JOC*Note*

A Practical and Improved Synthesis of (3*S*,5*S*)-3-[(*tert*-Butyloxycarbonyl)methyl]-5-[(methanesulfonyloxy)methyl]-2-pyrrolidinone

Nathan K. Yee,* Yong Dong, Suresh R. Kapadia, and Jinhua J. Song

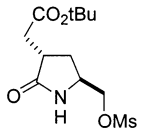
Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368

nyee@rdg.boehringer-ingelheim.com

Received June 26, 2002

Abstract: A practical and improved synthesis of (*3S,5S*)-3-[(*tert*-butyloxycarbonyl)methyl]-5-[(methanesulfonyloxy)-methyl]-2-pyrrolidinone (**1**) is described. The key transformations involve a highly efficient reaction sequence consisting of ethoxycarbonylation, alkylation, hydrolysis, and decarboxylation to produce compound **10**. The process described herein is practical, robust, and cost-effective, and it has been successfully implemented in a pilot plant to produce a multikilogram quantity of mesylate **1**.

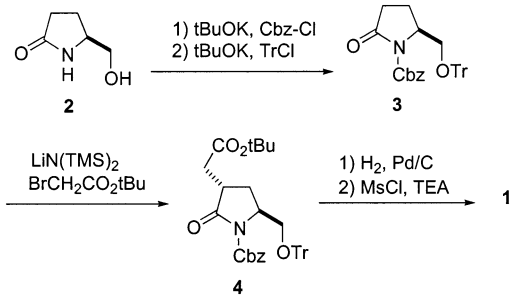
Our drug discovery program identified a series of 3,5-disubstituted-2-pyrrolidinones as potent inhibitors for the collagen-induced thrombocyte aggregation, and thus they became potential drug candidates for the treatment of a variety of inflammation diseases.[1] To support related preclinical and clinical studies, we needed to synthesize a key intermediate, (*3S,5S*)-3-[(*tert*-butyloxycarbonyl)-methyl]-5-[(methanesulfonyloxy)methyl]-2-pyrrolidinone (**1**),[2] in large quantity, which called for a scalable route in a production environment.



1

The original preparation of **1** started with commercially available (*5S*)-5-hydroxymethyl-2-pyrrolidinone **2** (Scheme 1).[1] The carboxybenzyl (Cbz) and trityl (Tr) groups were employed to protect the NH and OH functionalities to give **3**. Treatment of **3** with $LiN(TMS)_2$ at −65 °C followed by *tert*-butyl bromoacetate gave predominantly trans[3] alkylated product **4**. The bulky trityl group in **3** and low temperature (−65 °C) for alkylation were required to achieve the desired trans stereochemistry. Hydrogenation

SCHEME 1

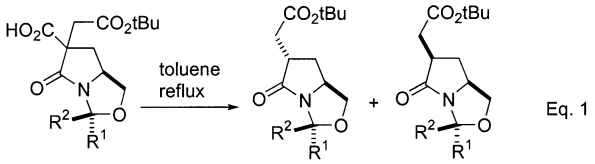


of **4** over activated Pd/C followed by methanesulfonylation afforded the mesylate **1**.

Some obstacles hindered its use for scale-up production aiming at potential drug commercialization. The low-temperature conditions are not favored in the production environment, and the costs associated with protecting groups (Cbz and Trityl groups) are high. Therefore, a more practical and cost-effective synthesis of **1** was required for further scale-up. In this Note, we will describe a more efficient synthesis of **1** in terms of operational simplicity and cost-effectiveness.

The trans stereochemistry in the disubstituted 2-pyrrolidinone **1** is the key structural feature. Several methodologies involving the trans or cis stereoselective alkylation of pyroglutamic acid derivatives are reported in the literature.[4] Most of them employ bulky substituents at C-5 (such as CO_2tBu, CH_2OSiMe_2tBu, or trityl groups) and low-temperature conditions to achieve acceptable trans selectivity (trans:cis ratio >85:15). On the other hand, the stereoselective decarboxylation approach developed by Moloney et al.[5] is most attractive to us due to its high trans:cis selectivity and simplicity. Further modification of this method seemed to well satisfy our need for the synthesis of **1**.

The impact of the different R groups on the trans selectivity in decarboxylation of substrates **5a**−**e** was first investigated (eq 1). Excellent stereoselectivity with trans:



Eq. 1

5a: R^1 = Ph, R^2 = H
5b: R^1 = 4-MeOPh, R^2 = H
5c: R^1 = tBu, R^2 = H
5d: R^1 = iPr, R^2 = H
5e: R^1 = Me, R^2 = Me

6a-e

cis ∼ 95:5 was obtained when R = Ph, 4-MeOPh, *i*-Pr, and *t*-Bu, while acetonide **5e** resulted in a moderate selectivity with trans:cis ∼ 85:15. Considering the needed reactivity, the crystallinity of the intermediates, and the protection/deprotection efficiency,[6] we chose **5a** to carry out the synthesis of **1**.

The synthesis of **1** started with (5*S*)-5-hydroxymethyl-2-pyrrolidinone (**2**) (Scheme 2). Formation of *N*,*O*-acetal

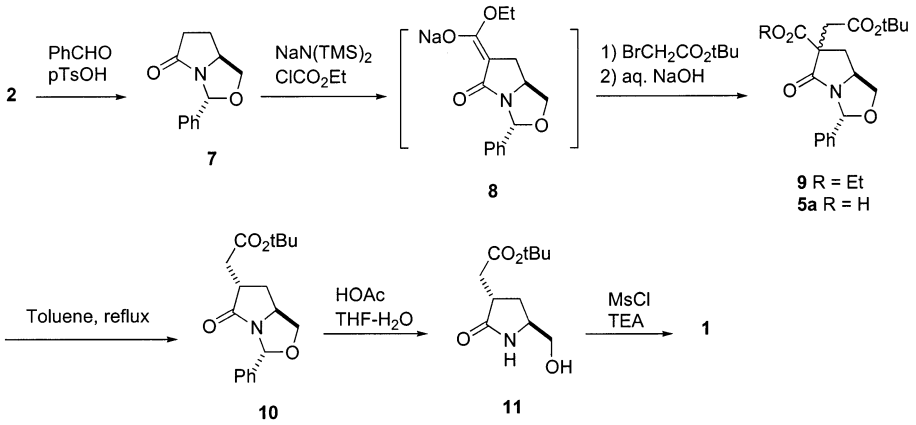
(1) (a) Austel, V.; Eisert, W.; Himmelsbach, F.; Linz, G.; Mueller, T.; Pieper, H.; Weisenberger, J. U.S. Patent 5,455,348, Oct 2, 1995. (b) Himmelsbach, F.; Austel, V.; Pieper, H.; Eisert, W.; Mueller, T.; Weisenberger, J.; Linz, G.; Krueger, G. U.S. Patent 5,591,769, Jan 7, 1997.

(2) *tert*-Butyl ester functionality was specifically chosen for the crystallinity of the intermediates in the synthesis.

(3) The trans/cis stereochemical notation refers to the C3 and C5 positions.

10.1021/jo020433f CCC: $22.00 © 2002 American Chemical Society
Published on Web 10/31/2002

SCHEME 2



7 (PhCHO, pTsOH, toluene, 80% yield)[4a] was straightforward, and excess benzaldehyde was removed by bisulfite washings. Ethoxycarbonylation of **7** was first attempted according to Moloney's procedure (NaH, $EtOCO_2Et$, toluene, reflux).[5] Under these conditions, a complex mixture was obtained and the desired ethoxycarbonylated product was isolated by column chromatography in moderate yields (50−60%). Attempts to optimize this reaction by using lower temperature or a different solvent such as THF were not successful. It is believed the higher temperature is first required to generate the enolate by NaH and the resulting transient enolate **8**, produced from the ethoxycarbonylated intermediate, is not stable under these forcing conditions. At this point, a more direct ethoxycarbonylation/alkylation method was investigated. The use of strong base such as $NaN(TMS)_2$ can efficiently produce the enolate under milder conditions (−78 to 0 °C). Furthermore, an ethoxycarbonylating reagent such as chloroformate[7] is more reactive and its byproduct (NaCl) will not affect the following alkylating step. Therefore, a direct one-pot procedure for ethoxycarbonylation and alkylation is envisioned for this preparation. Under the optimized conditions, the *N*,*O*-acetal **7** was treated with 2 equiv of $NaN(TMS)_2$ at −10 to 0 °C to generate the corresponding enolate (Scheme 2). This enolate reacted with ethyl chloroformate at the same temperature to afford the expected enolate intermediate **8**. Under these conditions, the reaction was rapid and clean. Therefore, direct addition of *tert*-butyl bromoacetate to this resulting enolate (0 °C to room temperature) gave the desired alkylated diastereomeric product **9** smoothly. A simple aqueous/organic extractive workup procedure afforded clean product **9** in essentially quantitative yield. The crude product so obtained was used directly for the next step.

Basic hydrolysis of **9** (aq NaOH, MeCN, rt) proceeded smoothly and cleanly. The sodium salt of the carboxylic acid **5a** was suspended in water and the aqueous layer was washed with toluene to remove all possible organic soluble side-products and impurities. The pure carboxylic acid **5a** was obtained after acidification by aq HCl.

Decarboxylation of **5a** was first achieved according to the literature procedure described by Moloney,[5] in which the neat substrate **5a** was heated to 130 °C under vacuum. These conditions were not practical for large-scale production, and an alternative was sought to effect the same transformation. Attempts to perform direct decarboxylation of ethyl ester **9** (NaCl, DMSO, 130−175 °C)[8] only led to recovery of starting material along with some decomposition. Later, it was found that refluxing a suspension of carboxylic acid **5a** in toluene achieved decarboxylation in 2 to 3 h to give **10** cleanly with trans:cis = 95:5.[9] The overall yield, for the entire 4-step sequence consisting of ethoxycarbonylation, alkylation, hydrolysis, and decarboxylation, ranged from 82% to 90%. This high efficiency was successfully demonstrated on a multikilogram scale in the pilot plant.

Deprotection of the *N*,*O*-acetal **10** is not trivial. Reductive cleavage of the *N*,*O*-acetal group (hydrazine, Pd/C,

(4) (a) Thottathil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem*. **1986**, *51*, 3140. (b) Thottathil, J. K.; Przybyla, C.; Malley, M.; Gougoutas, J. Z. *Tetrahedron Lett*. **1986**, *27*, 1533. (c) Brena-Valle, L. J.; Sanchez, R. C.; Cruz-Almanza, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1019. (d) Woo, K.-C.; Jones, K. *Tetrahedron Lett*. **1991**, *32*, 6949. (e) Baldwin, J. E.; Miranda, T.; Moloney, M. *Tetrahedron* **1989**, *45*, 7459. (f) Gu, Z.-Q.; Lin, X.-F.; Hesson, D. P. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 1973. (g) Langlois, N.; Rojas, A. *Tetrahedron Lett*. **1993**, *34*, 2477. (h) Hon, Y.-S.; Chang, Y.-C.; Gong, M.-L. *Heterocycles* **1990**, *31*, 191. (i) Ezquerra, J.; Pedregal, C.; Rubio, A.; Yruretagoyena, B.; Escribano, A.; Sanchez-Ferrando, F. *Tetrahedron* **1993**, *49*, 8665. (j) Dikshit, D. K.; Bajpai, S. N. *Tetrahedron Lett*. **1995**, *36*, 3231. (k) Ezquerra, J.; Pedregal, C. *Tetrahedron: Asymmetry* **1994**, *5*, 921. (l) Baldwin, J. E.; Moloney, M. G.; Shim, S. B. *Tetrahedron Lett*. **1991**, *32*, 1379. (m) Armstrong, R. W.; DeMattei, J. A. *Tetrahedron Lett*. **1991**, *32*, 5749.

(5) (a) Beard, M. J.; Bailey, J. H.; Cherry, D. T.; Moloney, M. G.; Shim, S. B.; Statham, K. A. *Tetrahedron* **1996**, *52*, 3719. (b) Bamford, M. J.; Beard, M.; Cherry, D. T.; Moloney, M. G. *Tetrahedron: Asymmetry* **1995**, *6*, 337.

(6) Acetal **5b** is too labile under decarboxylation conditions. For **5c** and **5d**, isobutyraldehyde (bp 63 °C) and pivalaldehyde (bp 74 °C) can be conveniently removed by evaporation either in protection or deprotection steps, but they are more difficult to deprotect under mild conditions.

(7) (a) Ackermann, J.; Matthes, M.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 122. (b) Attwood, M. R.; Carr, M. G.; Jordan, S. *Tetrahedron Lett*. **1990**, *31*, 283. (c) Tanaka, K.; Yoshifuji, S.; Nitta, Y. *Chem. Pharm. Bull*. **1986**, *34*, 3879.

(8) (a) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett*. **1973**, *12*, 957. (b) Bernard, A. M.; Cerioni, G.; Piras, P. P.; Seu, G. *Synthesis* **1990**, 871. (c) Bringmann, G.; Geuder, T. *Synthesis* **1991**, 829.

(9) The corresponding cis isomer of **10** was independently prepared (**7**, $LiN(TMS)_2$, $BrCH_2CO_2tBu$, −78 °C). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44 (m, 2H), 7.35 (m, 3H), 6.32 (s, 1H), 4.24 (t, J = 7.36 Hz, 1H), 4.12 (m, 1H), 3.59 (t, J = 7.12 Hz, 1H), 3.26 (m, 1H), 2.82 (dd, J = 3.84, 17.3 Hz, 1H), 2.68 (m, 1H), 2.28 (dd, J = 8.92, 16.4 Hz, 1H), 1.66 (m, 1H), 1.46 (s, 9H). The trans/cis stereochemistry of **10** was unambiguously assigned based on COSY and NOESY experiments which were similar to those reported in ref 4m. The trans/cis ratio was determined by ^1H NMR integration in which the C-4 protons are characteristic for the trans isomer (δ 3.41 ppm) and the cis isomer (δ 3.59 ppm).

MeOH,[10] or H_2, $Pd(OH)_2$, MeOH[11]) was attempted and failed. Selective acidic hydrolysis of the *N*,*O*-acetal group in the presence of the *tert*-butyl ester group was investigated. It was found that the hydrolysis catalyzed by Lewis acids such as pTsOH or PPTS in MeOH−H_2O led to some success. The HOAc−THF−H_2O system developed by Nagasaka[12] seemed to give the best results. The optimized ratio of HOAc−THF−H_2O was 2:3:1, under which the *N*,*O*-acetal group was hydrolyzed at reflux (80 °C) to give crude alcohol **11** (∼80% assay yield[13] by ^{1}H NMR). The crude product **11** was used for the next step without purification.

Formation of mesylate **1** (MsCl, CH_2Cl_2, 0 °C) proceeded smoothly: treatment of the crude **1** with MTBE gave crystalline mesylate **1** in 66% overall yield over two steps from *N*,*O*-acetal **10**. High chemical and optical purities of mesylate **1** (>99% by HPLC, trans:cis = 99.7:0.3) were achieved,[14] and thus satisfied purity specifications required for the manufacture of related drug substances.

In summary, we have developed a practical and improved synthesis of mesylate **1** in terms of operational simplicity and cost-effectiveness. The key transformations involve a highly efficient reaction sequence consisting of ethoxycarbonylation, alkylation, hydrolysis, and decarboxylation, to produce compound **10**. The one-pot procedure, developed for carboxylation [$NaN(TMS)_2$, $ClCO_2Et$, 0 °C] followed by direct alkylation (RBr, 0 °C to room temperature), made significant improvements to the original protocol by Moloney.[5] In comparison with the early synthesis of **1** (Scheme 1), this process removes the low-temperature conditions, which is undesired in the production environment. Also, the higher cost associated with the Cbz and Tr protecting groups was eliminated while inexpensive benzaldehyde was used to protect both the NH and OH functionalities. Therefore, the process described herein is practical, robust, and cost-effective, and it has been successfully implemented in the pilot plant to produce a multikilogram quantity of mesylate **1**.

Experimental Section[15]

(2*R*,5*S*)-2-Phenyl-3-oxa-1-aza-bicyclo[3,3,0]octane (7) was prepared according to literature procedure by Thoittiol et al.[4a] except the crude product **7** was used directly without any purification: 146 g (83%). Its ^{1}H NMR spectrum was identical with those reported.

(2*R*,5*S*,7*S*)-1-Aza-7-[(*tert*-Butoxycarbonyl)methyl]-3-oxa-2-phenylbicyclo[3,3,0]octan-8-one (10). In a 5-L round-bottomed flask equipped with a mechanical stirrer, a solution of $NaN(TMS)_2$ (1.0 M in THF, 1.705 L, 1.705 mol) was cooled to about −10 °C. A solution of *N*,*O*-acetal **7** (157.5 g, 0.775 mol) in 90 mL of anhydrous THF was added dropwise over 30 min at −10 to 0 °C. The reaction mixture was stirred at the same temperature for 1 h. Ethyl chloroformate (78.0 mL, 0.815 mol) was added at −10 to 0 °C over 1.5 h and the reaction mixture was stirred at −5 to 0 °C for 1.5 h. TLC analysis (50% EtOAc in hexane) indicated the reaction was complete. *tert*-Butyl bromoacetate (150 mL, 1.015 mol) was added over 30 min at −5 to 5 °C. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1.5 h. TLC analysis showed the reaction was complete. The reaction mixture was cooled to 0 °C and quenched with saturated NH_4Cl (100 mL). The mixture was concentrated to dryness and the residue was dissolved with 800 mL of EtOAc. The organic layer was extracted with water (800 mL). The aqueous layer was extracted with EtOAc (2 × 300 mL). The combined organic layers were washed with water (300 mL) and saturated NaCl (300 mL). The organic layer was concentrated to half and then hexane (700 mL) was added. The resulting solution was filtered through silica gel (50 g) followed by rinsing the filter cake with EtOAc (200 mL). Concentration of the organic layer afforded 323.2 g of crude product **9**. The analytically pure sample of **9** was obtained by column chromatography. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45−7.30 (m, 5H), 6.29 (s, 0.28H), 6.27 (s, 0.72H), 4.31 (m, 3H), 4.12−4.09 (m, 1H), 3.75 (t, J = 8.62 Hz, 0.78H), 3.62 (t, J = 7.94 Hz, 0.28H), 3.22 (dd, J = 7.54, 17.4 Hz, 1H), 3.10 (dd, J = 7.02, 13.1 Hz, 0.28H), 2.81 (dd, J = 4.34, 14.2 Hz, 0.74H), 2.68 (dd, J = 6.14, 17.0 Hz, 1H), 2.47 (dd, J = 8.07, 14.2 Hz, 0.74H), 1.92 (dd, J = 7.10, 13.2 Hz, 0.27H), 1.44 (s, 2.64H), 1.40 (s, 6.72H), 1.30 (m, 3H).

The crude **9** (323.2 g, max 0.775 mol) was dissolved in MeCN (800 mL). The solution was cooled at 0 °C as aqueous 3 N NaOH (390 mL, 1.17 mol) was added. The mixture was then stirred at room temperature overnight (18 h). TLC analysis (25% EtOAc in hexane) indicated the reaction was complete. The reaction mixture was concentrated and the residue was dissolved in water (200 mL). After the aqueous layer was washed with toluene (3 × 150 mL) to remove any organic byproducts, the aqueous layer was mixed with EtOAc (900 mL) and then cooled to 0 °C. Concentrated HCl (∼97 mL) was added at the rate to keep the internal temperature below 5 °C to acidify until pH 2−3. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 300 mL). The combined organic layers were washed with water (2 × 200 mL), dried over $MgSO_4$, and concentrated. The residue was stripped with toluene (2 × 500 mL) to give carboxylic acid **5a**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (m, 2H), 7.36 (m, 3H), 6.29 (s, 1H), 4.30 (m, 1.37H), 4.15 (m, 0.85H), 3.69 (m, 1H), 3.19 (d, J = 17.4 Hz, 0.32H), 3.10 (d, J = 16.4 Hz, 1.36H), 2.74 (m, 1.6H), 2.54 (dd, J = 7.92, 14.2 Hz, 0.67H), 1.95 (m, 0.36H), 1.45 (s, 3.5H), 1.38 (s, 5.48H). Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88. Found: C, 62.66; H, 6.64; N, 3.98.

The above crude **5a** was suspended in toluene (800 mL) and the mixture was heated at reflux for 2 h, which became a clear solution during this period. After cooling to room temperature, the reaction mixture was washed with a 1:1 mixture (400 mL) of saturated $NaHCO_3$ and saturated NaCl and then saturated NaCl (200 mL). The organic layer was dried over $MgSO_4$ and concentrated to dryness to afford 234.8 g of crude product **10**, which contained 15.6 wt % of toluene in this product based on the ^{1}H NMR spectrum. The corrected overall yield was 198.2 g (87%) from compound **7**. This crude product was used directly for the next step without any purification. Mp 72−73 °C. $[\alpha]_D^{25}$ +156.4° (*c* =1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (m, 2H), 7.32 (m, 3H), 6.30 (s, 1H), 4.22 (dd, J = 6.44, 7.96 Hz, 1H), 4.04 (m, 1H), 3.41 (t, J = 9.16 Hz, 1H), 3.00 (m, 1H), 2.80 (dd, J = 3.88, 16.24 Hz, 1H), 2.48 (dd, J = 10.0, 16.2 Hz, 1H), 2.26 (m, 1H), 2.10 (m, 1H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.8, 170.6, 138.8, 128.5, 125.8, 87.6, 70.6, 57.0, 40.8, 37.6, 28.0, 27.1. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.95; H, 7.24; N, 4.31.

(3*S*,5*S*)-3-[(*tert*-Butyloxycarbonyl)methyl]-5-[(methanesulfonyloxy)methyl]-2-pyrrolidinone (1). A solution of the above crude **10** (50 g, ∼85% purity, 134 mmol) in HOAc (100 mL), THF (150 mL), and water (50 mL) was heated at reflux

(10) Hamada, Y.; Hara, O.; Kawai, A.; Kohno, Y.; Shioiri, T. *Tetrahedron* **1991**, *47*, 8635.

(11) The C−O bond was cleaved and the corresponding *N*-benzyl product was obtained.

(12) (a) Nagasaka, T.; Imai, T. *Heterocycles* **1995**, *41*, 1927. (b) Nagasaka, T.; Imai, T. *Chem. Pharm. Bull.* **1995**, *43*, 1081.

(13) ^{1}H NMR spectrum of crude **11** revealed that ∼5% starting material **10** remained intact as well as some unidentified side-products.

(14) The chemical purity of **1** was determined by HPLC. Column: Inertsil ODS-2, 5 μm (150 × 4.6 mm). Temperature: 40 °C. Mobile phase: aq 0.1% H_3PO_4/MeCN (85:15). Flow rate: 1.2 mL/min. Detection: 201 nm. Retention time: 24.39 min (*trans*-**1**), 27.55 min (*cis*-**1**). The optical purity of **1** was determined by the ^{1}H NMR of the corresponding Mosher ester of **11** derived from both (5*S*)- and (5*R*)-**2**.

(15) For general procedures, see: Yee, N. K.; Nummy, L. J.; Byrne, D. P.; Smith, L. L.; Roth, G. P. *J. Org. Chem.* **1998**, *63*, 326

(internal temperature: 81 °C) overnight (18 h). The reaction mixture was then concentrated to dryness. After the residue was stripped from toluene (2 × 150 mL), it was dissolved in water (150 mL). The aqueous layer was washed with hexane (3 × 100 mL) and solid NaCl was added to saturate the aqueous layer. The aqueous layer was extracted with EtOAc (2 × 100 mL) and the combined organic layers were concentrated to dryness. The residue was stripped with toluene (2 × 100 mL) to give 31.6 g of crude alcohol **11**. Analytically pure sample was obtained by column chromatography. Mp 67−68 °C. $[\alpha]_D^{25}$ +10.34° (*c* 1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (s, 1H), 4.16 (t, J = 5.83 Hz, 1H), 3.69 (m, 1H), 3.62 (m, 1H), 3.43 (m, 1H), 2.80 (m, 1H), 2.67 (dd, J = 3.99, 16.4 Hz, 1H), 2.30 (dd, J = 9.28, 16.3 Hz, 1H), 2.11 (m, 1H), 1.93 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.6, 171.2, 80.9, 65.6, 54.3, 37.6, 36.9, 29.3, 28.1. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.42; H, 8.36; N, 6.11.

The crude alcohol **11** (20 g, max. 84.8 mmol) was dissolved in CH_2Cl_2 (300 mL) and the reaction mixture was cooled to 0 °C. Triethylamine (15 mL, 107 mmol) followed by methanesulfonyl chloride (11.0 g, 96 mmol) was added at the same temperature. After the reaction mixture was stirred at 0 °C for 1 h, water (200 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was treated with CH_2Cl_2 (20 mL) and MTBE (80 mL). Crystalline mesylate **1** was smoothly formed and collected by filtration to afford 17.2 g (66% yield from **10**) of the analytically pure product **1** as the first crop. The filtrate contained ∼10% of mesylate **1** and no attempt was made to obtain the second crop. Mp 114−117 °C. $[\alpha]_D^{25}$ +76.2 to 82.1° (*c* 5.03, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.00 (s, 1H), 4.21 (dd, J = 4.10, 10.24 Hz, 1H), 4.08 (dd, J = 6.71, 10.18 Hz, 1H), 3.93 (br s, 1H), 3.05 (s, 3H), 2.82 (m, 1H), 2.73 (dd, J = 3.86, 16.60 Hz, 1H), 2.35 (dd, J = 9.10, 16.60 Hz, 1H), 2.20 (m, 1H), 2.06 (m, 1H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.7, 170.8, 81.0, 71.0, 50.8, 37.4, 36.6, 36.5, 29.1, 28. Anal. Calcd for $C_{12}H_{21}NO_6S$: C, 46.89; H, 6.89; N, 4.56. Found: C, 46.92; H, 6.94; N, 4.43.

JO020433F