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Synthesis of Enantiopure 3-Substituted Morpholines

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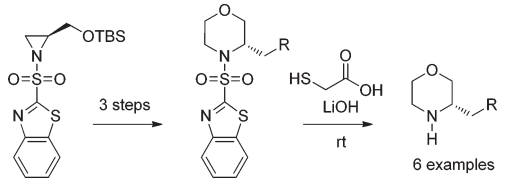
Received August 1, 2010



Enantiopure 3-substituted morpholines were assembled through ring-opening of a *N*-2-benzothiazolesulfonyl (Bts) activated aziridine with organocuprates followed by a ring annulation reaction with a vinylsulfonium salt under microwave conditions. Deprotection of the *N*-Bts group proceeds under very mild conditions with 2-mercaptoacetic acid and LiOH at rt.

The morpholine moiety has found widespread use in medicinal chemistry, and many drugs contain this subunit.[1] Due to the eletronegativity of oxygen, morpholine is a weaker base than, e.g., piperidine, which often provides improved physiochemical properties.[1] Although it is a very popular building block in drug discovery, the number of commercially available substituted morpholines is quite limited. Synthetic routes to substituted morpholines usually involve β-amino alcohols that are cyclized into 3-oxomorpholines and reduced.[2] Recently, Yar et al. reported an improved procedure in which vinyl- and 2-bromoethylsulfonium salts are used for the direct conversion of *N*-sulfonyl-protected β-amino alcohols into *N*-sulfonyl-protected morpholines.[3,4] Enantiopure β-amino alcohols can be accessed through the chiral pool of amino acids or a number of different asymmetric methodologies like the Sharpless aminohydroxylation.[5] However, the number of easily accessible enantiopure β-amino alcohols are still limited so new strategies are continuously being developed.

Herein, we wish to describe a novel approach to enantiopure 3-substituted morpholines based on the strategy outlined in Figure 1. Regioselective and stereospecific ring-opening of a suitably functionalized aziridine with organocuprates should provide *N*-sulfonyl-protected β-amino alcohols[6] that would be directly applicable in the synthesis of morpholines as described by Yar et al.[3,4]

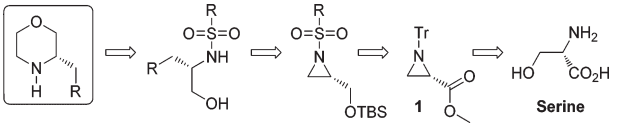


FIGURE 1. Retrosynthetic approach to substituted morpholines.

We envisioned that enantiopure methyl 1-tritylaziridine-2-carboxylate **1** would be a convenient starting point for the synthesis of the chiral morpholines since both enantiomers of **1** are commercially available or readily prepared on large scale (>100 g) from D- or L-serine in three high yielding steps without chromatographic purification.[7]

Different groups have been employed for the activation of aziridines,[8] but this is most effectively done with sulfonamides like the tosyl group due to its electron-withdrawing nature.[9−11] Although progress has been made toward the development of new protocols for the deprotection of the tosyl group,[12] this transformation often requires quite harsh conditions like strong acids or dissolving metal reductions.

The 2- and 4-nitrobenzenesulfonyl (nosyl) groups introduced by Fukuyama have been very well accepted by the synthetic community.[13,14] The most important feature of the nosyl group (compared to the tosyl group) is that the amines can be liberated under very mild conditions with thiolates. However, the electrophilic nature of the nitro group limits the types of reagents which are compatible with the nosyl group, in particular, organometallic and strongly reducing agents. We recently reported a study where heterocyclic sulfonamides were screened for their ability to activate 2-methylaziridine toward ring-opening while still being easily cleavable with thiolates.[15] From that investigation, the 2-pyrimidinesulfonyl (pymisyl) group and the 2-benzothiazolesulfonyl (Bts) groups emerged as potential

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(3) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3784.

(4) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 257.

(5) O'Brien, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 326.

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(7) Compound **1** can be prepared from serine by formation of the methyl ester with acetyl chloride in methanol, *N*-tritylation with trityl chloride and Et_3N, and finally one-pot O-mesylation and intramolecular aziridine ring formation by methanesulfonyl chloride and Et_3N; see the Supporting Information for references.

(8) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.

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(11) Beresford, K. J. M.; Church, N. J.; Young, D. W. *Org. Biomol. Chem.* **2006**, *4*, 2888.

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(13) Fukuyama, T.; Jow, C. K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

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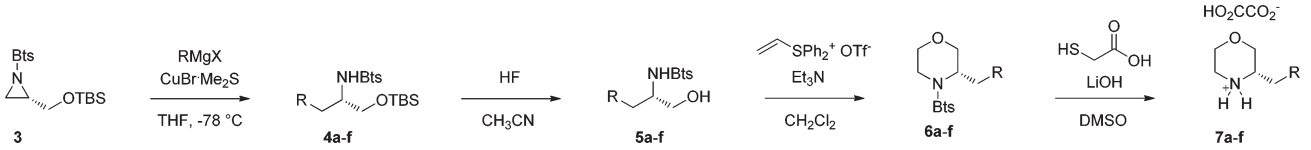
Published on Web 09/29/2010 DOI: 10.1021/jo101339g

TABLE 1. Four-Step Synthesis of 3-Substituted Morpholines Starting from 3

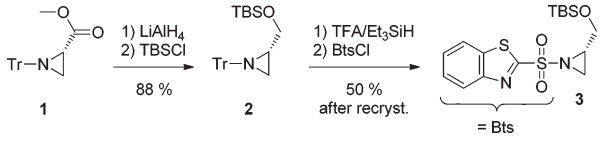


entry	R =	product	yield[a] (%)	product	yield[a] (%)	product	yield[a] (%)	product	yield[b] (%)
1	Me-	**4a**	91	**5a**	83	**6a**	83	**7a**	81[c]
2	Et-	**4b**	66	**5b**	92	**6b**	86	**7b**	74
3	vinyl-	**4c**	87	**5c**	83	**6c**	75	**7c**	75
4	cyclopropyl-	**4d**	86	**5d**	91	**6d**	76	**7d**	57
5	Ph-	**4e**	87	**5e**	89	**6e**	76	**7e**	75
6	4-MeO-Ph-	**4f**	70	**5f**	90	**6f**	72	**7f**	78

[a]Isolated yields after chromatographic purification. [b]Isolated yields after aqueous work up and precipitation with oxalic acid. [c]Isolated as a mixture of hydrogenoxalate and oxalate salts.

nosyl surrogates with the noteworthy addition of being compatible with organocuprate reagents. In this study, the pymisyl performed better than the Bts group, and therefore, it was initially tested in the sequence outlined in Figure 1. The ring-opening with organocuprate reagents worked well, giving the desired products in 83−89% yield. However, deprotection of the TBS group was accompanied by the formation of byproducts, and the yield of the pymisyl protected β-amino alcohols was low. Numerous different conditions were tested, but the formation of byproduct could not be suppressed and instead we turned our attention to the Bts group.[16]

SCHEME 1. Synthesis of Bts-Protected Aziridine 3 from 1

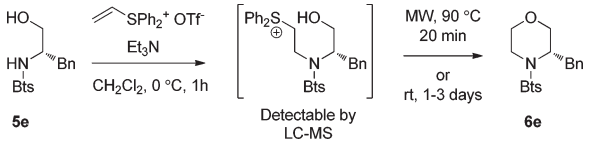


The key Bts-protected aziridine **3** was accessed from **1** as outlined in Scheme 1. Reduction of **1** with $LiAlH_4$ followed by O-silylation of the resulting alcohol with TBSCl gave **2** in 88% yield. Subsequently, the trityl group was removed with TFA/Et_3SiH followed by treatment of the aziridinium salt with BtsCl which provided the desired building block **3** in 50% yield from **2** after recrystallization.

The $CuBr \cdot Me_2S$ catalyzed ring-opening of **3** with Grignard reagents was attempted. Alkyl, vinyl, cyclopropyl, and aryl Grignard reagents worked well in analogy with the results obtained with the pymisyl-protected aziridine. Thus, the desired products **4a**−**f** were isolated in 66−91% yield, see Table 1. To our delight, the removal of the TBS group was not compromised by the same problems that plagued the pymisyl-protected products.[16] Deprotection proceeded smoothly with both TBAF in THF and 40% HF in CH_3CN, the latter being preferred due to ease of work up, and the Bts protected β-amino alcohols **5a**−**f** were isolated in 82−93% yield.

Subsequently, ring formation to the corresponding morpholines using vinyldiphenylsulfonium triflate as described by Yar et al.[3] was attempted. When the reaction mixture was allowed to stir overnight at rt, low conversion was observed. LC−MS confirmed that the reaction proceeded in two discrete steps; the first being addition of the deprotonated sulfonamide to the vinylsulfonium ion forming a new sulfonium salt; see Scheme 2.

SCHEME 2. Observed Intermediate in the Morpholin Synthesis



This proceeded within 1 h at 0 °C, but the subsequent ring closure via extrusion of diphenyl sulfide proved to be very slow at ambient temperature, and several days were required to obtain full conversion. Microwave heating (90 °C in CH_2Cl_2 at 3−4 bar) considerably shortened the reaction times, and under these conditions, only 15−20 min was required to reach full conversion. Subsequently, the Bts-protected morpholines **6a**−**f** were isolated in 72−86% yield; see Table 1. We propose that microwave heating will also prove beneficial to the annulation reaction of other *N*-sulfonylated β-amino alcohols and significantly shorten reaction times.

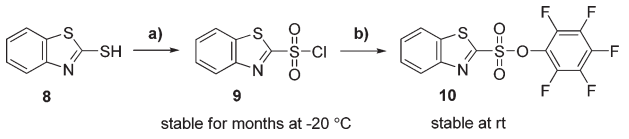
To verify that the stereochemical integrity was preserved in the sequence from serine to the 3-substituted morpholines, compound **6e** was compared with a racemic sample using chiral HPLC. To our delight, only a single enantiomer could be detected; see the Supporting Information for details.

Finally, the Bts group was removed under very mild conditions with 2-mercaptoacetic acid and lithium hydroxide in DMSO[17] at rt. The free morpholines were extracted into Et_2O and precipitated with anhydrous oxalic acid to yield the pure morpholines **7a**−**f** as hydrogenoxalate salts in 57−78% yield. The overall yield of the morpholines from the key intermediate **3** is in the range of 34−51% over four steps.

(16) Full experimental details on the ring opening of the pymisyl-protected aziridine is provided in the Supporting Information, including details of the unfruitful attempts to deprotect the TBS-group from the pymisyl-protected amino alcohols. The resulting *N*-pymisyl protected amino alcohols are not stable and presumably decompose via Smiles-type rearrangements. See: (a) Kleb, K. G. *Angew. Chem., Int. Ed.* **1968**, *7*, 291. (b) Truce, W. E.; Kreider, E. M.; Brand, W. W. *Org. React.* **1970**, *18*, 99. (c) Wang, H. Y.; Liao, Y. X.; Guo, Y. L.; Tang, Q. H.; Lu, L. *Synlett* **2005**, *8*, 1239.

(17) The use of DMF as solvent gave morpholines contaminated with small amounts of dimethylammonium oxalates.

SCHEME 3. Synthesis and Stability of BtsCl and BtsOPFP[a]



[a]Key: (a) NaOCl, HCl, CH_2Cl_2, −10 °C;[20] (b) HOPFP, Et_3N, CH_2Cl_2, −30 °C.[21]

The very mild conditions used for the deprotection highlight the advantage of using the Bts-group. BtsCl, originally introduced by Vedejs,[18] is readily prepared from inexpensive[19] 2-mercaptobenzothiazole (**8**) using NaOCl as the oxidant;[20] see Scheme 3. BtsCl can be stored for several months in the freezer with minimal deterioration. Alternatively, BtsCl can be converted to the corresponding pentafluorophenyl sulfonate ester (BtsOPFP) (**10**), which is stable at rt and reacts readily with primary and secondary amines to form the corresponding Bts-protected amines in very high yields.[21] Most importantly, the Bts group is readily removed under mild conditions using thiolates,[22] analogously to the nosyl group. Thus, the Bts group should be applicable in many other settings where the tosyl and nosyl groups currently are being used.

In conclusion, we have developed a new Cu-catalyzed ring-opening of an *N*-Bts activated aziridine with Grignard reagents. Subsequent ring annulation and deprotection under mild conditions provided enantiopure 3-substituted morpholines. This efficient protocol can be used to access both enantiomers of 3-substituted morpholines, not directly accessible from the chiral pool of amino acids.

Experimental Section

(*S*)-2-(2-((*tert*-Butyldimethylsilyloxy)methyl)aziridin-1-ylsulfonyl)benzo[*d*]thiazole (3). Trifluoroacetic acid (5.51 mL, 72 mmol) was added dropwise by syringe to a stirred solution of **2** (7.73 g, 18 mmol) and triethylsilane (11.5 mL, 72 mmol) in dry CH_2Cl_2 (90 mL) at −5 °C under argon. The mixture was stirred 2.5 h at −5 to +4 °C until TLC showed full consumption of the starting material. The reaction mixture was poured into cold 2 M K_2CO_3 (90 mL) under vigorous stirring. The layers were separated, and the aqueous layer was extracted with ether (2 × 30 mL). The combined organic layers were concentrated in vacuo to remove the CH_2Cl_2. The residue was dissolved in EtOAc (80 mL), 2 M K_2CO_3 (35 mL) was added, and the mixture was cooled to 0 °C in an ice bath. Solid benzothiazole-2-sulfonyl chloride (BtsCl) (4.00 g, 17.1 mmol) was added in small portions under vigorous stirring. After 2 h at 0 °C, the mixture was allowed to warm to rt. Excess BtsCl was quenched with 25% NH_4OH (2 × 200 μL) until TLC showed full conversion. The reaction mixture was then diluted with EtOAc (20 mL), and the layers were separated. The aqueous layer was extracted with ether (40 mL). The combined organic layers were washed with 0.5 M NaH_2PO_4 (40 mL), water (40 mL), and satd Na_2SO_4 (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (FC) on silica (EtOAc/PE, 5:95 to 14:86) providing 4.96 g of material containing 3% of a chloride ring opened byproduct and some triethylsilyl-containing byproduct. Recrystallization from methanol by dissolving it in 40 °C warm methanol and cooling to −78 °C afforded **3** (3.30 g, 50%) as a slightly rose-colored solid: mp 56.5−57.5 °C; $[\alpha]^{20}_D$ = −32.0 (*c* 1.10, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31−8.20 (m, 1H), 8.05−7.95 (m, 1H), 7.69−7.54 (m, 2H), 3.84−3.72 (m, 2H), 3.31−3.19 (m, 1H), 2.93 (d, *J* = 7.0, 1H), 2.50 (d, *J* = 4.8, 1H), 0.80 (s, 9H), −0.02 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 152.5, 137.0, 128.2, 127.7, 125.8, 122.3, 61.8, 42.2, 32.2, 25.8, 18.4, −5.3, −5.4; HRMS calcd for $C_{16}H_{25}N_2O_3S_2Si$ [M + H] 385.1075, found 385.1061.

General Procedure for Ring-Opening of 3 with Grignard Reagents: Synthesis of (*S*)-*N*-(1-(*tert*-Butyldimethylsilyloxy)-pentan-2-yl)benzo[*d*]thiazole-2-sulfonamide (4b). Copper(I) bromide dimethyl sulfide (72 mg, 0.35 mmol) was added to a flame-dried Schlenk flask under argon. Dry THF (14 mL) was added, and the slurry was stirred at rt for 15 min and then cooled to −55 °C (externally). Ethylmagnesium bromide (3.10 mL, 0.97 M, 3.00 mmol) in THF was added dropwise at −55 °C. The resulting mixture was stirred at −55 to −50 °C for 30 min and then cooled to −78 °C. Compound **3** (769 mg, 2.00 mmol) in dry THF (3.5 mL) was added dropwise by syringe. The reaction mixture was stirred at −78 °C for 1 h and then quenched with 8 mL of an aqueous $(NH_4)_2SO_4/NH_3$ solution (1 mol of $(NH_4)_2SO_4$ and 30 mL of 25% NH_4OH diluted to 500 mL with water) at −78 °C and then allowed to warm to rt. The mixture was transferred to a 100 mL flask, and the THF was removed in vacuo. The aqueous residue was extracted with ether (1 × 25 mL and 2 × 15 mL), and the combined organic phases were washed with 0.05 M Na_2EDTA (10 mL) and brine (20 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by FC on silica (EtOAc/PE, 0:100−1:3) to afford **4b** (545 mg, 66%) as a colorless solid: mp 49.5−50.5 °C; $[\alpha]^{20}_D$ = −10.2 (*c* 1.07, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19−8.13 (m, 1H), 8.00 −7.94 (m, 1H), 7.65−7.51 (m, 2H), 5.25 (d, *J* = 8.4, 1H), 3.71−3.48 (m, 3H), 1.61−1.50 (m, 2H), 1.47−1.23 (m, 2H), 0.87 (t, *J* = 7.3, 3H), 0.81 (s, 9H), −0.05 (s, 3H), −0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 152.6, 136.6, 127.7, 127.5, 125.3, 122.3, 64.3, 56.1, 34.5, 25.9, 19.0, 18.4, 13.9, −5.5; HRMS calcd for $C_{18}H_{31}N_2O_3S_2Si$ [M + H] 415.1545, found 415.1532.

General Procedure for the Deprotection of the TBS Group Exemplified by the Synthesis (*S*)-*N*-(1-Hydroxypentan-2-yl)benzo-[*d*]thiazole-2-sulfonamide (5b). HF (87 μL, 40%, 1.23 mmol, 1.5 equiv) was added to a stirred solution of **4b** (415 mg, 1.30 mmol) in acetonitrile (2.3 mL) cooled to 0 °C in an ice bath. The mixture was stirred 30 min at 0 °C and then at ambient tempratue for 2 h while the reaction progress was monitored by TLC and UPLC−MS. The reaction mixture was then neutralized with satd $NaHCO_3$ and concentrated in vacuo to remove acetonitrile. The residue was partitioned between brine (10 mL) and EtOAc (15 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The solid residue was purified by FC on silica (EtOAc/PE, 7:13) to afford the title compound **5b** as a colorless solid (361 mg, 92%): mp 136−137 °C; $[\alpha]^{20}_D$ = +4.5 (*c* 1.00, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12−8.06 (m, 1H), 7.98−7.93 (m, 1H), 7.62−7.51 (m, 2H), 5.74 (d, *J* = 8.1, 1H), 3.80−3.65 (m, 2H), 3.57 (dd, *J* = 5.7, 11.8, 1H), 3.26 (s, 1H), 1.61−1.50 (m, 2H), 1.49−1.28 (m, 2H), 0.88 (t, *J* = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 151.6, 136.4, 127.9, 127.7, 124.9, 122.4, 64.6, 57.4, 34.5, 19.0, 13.8; HRMS calcd for $C_{12}H_{17}N_2O_3S_2$ [M + H] 301.0681, found 301.0693.

General Procedure for the Annulation Reaction: Synthesis of (*S*)-3-Propyl-4-(benzo[*d*]thiazol-2-ylsulfonyl)morpholine (6b). To a 20 mL capped microwave vial under argon was added triethylamine (600 μL, 4.26 mmol, 4 equiv) dropwise to a stirred mixture of **5b** (320 mg, 1.07 mmol) in dry CH_2Cl_2 (8 mL) at 0 °C.

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(19) 2-Mercaptobenzothiazole is used on large scale in several industrial settings, among them as a vulcanizing agent in the rubber and latex industry. Thus, 2-mercaptobenzothiazole is readily available at very low cost.
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(22) Wuts, P. G. M.; Gu, R. L.; Northuis, J. M.; Thomas, C. L. *Tetrahedron Lett.* **1998**, *39*, 9155.

The mixture was stirred for 5 min at 0 °C, and then diphenylvinylsulfonium trifluoromethanesulfonate[3] (584 mg, 1.60 mmol) in dry CH_2Cl_2 (7 mL) was added dropwise by syringe. The mixture was stirred for 1 h at 0 °C. By then, UPLC−MS showed full conversion of **5b** into an uncyclized sulfonium intermediate. The reaction mixture was then heated to 90 °C (3−4 bar) in a microwave reactor for 15 min. The reaction mixture was then partitioned between 1 M NaH_2PO_4 (16 mL) and CH_2Cl_2 (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2×15 mL). Drying over Na_2SO_4 and concentration in vacuo gave an oily residue. Purification by FC on silica (EtOAc/CH_2Cl_2/PE, 1:1:8) gave **6b** (300 mg, 86%) as a colorless oil that solidified after standing at 4 °C: mp 69−70 °C; $[\alpha]^{20}_D = +59.0$ (*c* 1.06, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21−8.15 (m, 1H), 8.01−7.95 (m, 1H), 7.65−7.52 (m, 2H), 3.96 (td, J = 2.9, 7.5, 1H), 3.87−3.65 (m, 3H), 3.57−3.37 (m, 3H), 1.84−1.64 (m, 2H), 1.47−1.31 (m, 2H), 0.93 (t, J = 7.3, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 152.7, 136.5, 127.7, 127.6, 125.3, 122.3, 68.5, 66.1, 54.5, 41.8, 30.9, 19.5, 13.9; HRMS calcd for $C_{14}H_{19}N_2O_3S_2$ [M + H] 327.0837, found 327.0823.

General Procedure for Deprotection of the Bts Group and Isolation of the Morpholines as Hydrogen Oxalates. 2-Mercaptoacetic acid (137 μL, 2 mmol, 2 equiv, freshly distilled) was added to a stirred suspension of lithium hydroxide monohydrate (168 mg, 4 mmol, 4 equiv) in DMSO (2 mL) under argon. The mixture was stirred 5 min at rt. Compound **6a**−**f** (1.0 mmol) in DMSO (1 mL) was added and the mixture stirred at rt until TLC/UPLC−MS showed full conversion of **6a**−**f** (5 min−30 min). The reaction mixture was partitioned between 2 M K_2CO_3 (12 mL) and ether (16 mL). The aqueous layer was extracted 3−5 times with ether (16 mL) until TLC (MeOH/CH_2Cl_2, 1:4, ninhydrin) showed only traces of product in the extract. The combined organic layers were dried twice over solid crushed KOH. Anhydrous oxalic acid (99 mg, 1.1 mmol, 1.1 equiv) in dry ether (1−2 mL) was added, and the precipitate was filtered through a glass sintered funnel size 4, washed with dry ether, and dried under high vacuum.

Acknowledgment. J.B. is grateful to LEO Pharma and the Drug Research Academy for a grant. We also thank the staff at LEO Pharma, in particular Charlotte Rune, Karin Kryger, Hans Henrik Grant, and Else Kristoffersen.

Supporting Information Available: Full experimental details including copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.