Toczko, J. F.; Roberts, J. C. *J. Org. Chem.* **2002**, *67*, 5032.

(4) Goodman, S. N.; Jacobsen, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 4703.

(5) Enders, D.; Meyer, O.; Raabe, G.; Runsink, J. *Synthesis* **1994**, 66.

(6) Takahata, H.; Takahashi, S.; Kouno, S.; Momose, T. *J. Org. Chem.* **1998**, *63*, 2224.

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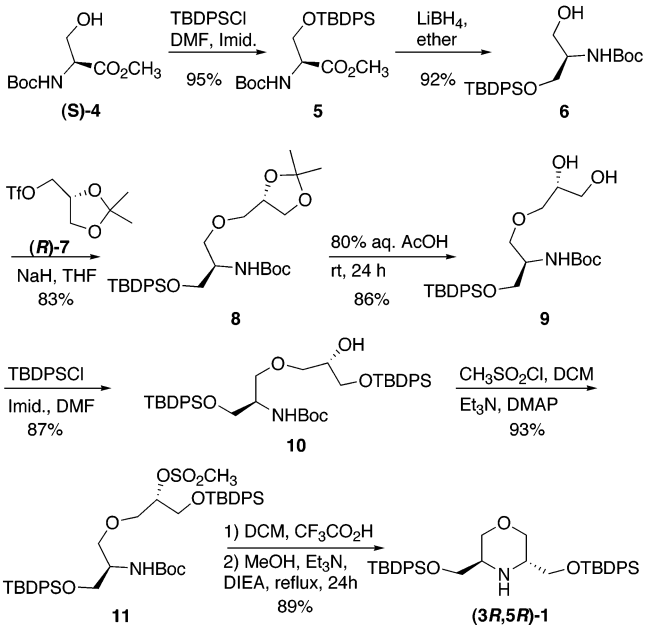
The latter strategy exploited the double Sharpless asymmetric dihydroxylation of α,ω-terminal dienes. The major problem associated with this approach was the efficient separation[7] of the enantiomerically pure morpholine derivative from its *meso*-isomer. Moreover, the methodology was not general and could not be used for the synthesis of *trans*-3,5-bis-(benzyloxymethyl)morpholine **3** or other differently O-protected derivatives of *trans*-3,5-bis(hydroxymethyl)-morpholine. Thus, it is of great interest that practical and efficient synthetic methods are developed for the construction of 3,5-disubstituted chiral morpholines. Herein, we report a novel synthetic approach to a range of conveniently protected chiral morpholines that have excellent optical purity; our strategy utilizes optically pure serine and solketal[8] as key starting materials.

L-*N*-Boc-serine methyl ester (*S*)-**4**, obtained from L-serine, was treated with TBDPSCl to give the *O*-silyl derivative **5** in 95% yield. Ester **5** was then reduced with $LiBH_4$ in ether to alcohol **6**, and the latter was subjected to a coupling with (*R*)-2,3-*O*-isopropylideneglycerol triflate[9] (*R*)-**7** mediated by 2 equiv of NaH in THF to furnish **8**. Acid hydrolysis[10] of **8**, followed by regioselective O-silylation of the primary hydroxyl in diol **9** with TBDPSCl, gave **10**. Conversion of the alcohol in **10** to a triflate and subsequent deprotection of the amino group followed by cyclization with triethylamine in methanol (0−5 °C, 15 min) gave (3*R*,5*R*)-3,5-bis-(*tert*-butyldiphenylsilyloxymethyl)morpholine (3*R*,5*R*)-**1** in 90% yield, but with only 70% diastereomeric excess. However, changing the leaving group to a mesylate circumvented this problem. Thus, **10** was converted to (3*R*,5*R*)-**1**[11] (de > 97%, ee > 99% by chiral HPLC analysis) by the three-step sequence of O-mesylation, removal of the Boc-group from mesylate derivative **11**, and finally base-mediated cyclization at reflux in methanol (Scheme 1). The overall yield of (3*R*,5*R*)-**1** starting from (*S*)-**4** was 45%. Likewise, (3*S*,5*S*)-**1** (de > 94%, ee > 99%) was prepared from D-*N*-Boc-serine methyl ester (*R*)-**4** and (*S*)-2,3-*O*-isopropylideneglycerol triflate (*S*)-**7** in 44% overall yield.

Scheme 1



The same synthetic protocol was attempted for the preparation of (3*S*,5*S*)-3,5-bis(benzyloxymethyl)morpholine (3*S*,5*S*)-**3** from D-*N*-Boc-serine methyl ester (*R*)-**4** and (*R*)-2,3-*O*-isopropylideneglycerol triflate (*R*)-**7**. (*R*)-**4** was converted[12] to alcohol (*R*)-**12** by a four-step sequence involving protection of the hydroxyl group as an *O*-THP ether, reduction of the ester to the alcohol with $LiBH_4$ in ether, O-benzylation of the resulting alcohol with benzyl bromide in the presence of NaH and catalytic TBAI, and removal of the *O*-THP group. Coupling of (*R*)-**12** with (*R*)-**7** in the presence of 2 equiv of NaH in THF gave **13**. Acid hydrolysis of **13** and subsequent reaction of the resulting diol **14** with triphenylphosphine and DEAD afforded epoxide **15** (Scheme 2). To our surprise, the known procedures[13] to open an epoxide with a benzyloxide/benzyl alcohol nucleophile failed to afford **16**. Furthermore, regioselective O-benzylation of the primary alcoholic group of diol **14** gave the desired compound **16** at best in 20% yield. Therefore, this approach for the preparation of *trans*-3,5-bis(benzyloxymethyl)morpholine **3** was abandoned. Instead, application of diol **14** to the synthesis of *trans*-3-(benzyloxymethyl)-5-(*tert*-butyldiphenylsilyloxymethyl)morpholine **2**, a potentially useful chiral building block in peptide and chelate chemistry,[14] was pursued.

Regioselective O-silylation of diol **14** with TBDPSCl, followed by activation of the hydroxyl group of **17** with

(7) In ref 27 of their article, Takahata et al. mentioned the separation of the morpholine enantiomer from its *meso*-isomer by the fractionation procedure.

(8) *R*)- and (*S*)-Solketal was purchased in kilogram scale from CHEMI S. p. A. (Via del Lavoratori 54, 20092 Cinisello Balsamo (MI), Italy).

(9) Cassel, S.; Debaig, C.; Benvegnu, T.; Chaimbault, P.; Laffose, M.; Plusquellec, P. R. *Eur. J. Org. Chem.* **2001**, 875. Pyridine was used as a base instead of triethylamine.

(10) Lewbart, M. L.; Schneider, J. J. *J. Org. Chem.* **1969**, *34*, 3505.

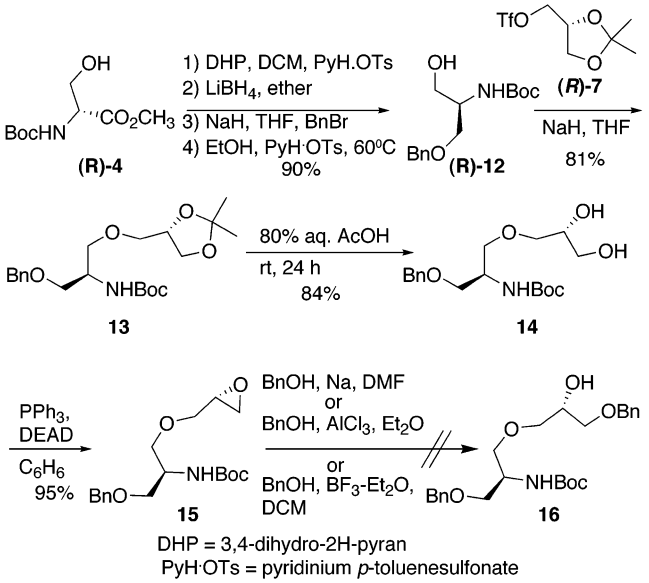
(11) (3*R*,5*R*)-**1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (18H, s, 2 × SiC-$(CH_3)_3$), 3.11 (2H, m, 2 × CHN), 3.41 (2H_a, dd, J = 12, 6 Hz, 2 × CH_aH_b-OC), 3.56 (2H_a, dd, J = 9, 6 Hz, 2 × CH_aH_bOSi), 3.74 (4H_b, m, 2 × CH_aH_bOC, 2 × CH_aH_bOSi), 7.4 (12H, m, ArH), 7.66 (8H, m, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.2, 26.8, 51.7, 63.9, 68.7, 127.7, 129.7, 133.2, 135.5; IR (neat) 3338, 2930, 2857, 1740, 1471, 1427, 1112, 824, 740, 702 cm^{-1}; HRMS (ESI) $(M + H)^+$ *m*/*z* calcd for $C_{38}H_{50}NO_3Si_2$ 624.3324, found 624.3324. Anal. Calcd for $C_{38}H_{49}NO_3Si_2$: C, 73.15; H, 7.92; N, 2.24. Found: C, 73.18; H, 8.12; N, 2.23. $[\alpha]^{24}_D$ 10.7 (*c* 1.1, $CHCl_3$) [lit.[6] $[\alpha]^{26}_D$ 10.3 (*c* 0.87, $CHCl_3$); de > 97%, ee > 99%; (i) HPLC analysis at 265 nm, symmetry column C_{18} (5 μm) 4.6 × 150 mm, H_2O/CH_3CN 40/60 + 0.1% HCO_2H, 1 mL/min, rt, retention time = 7.0 and 10.9 min for the two diastereomers, respectively; (ii) HPLC analysis at 220 nm, Chiralcel OD column (5 μm) 4.6 × 250 mm, hexane/2-propanol 99/1, 1 mL/min, rt, retention time = 5.1, 6.4 and 8.6 min for the (3*S*,5*S*)-, (3*R*,5*R*)-, and *meso*-isomers, respectively. (±)-**1** was prepared from racemic serine and solketal. (3*S*,5*S*)-**1**: $[\alpha]^{25}_D$ −10.1 (c 1, $CHCl_3$) [lit.[6] $[\alpha]^{26}_D$ −10.6 (*c* 0.74, $CHCl_3$); de > 94%, ee > 99% (chiral HPLC analysis).

(12) Sasaki, N. A.; Hashimoto, C.; Potier, P. *Tetrahedron Lett.* **1987**, *28*, 6069.

(13) (a) Abushanab, E.; Vemishett, P.; Leiby, R. W.; Singh, H. K.; Millilineni, A. B.; Wu, D. C.-J.; Saibaba, R.; Panzica, R. P. *J. Org. Chem.* **1988**, *53*, 2598. (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Synthesis* **1988**, 685. (c) Guivisdalsky, P. N.; Bittman, R. *J. Am. Chem. Soc.* **1989**, *111*, 3077.

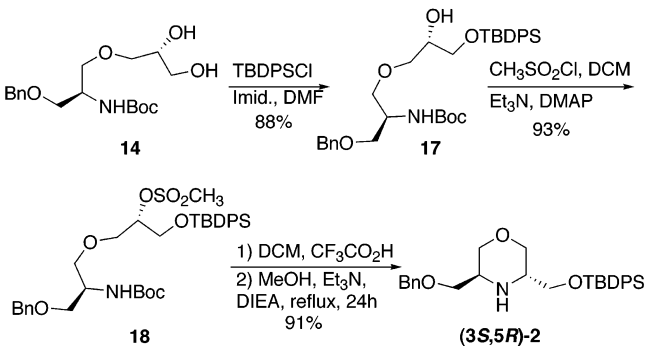
(14) (a) Kozlomski, M. C.; Bartlett, P. A. *J. Org. Chem.* **1996**, *61*, 7681. (b) Klaveness, J.; Rongved, P.; Berg, A. Patent No. WO 9110669, July 25, 1991. (c) Almen, T.; Berg, A.; Dugstag, H.; Klaveness, J.; Krautwurst, K. D.; Rongved, P. Patent No. WO 9008138, July 26, 1990.

Scheme 2



methanesulfonyl chloride, afforded **18**. Deprotection of the amino group in **18** and subsequent cyclization gave (3*S*,5*R*)-3-(benzyloxymethyl)-5-(*tert*-butyldiphenylsilyloxymethyl)-morpholine[15] (3*S*,5*R*)-**2** (de and ee > 99% by chiral HPLC analysis) (Scheme 3). The overall yield of (3*S*,5*R*)-**2** starting

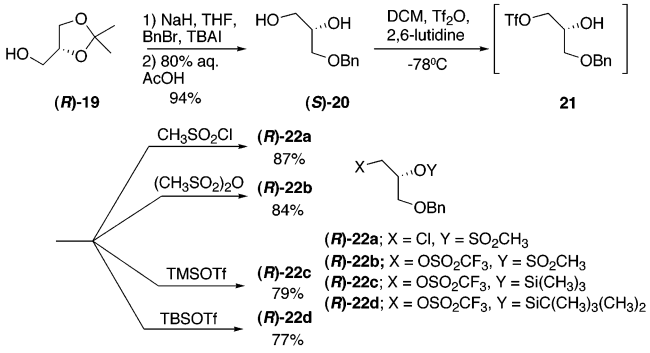
Scheme 3



from (*R*)-**4** was 46%. Using the same approach, (3*R*,5*S*)-**2** (de > 97% and ee > 99%) was prepared from L-*N*-Boc-serine methyl ester (*S*)-**4** and (*S*)-2,3-*O*-isopropylideneglycerol triflate (*S*)-**7** in 45% overall yield.

Failure of the above general methodology for the preparation of *trans*-3,5-bis(benzyloxymethyl)morpholine **3** prompted us to modify the solketal substrate before coupling with (*R*)-**12**. In the beginning, we envisaged converting (*S*)-3-benzyloxy-propane-1,2-diol[16] (*S*)-**20**, obtained from (*R*)-solketal (*R*)-**19**, to (2*R*)-3-benzyloxy-2-methanesulfonyloxypropyl trifluoromethanesulfonate (*R*)-**22b** before subjecting it to a coupling reaction. Accordingly, (2*R*)-3-benzyloxy-2-hydroxypropyl trifluoromethanesulfonate **21** was prepared in situ by reaction of (*S*)-**20** with triflic anhydride. Unfortunately, **21** gave (2*R*)-3-benzyloxy-2-methanesulfonyloxypropyl chloride (*R*)-**22a** by treatment with methanesulfonyl chloride and not the desired (*R*)-**22b**. Replacement of methanesulfonyl chloride by methanesulfonic anhydride indeed gave the desired triflate derivative (*R*)-**22b**, but it failed to couple with (*R*)-**12**, probably because of its instability under the reaction conditions. Although (2*R*)-3-benzyloxy-2-trimethylsilyloxypropyl trifluoromethanesulfonate (*R*)-**22c** was obtained in 79% yield by treatment with trimethylsilyl trifluoromethanesulfonate (TMSOTf), the yield of the subsequent coupling step with (*R*)-**12** was at best 20% under various reaction conditions. Finally, use of the *tert*-butyldimethylsilyl group for protection by employing *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) circumvented the problem. The resulting (2*R*)-3-benzyloxy-2-*tert*-butyldimethylsilyloxypropyl trifluoromethanesulfonate[17] (*R*)-**22d** coupled smoothly with (*R*)-**12** to give **23** in 81% yield (Scheme 4).

Scheme 4



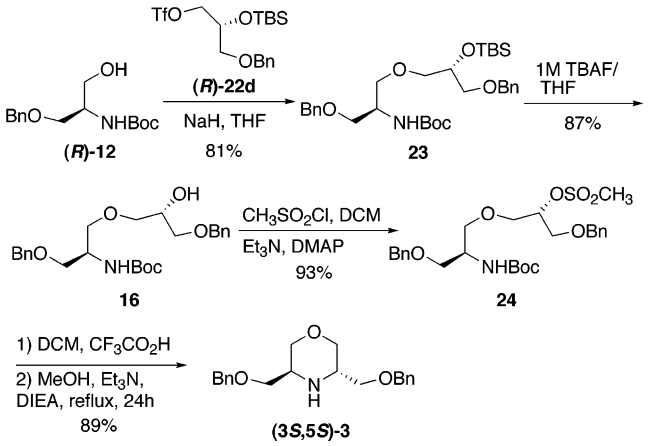
Cleavage of the silyl group from **23** with TBAF and mesylation of the resulting alcohol **16** with methanesulfonyl chloride afforded **24**. Deprotection of the amino group of **24** and subsequent base-mediated cyclization furnished (3*S*,5*S*)-3,5-bis(benzyloxymethyl)morpholine[18] (3*S*,5*S*)-**3** (de > 99%, ee > 98% by chiral HPLC analysis) (Scheme 5). The overall yield of (3*S*,5*S*)-**3** starting from (*R*)-**19** was 42%.

(15) (3*S*,5*R*)-**2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1 (9H, s, $SiC(CH_3)_3$), 2.74 (1H, br, NH), 3.12 (1H, m, BnOCCHN), 3.24 (1H, m, SiOCCHN), 3.56 ($3H_a$ + 2H, m, CH_aH_bOSi, 2 × CH_aH_bO, $BnOCH_2$), 3.77 ($3H_b$, m, 2 × CH_aH_bO, CH_aH_bOSi), 4.59 (2H, s, $ArCH_2$), 7.39 (11H, m, ArH), 7.71 (4H, m, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.3, 26.9, 48.8, 51.8, 63.5, 68.5, 68.8, 70.1, 73.5, 127.7, 127.8, 128.4, 129.8, 133.4, 135.6, 138.2; IR (neat) 3070, 2928, 2856, 1589, 1471, 1454, 1427, 1390, 1362, 1335, 1111, 823, 740, 701 cm^{-1}; HRMS (ESI) $(M + H)^+$ *m*/*z* calcd for $C_{29}H_{38}NO_3Si$ 476.2615, found 476.2610. Anal. Calcd for $C_{29}H_{37}NO_3Si$: C, 73.22; H, 7.84; N, 2.94. Found: C, 73.14; H, 7.91; N, 2.81. $[\alpha]^{24}_D$ 12.4 (c 1.4, $CHCl_3$); de and ee > 99%; (i) HPLC analysis at 220 nm, symmetry column C_{18} (5 μm) 4.6 × 250 mm, H_2O/CH_3CN 48/52 + 0.1% HCO_2H, 1 mL/min, rt, retention time = 30.6 and 33.1 min for the two diastereomers, respectively; (ii) HPLC analysis at 220 nm, Chiralcel OD column (10 μm) 4.6 × 250 mm, hexane/2-propanol 99/1, 1 mL/min, rt, retention time = 16.6 and 18.2 min for the pair of cis enantiomers and 13.0 and 18.3 min for the (3*R*,5*S*)- and (3*S*,5*R*)-isomers, respectively. (±)-**2** was prepared from racemic serine and solketal. (3*R*,5*S*)-**2**: $[\alpha]^{25}_D$ −11.9 (*c* 1.1, $CHCl_3$); de > 97% and ee > 99% (chiral HPLC analysis).

(16) Yamauchi, K.; Une, F.; Tabata, S.; Kinoshita, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 765.

(17) Mori, Y.; Sawada, T.; Furukawa, H. *Tetrahedron Lett.* **1999**, *40*, 731.

Scheme 5



In the same fashion, (3*R*,5*R*)-**3** (de and ee > 99%) was obtained from D-*N*-Boc-serine methyl ester (*R*)-**4** and (*S*)-solketal (*S*)-**19** in 43% overall yield.

In summary, a simple and practical protocol for preparing C_2-symmetric *trans*-3,5-bis(benzyl/*tert*-butyldiphenylsilyloxymethyl)morpholines with excellent optical purity has been developed by employing commercially available chiral serine and solketal. The generality of the methodology can be extended to preparation of other O-protected derivatives of *trans*-3,5-bis(hydroxymethyl)morpholines. Use of these C_2-symmetric morpholine entities as chiral auxiliaries/ligand catalysts in asymmetric syntheses is under progress in our laboratory.

Acknowledgment. We thank Benjamin Dumontet and Marie-Thérèse Adeline for technical assistance in HPLC analyses and Institut de Chimie des Substances Naturelles (CNRS, Gif-sur-Yvette) for financial assistance to R.D.

Supporting Information Available: Experimental details and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) (3*S*,5*S*)-**3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (1H, br, NH), 3.16 (2H, m, 2 × CHN), 3.47 (2H$_a$ + 4H, m, 2 × CH$_a$H$_b$OC, 2 × CH$_2$OBn), 3.73 (2H$_b$, dd, J = 12, 3 Hz, 2 × CH$_a$H$_b$OC), 4.51 (2H, s, ArCH$_2$), 4.52 (2H, s, ArCH$_2$), 7.3 (10H, m, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 49.8, 68.7, 69.9, 73.4, 127.7, 128.4, 138.1; IR (neat) 3340, 2856, 1736, 1496, 1453, 1366, 1242, 1100, 1028, 738, 698 cm^{-1}; HRMS (ESI) (M + H)$^+$ *m*/*z* calcd for $C_{20}H_{25}NO_3$ 328.1907, found 328.1911. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.45; H, 7.86; N, 4.22. $[\alpha]^{24}_D$ 12.7 (*c* 1.1, $CHCl_3$); de > 99%, ee > 98%; (i) HPLC analysis at 258 nm, symmetry column C_{18} (5 μm) 4.6 × 250 mm, H_2O/CH_3CN 70/30 + 0.1% HCO_2H, 1 mL/min, rt, retention time = 15.6 and 18.3 min for the two diastereomers; (ii) HPLC analysis at 258 nm, Chiralcel OD column (10 μm) 4.6 × 250 mm, hexane/2-propanol 98/2 + 0.1% HCO_2H, 1 mL/min, rt, retention time = 16.5, 19 and 21.9 min for the *meso*-, (3*R*,5*R*)-, and (3*S*,5*S*)-isomers, respectively. (±)-**3** was prepared from racemic serine and solketal. (3*R*,5*R*)-**3**: $[\alpha]^{23}_D$ −12.3 (*c* 1, $CHCl_3$); de and ee > 99% (chiral HPLC analysis).