A Short, Efficient, and Stereoselective Procedure for the Synthesis of *cis*-3-Hydroxymethyl-aziridine-2-carboxylic Acid Derivatives, Important Intermediates in the Synthesis of Mitomycinoids

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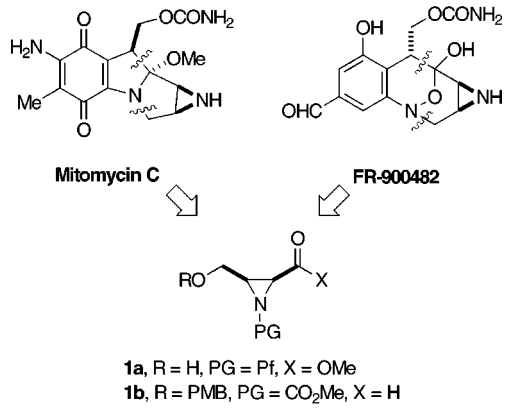
Received May 15, 2000

The mitomycinoid family of natural products (mitomycin C, FR-900482, and congeners) has attracted and retained the attention of the scientific community for a long time as a result of the high antitumor activity displayed by its members.[1] Mitomycin C is a widely prescribed antitumor agent with demonstrated clinical value,[1] and other congeners of mitomycin C and FR-900482 are advancing toward clinical application.[1,2] It is well established that the mitomycinoid's mode of antitumor action requires a bioreductive activation to provide an electrophilic mitosene capable to cross link DNA via alkylation at two electrophilic sites (the aziridine ring and the carbamoyloxy linkage). It can thus be seen that mitomycinoids are actually naturally occurring pro-drugs that must be activated in vivo.[3] This extraordinary antitumor activity along with mitomycinoid's unique structural features have attracted the interest of synthetic chemists; several approaches and a few total syntheses have been published.[4] We have been deeply fascinated by those synthetic programs involving a highly functionalized four-carbon building block **1**. Fragment **1**



1a, R = H, PG = Pf, X = OMe
1b, R = PMB, PG = CO_2Me, X = H

incorporates not only the very sensitive *cis*-aziridine ring present in the aliphatic portion of mitomycinoids but also two of the three stereogenic centers in the target molecules. Nevertheless, the reported procedures for the synthesis of **1** are low yielding and time-consuming. Thus, while Rapoport's synthesis of aziridine **1a** involves 12 steps (6% yield from L-methionine),[5] a synthesis of **1b** has been described more recently in 10 steps (21% yield from *cis*-2-butene-1,4-diol), but the final product was not enantiomerically pure (88% ee).[2] Here we present a short route to the enantiomerically pure aziridines **6** and **7**, hydroxyl-activated analogues of **1a**,[6] in only six steps and 47% yield from L-aspartic acid.

Several methods have been described in the literature for the synthesis of *cis*-aziridine-2-carboxylic acids.[7,8] We envisioned a straightforward route to **6** and **7** involving a regioselective cyclization of a suitable 3-amino-1,2-diol (**3**), as reported by Pericàs and Riera.[9] Aminodiol **3** should be easily accessible from hydroxyaspartate **2**, previously reported by us and ultimately derived from L-aspartic acid.[10]

Thus, chemoselective reduction of the α-hydroxyester function in **2** with $BH_3{\cdot}SMe_2$ in the presence of catalytic $NaBH_4$, as reported by Moriwake,[11] led to the desired diol **3** in 88% yield. Although $NaBH_4$ alone has also been reported for the selective reduction of α-hydroxyesters,[12] it proved to be less satisfactory.[13] Treatment of **3** with excess MsCl or TsCl gave the dimesylated and ditosylated products **4** and **5** in 97% and 83% yields, respectively.

(1) Danishefsky, S. J.; Schkeryantz, J. M. *Synlett* **1995**, 475.
(2) Williams, R. M.; Rollins, S. B.; Judd, T. C. *Tetrahedron* **2000**, *56*, 521.
(3) Rajski, S. R.; Williams, R. M. *Chem. Rev.* **1998**, *98*, 2723.
(4) Total syntheses: (a) Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. *Tetrahedron Lett.* **1977**, *18*, 4295. (b) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1987**, *109*, 7881. (c) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1989**, *111*, 8303. (d) Fukuyama, T.; Xu, L.; Goto, S. *J. Am. Chem. Soc.* **1992**, *114*, 383. (e) Schkeryantz, J. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4722. (f) Katoh, T.; Itoh, E.; Yoshino, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10229. (g) Yoshino, T.; Nagata, Y.; Itoh, E.; Hashimoto, M.; Katoh, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10239. (h) Katoh, T.; Nagata, Y.; Yoshino, T.; Nakatani, S.; Terashima, S. *Tetrahedron* **1997**, *53*, 10253.
(5) Jones, R. J.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 1144.
(6) The nucleophilic displacement of an activated derivative of the hydroxyl group in **1a** in the context of mitomycinoids' synthesis has been reported by Rapoport (ref 5).
(7) (a) Fujisawa, T.; Hayakawa, R.; Shimizu, M. *Tetrahedron Lett.* **1992**, *33*, 7903. (b) For a racemic synthesis of **1c** (R = MOM, PG = Tr, X = OEt) involving a lithiated aziridine see: Vedejs, E.; Moss, W. O. *J. Am. Chem. Soc.* **1993**, *115*, 1607. (c) For the synthesis of a *trans* analogue of **1** see: Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1994**, *59*, 7962. (d) Davis, F. A.; Zhou, P.; Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243 and references therein. (e) Davis, F. A.; Reddy, G. V.; Liu, H. *J. Am. Chem. Soc.* **1995**, *117*, 3651. (f) Cantrill, A. A.; Hall, L. D.; Jarvis, A. N.; Osborn, H. M. I.; Raphy, J.; Sweeney, J. B. *Chem. Commun.* **1996**, 2631. (g) Dauban, P.; Chiaroni, A.; Riche, C.; Dodd, R. H. *J. Org. Chem.* **1996**, *61*, 2488. (h) McLaren, A. B.; Sweeney, J. B. *Org. Lett.* **1999**, *1*, 1339. (i) For a synthesis of *N*-alkoxy analogues of **1** see: Hanessian, S.; Cantin, L.-D. *Tetrahedron Lett.* **2000**, *41*, 787.
(8) Reviews on aziridine synthesis: (a) Tanner, D. *Pure Appl. Chem.* **1993**, *65*, 1319. (b) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599. (c) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science Ltd.: New York, 1996; Vol. 1A, p 1. (d) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693. (e) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519.
(9) Poch, M.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1991**, *32*, 6935.
(10) Diester **2** was synthesised by diastereoselective hydroxylation of *N*-Pf-aspartate enolates (60%, three steps from L-aspartic acid) as described in (a) Fernández-Megía, E.; Paz, M. M.; Sardina, F. J. *J. Org. Chem.* **1994**, *59*, 7643. (b) Fernández-Megía, E.; Iglesias-Pintos, J. M.; Sardina, F. J. *J. Org. Chem.* **1997**, *62*, 4770. For alternative methods for the synthesis of hydroxyaspartates see: (c) Hanessian, S.; Vanasse, B. *Can. J. Chem.* **1993**, *71*, 1401 and references therein. (d) Charvillon, F. B.; Amouroux, R. *Synth. Commun.* **1997**, *27*, 395 and references therein. (e) Cardillo, G.; Gentilucci, L.; Tolomelli, A.; Tomasini, C. *Synlett* **1999**, 1727.
(11) Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389.
(12) Tsuboi, S.; Furutani, H.; Utaka, M.; Takeda, A. *Tetrahedron Lett.* **1987**, *28*, 2709.
(13) Lower yields of **3** (77%) along with some of the corresponding triol from overreduction (5%) were obtained.

10.1021/jo000732+ CCC: $19.00
Published on Web 09/09/2000

Scheme 1

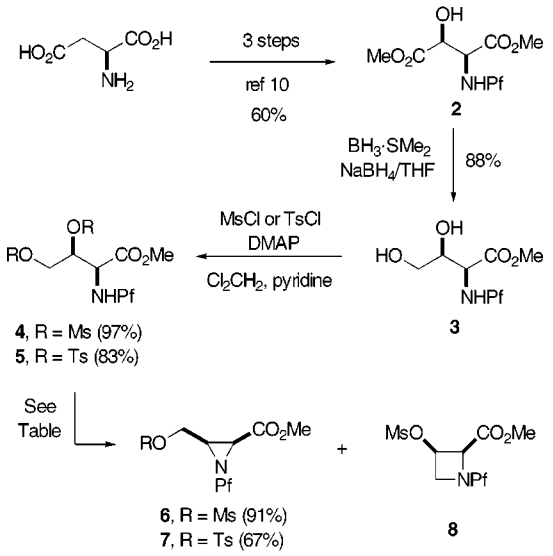
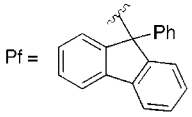


Table. Cyclization Conditions for Dimesylate 4

entry	conditions	T (°C)	ratio 6:8
1	THF-Et_3N	reflux	no reaction
2	DMF-Et_3N	80	4:1
3	DMF-Et_3N-$LiClO_4$	92	7:1
4	THF-Et_3N-$LiClO_4$	reflux	25:1 (71%)[a]
5	Dioxane- $LiClO_4$ s-Collidine	75	100:0 (91%)[a]

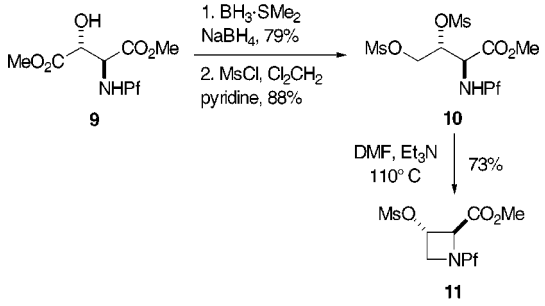
[a] Yield after column chromatography



Dimesylate **4** was subjected to the cyclization conditions summarized in Scheme 1. While treatment of **4** with THF−Et_3N at reflux gave no conversion to cyclized products (entry 1), the use of DMF as solvent afforded a 4:1 mixture of the desired aziridine **6** and the corresponding azetidine **8** (entry 2).[14,15] The introduction of $LiClO_4$ increased both reactivity and selectivity, and after careful optimization of conditions, aziridine **6** could be obtained as the sole reaction product in 91% yield (entry 5). Under identical reaction conditions, ditosylate **5** gave aziridine **7** exclusively (67% yield).[14] No products from sulfonate elimination reactions were detected.

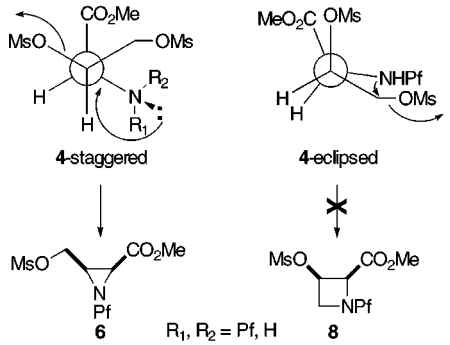
When the same reaction sequence was applied to the diastereomeric hydroxyaspartate **9** (also readily available in three steps from L-aspartic acid),[10a] dimesylate **10** was obtained in 70% overall yield.[16] However, in stark contrast with **4** and **5** and other literature precedents,[9]

Scheme 2



when dimesylate **10** was subjected to several different cyclization conditions, azetidine **11** was always found as the exclusive product (Scheme 2).[15] The corresponding *trans*-aziridine **12** was never observed, even under those conditions (THF−Et_3N, $LiClO_4$, reflux) most favorable for the formation of the diastereomeric *cis*-aziridine **6**. Again, as reported for **6** and **7**, no elimination products were detected in this reaction.

The different outcomes on the cyclization reactions of **4** (and **5**) and **10** have been rationalized by inspection of the Newman projections of the required conformations involved for the ring closure of each stereoisomer. Thus, the cyclization of **4** (and **5**) should proceed mainly through the staggered conformation to provide the aziridine **6** (and **7**), since the eclipsed conformation that leads to azetidine **8** has two very unfavorable interactions (CO_2Me-OMs and NHPf-CH_2OMs). The addition of $LiClO_4$ favors the formation of the aziridine over the azetidine, probably by chelation of the Li cation with both mesylate groups. Although this point has not been demonstrated, the proposed chelation could explain the change in selectivity by placing the primary mesylate away from the trajectory of the nucleophile and therefore increasing the selectivity of the cyclization through the staggered conformation. According to this proposal, the $LiClO_4$ effect increases when the complexing ability of the solvent decreases (compare entries 3 and 5).



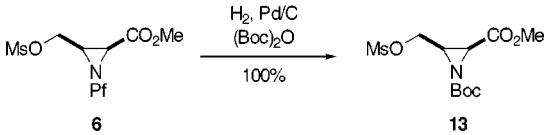
In the case of dimesylate **10**, the cyclization to give aziridine **12** should proceed through the staggered conformation. Here, as the nucleophile approaches C3, the bulky Pf group must eclipse either the CH_2OMs or the carboxymethyl group. These unfavorable interactions force the cyclization to proceed through the eclipsed conformation to give azetidine **11**. The lower bulkiness of the diphenylmethyl nitrogen protecting group in the

(14) Aziridines **6** and **7** were characterized according to their ^{1}H and ^{13}C NMR spectroscopic data and by comparison with compound **1a** (ref 5). See also ref 8c.

(15) Azetidines **8** and **11** were characterized according to their ^{1}H and ^{13}C NMR spectroscopic data and by comparison with reported data in the literature: (a) Duréault, A.; Portal, M.; Carreaux, F.; Depezay, J. C. *Tetrahedron* **1993**, *49*, 4201. (b) Blythin, D. J.; Green, M. J.; Lauzon, M. J. R.; Shue, H.-J. *J. Org. Chem.* **1994**, *59*, 6098. (c) De Kimpe, N. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science Ltd.: New York, 1996; Vol. 1B, p 507. For syntheses of azetidine-2-carboxylic acid derivatives see also: (d) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1994**, *50*, 265. (e) Rutjes, F. P. J. T.; Tjen, K. C. M. F.; Wolf, L. B.; Karstens, W. F. J.; Schoemaker, H. E.; Hiemstra, H. *Org. Lett.* **1999**, *1*, 717. (f) Hanessian, S.; Bernstein, N.; Yang, R.-Y.; Maguire, R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1437 and references therein.

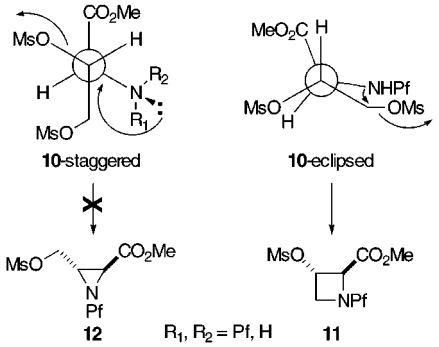
(16) The use of other reducing agents such as $NaBH_4$ or DIBALH led to the formation of substantial amounts of the corresponding γ-butyrolactone.

Scheme 3



6 **13**

examples reported by Pericàs and Riera could explain the formation of *trans*-aziridines there.[9]



At this point, there was an important question to address: the deprotection of the Pf group. Despite the reported difficulty of the hydrogenolytic deprotection of *N*-benzyl aziridines due to easy ring opening,[8c,17] the Pf group in **6** was successfully removed [H_2, 50 psi, Pd/C, $(Boc)_2O$] affording the corresponding *N*-Boc-aziridine **13** quantitatively (Scheme 3).[18]

In conclusion, an efficient route to the mesylated and tosylated *N*-Pf aziridines **6** and **7** has been described in three steps from aspartate **2** (six steps from L-aspartic acid). Under closely related conditions, azetidine **11** was obtained from aspartate **9**. The easy deprotection of the Pf group in **6** should spread the use of these building blocks in future synthetic programs directed toward mitomycinoids.

Experimental Section

General Methods. General experimental aspects have been published elsewhere.[19] *N*-Phenylfluorenyl-hydroxyaspartates **2** and **9** were prepared according to the published procedure.[10]

Methyl (2*S*,3*S*)-3,4-Dihydroxy-2-(9′-phenylfluoren-9′-ylamino)butyrate (3). A solution of BH_3·SMe_2 in THF (75 μL, 3.3 M, 0.31 mmol, 120 mol %) was added to a solution of hydroxyaspartate **2** (100 mg, 0.26 mmol) in THF (0.5 mL) at room temperature. The mixture was stirred for 30 min, and then $NaBH_4$ (1 mg) was added. Stirring was continued for 46 h, then MeOH and KH_2PO_4 were added, and the resulting suspension was stirred for an additional 30 min. Four such reactions were pooled, and the mixture was concentrated. The residue was purified by column chromatography (silica gel, EtOAc/hexanes 1/0.8) to give **3** (331 mg, 88%) as a white foam: $[\alpha]^{20}_D = -272.3$ (*c* 1.11, $CHCl_3$); ^{1}H NMR δ 7.71−7.68 (m, 2H), 7.38−7.33 (m, 5H), 7.27−7.23 (m, 5H), 7.17 (d, J = 7.6 Hz, 1H), 3.55−3.49 (m, 2H), 3,34 (dd, J = 3.2 Hz, J = 11.2 Hz, 1H), 3.31 (s, 3H), 2.69 (d, J = 5.8 Hz, 1H); ^{13}C NMR δ 174.1, 147.9, 147.4, 143.3, 141.1, 140.2, 128.8, 128.6, 128.5, 128.3, 127.5, 127.4, 126.5, 125.8, 125.0, 120.2, 120.0, 72.6, 71.5, 63.4, 57.7, 52.0; MS (FBA, positive ion) *m*/*z* (relative intensity) 390 ([M + H]$^+$, 2), 241 (100). Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.0; H, 6,0; N, 3.6. Found: C, 73.6; H, 6.2; N, 3.4.

Methyl (2*S*,3*R*)-3,4-Dihydroxy-2-(9′-phenylfluoren-9′-ylamino)butyrate. The same procedure as above was used, starting from hydroxyaspartate **9** (135 mg, 0.324 mmol). Reaction time was 31 h. The (2*S*,3*R*) diol (99 mg, 79%) was obtained as a white foam: $[\alpha]^{20}_D = -296.6°$ (*c* 1.52, $CHCl_3$); IR (film, cm^{-1}) 3369, 1729; ^{1}H NMR δ 7.73−7.67 (m, 2H), 7.39−7.14 (m, 11H), 3.68−3.56 (m, 3H), 3.25 (s, 3H), 2.82 (bs, 1H), 2.67 (d, J = 7.0 Hz, 1H); ^{13}C NMR δ 175.1, 148.4, 148.1, 143.7, 141.2, 140.3, 128.8, 128.6, 128.4, 128.2, 127.5, 127.4, 126.1, 125.9, 124.9, 120.3, 120.1, 72.9, 72.6, 64.0, 58.0, 51.7. Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.0; H, 6,0; N, 3.6. Found: C, 73.7; H, 6.3; N, 3.5.

Methyl (2*S*,3*S*)-3,4-Bismethanosulfoniloxy-2-(9′-phenylfluoren-9′-ylamino)butyrate (4). MsCl (200 μL, 2.571 mmol, 404 mol %) was added to a solution of **3** (247 mg, 0.635 mmol), DMAP (7.5 mg, 0.063 mmol, 10 mol %), and pyridine (0.309 mL, 3.81 mmol, 600 mol %) in CH_2Cl_2 (1.35 mL). The resulting solution was stirred for 12 h at room temperature, and then it was partitioned between CH_2Cl_2 (100 mL) and saturated $NaHCO_3$ (100 mL). The aqueous layer was back extracted with CH_2Cl_2 (75 mL), and the combined organic extracts were washed with 10% aqueous H_3PO_4 (75 mL) and brine (75 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (silica gel, EtOAc/hexanes 1/1.8) to give **4** (335 mg, 97%) as a white foam: $[\alpha]^{20}_D = -184.2°$ (*c* 1.72, $CHCl_3$); ^{1}H NMR δ 7.70 (t, J = 7.3 Hz, 2H), 7.45−7.18 (m, 11H), 4.78−4.75 (m, 1H), 4.58 (dd, J = 8.1 Hz, J = 11.4 Hz, 1H), 4.09 (dd, J = 3.0 Hz, J = 11.4 Hz, 1H), 3.38 (s, 3H), 3.32 (d, J = 9.9 Hz, 1H), 3.00 (s, 3H), 2.98 (s, 3H), 2.80 (dd, J = 3.1 Hz, J = 10.0 Hz, 1H); ^{13}C NMR δ 171.7, 147.8, 147.2, 143.2, 140.9, 140.0, 128.8, 128.7, 128.4, 128.2, 127.5, 127.4, 126.4, 125.9, 125.4, 120.1, 120.0, 79.1, 72.5, 67.7, 55.9, 52.2, 38.5. 37.4; MS (FBA, positive ion) *m*/*z* (relative intensity) 546 ([M + H]$^+$, 3), 241 (100). Anal. Calcd for $C_{26}H_{27}NO_8S_2$: C, 57.2; H, 5.0; N, 2.6. Found: C, 57.3; H, 4.8; N, 2.3.

Methyl (2*S*,3*R*)-3,4-Bismethanosulfoniloxy-2-(9′-phenylfluoren-9′-ylamino)butyrate (10). The same procedure as above was used, starting from the (2*S*,3*R*) diol (165 mg, 0.424 mmol). The reaction time was 5 h. Compound **10** (204 mg, 88%) was obtained as a white foam: $[\alpha]^{20}_D = -247.5°$ (*c* 0.96, $CHCl_3$); IR (KBr, cm^{-1}) 1740, 1449, 1349; ^{1}H NMR δ 7.73 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.41−7.34 (m, 5H), 7.29−7.23 (m, 5H), 7.15 (d, J = 7.5 Hz, 1H), 4.78 (ddd, J = 3.0 Hz, J = 5.7 Hz, J = 7.7 Hz, 1H), 4.60 (dd, J = 3.0 Hz, J = 11.5 Hz, 1H), 4.39 (dd, J = 5.8 Hz, J = 11.4 Hz, 1H), 3.33 (s, 3H), 3. 20 (d, J = 10.1 Hz, 1H), 2.97 (s, 3H), 2.93 (s, 3H), 2.87 (dd, J = 7.8 Hz, J = 10.1 Hz, 1H); ^{13}C NMR δ 172.8, 147.6, 147.5, 143.3, 141.3, 139.9, 128.8, 128.6, 128.5, 127.7, 127.6, 125.9, 125.8, 125.6, 120.2 (2 × C), 79.5, 72.7, 66.8, 55.7, 52.5, 38.7, 37.7; MS (FBA, positive ion) *m*/*z* (relative intensity) 546 ([M + H]$^+$, 0.2), 241 (59), 155 (100). Anal. Calcd for $C_{26}H_{27}NO_8S_2$: C, 57.2; H, 5.0; N, 2.6. Found: C, 57.2; H, 4.9; N, 2.5.

Methyl (2*S*,3*S*)-3,4-Bis-*p*-toluensulfonyloxy-2-(9′-phenylfluoren-9′-ylamino)butyrate (5). TsCl (94 mg, 0.49 mmol, 400 mol %) was added to a solution of **3** (48 mg, 0.12 mmol), DMAP (1.6 mg, 0.012 mmol, 10 mol %), and pyridine (0.06 mL, 3.81 mmol, 600 mol %) in CH_2Cl_2 (0.3 mL). The resulting solution was stirred for 10 h at room temperature, then it was partitioned between CH_2Cl_2 (25 mL) and 10% aqueous NaOH (25 mL). The aqueous layer was back extracted with CH_2Cl_2 (25 mL), and the combined organic layer was washed with 10% aqueous H_3PO_4 (25 mL) and brine (25 mL), dried, and concentrated to afford a residue, which was purified by column chromatography (silica gel, EtOAc/hexanes 1/2.5) to give **5** as a white solid (71 mg, 83%): mp 175−178 °C; $[\alpha]^{20}_D = -76.0°$ (*c* 0.83, $CHCl_3$); IR (KBr, cm^{-1}) 1745, 1348; ^{1}H NMR δ 7.8−7.1 (m, 13H), 4.54 (m, 1H), 4.10 (ddd, J = 4.1 Hz, J = 6.9 Hz, J = 11.3 Hz, 2H), 3.30 (s, 3H), 3.20 (d, J = 8.4 Hz, 1H), 2.80 (dd, J = 3.5 Hz, J = 5.3 Hz, 1H); ^{13}C NMR δ 172.2, 148.4, 147.9, 145.5, 145.4, 144.0, 141.5, 140.4, 133.5, 132.8, 130.3, 130.1, 129.2, 129.1, 128.8, 128.6, 128.5, 128.4, 127.9, 127.8, 126.8, 126.4, 125.7, 120.6, 120.4, 79.6, 73.1, 68.2, 56.3, 52.7, 22.1. Anal. Calcd for $C_{38}H_{35}NO_8S_2$: C, 65.4; H, 5.1; N, 2.0. Found: C, 65.3; H, 5.2; N, 2.1.

Methyl (2*S*,3*R*)-3-Methanosulfonyloxymethyl-1-(9′-phenylfluoren-9′-yl)aziridine Carboxylate (6). A suspension of **4** (137 mg, 0.343 mmol), $LiClO_4$ (365 mg, 3.43 mmol, 1000 mol %), and *s*-collidine (100 μL, 0.69 mmol, 200 mol %) in dioxane (2.3 mL) was stirred at 70 °C for 8 h. The reaction mixture was

(17) Ambrosi, H.-D.; Duczek, W.; Ramm, M.; Jähnisch, K. *Tetrahedron Lett.* **1994**, *35*, 7613.

(18) For the successful deprotection of a *N*-trityl aziridine-2-carboxylate see: Korn, A.; Rudolph-Böhner, S.; Moroder, L. *Tetrahedron* **1994**, *50*, 1717.

(19) Blanco, M.-J.; Sardina, F. J. *J. Org. Chem.* **1996**, *61*, 4748.

allowed to reach room temperature, and then it was partitioned between EtOAc (50 mL) and 5% aqueous HCl (50 mL). The aqueous layer was back extracted with EtOAc (20 mL), and the combined organic layer was washed with brine (30 mL), dried, and concentrated. The residue was purified by column chromatography (silica gel, EtOAc/hexanes 1/3) to give **6** (102 mg, 91%) as a white solid: mp 164 °C; $[\alpha]^{20}_D = -92.2°$ (*c* 1.33, $CHCl_3$); IR (KBr, cm^{-1}) 1737, 1348; ^1H NMR δ 7.71 (t, $J = 7.5$ Hz, 2H), 7.44−7.12 (m, 11H), 4.31 (dd, $J = 6.3$ Hz, $J = 10.8$ Hz, 1H), 4.20 (dd, $J = 5.8$ Hz, $J = 10.7$ Hz, 1H), 3.73 (s, 3H), 2.81 (s, 3H), 2.54 (d, $J = 6.2$ Hz, 1H), 1.95 (q, $J = 6.1$ Hz, 1H); ^{13}C NMR δ 169.3, 147.6, 144.5, 142.2, 141.5, 139.8, 129.3, 128.9, 128.3, 128.1, 127.6, 127.4, 126.8, 126.2, 125.8, 120.3, 120.1, 75.4, 67.3, 52.2, 37.3, 37.2, 37.0. Anal. Calcd for $C_{25}H_{23}NO_5S$: C, 66.8; H, 5.2; N, 3.1. Found: C, 66.7; H, 5.3; N, 3.1. Azetidine **8** was isolated in small amounts from reactions in which DMF was used as solvent: mp 160 °C; $[\alpha]^{20}_D = -103.5°$ (*c* 1.20, $CHCl_3$); IR (NaCl, cm^{-1}) 1751, 1350; ^1H NMR δ 7.76 (d, $J = 7.4$ Hz, 1H), 7.63 (d, $J = 7.4$ Hz, 1H), 7.53−7,14 (m, 11H), 4.99 (dt, $J = 3.0$ Hz, $J = 6.9$ Hz, 1H), 3.83−3.75 (m, 2H), 3.69 (d, $J = 7.6$ Hz, 1H), 3.45 (s, 3H), 2.96 (s, 3H); ^{13}C NMR δ 168.4, 146.3, 144.8, 142.0, 140.5, 139.6, 129.2, 128.8, 128.5, 127.8, 127.7, 127.6, 127.4, 127.1, 126.2, 120.3, 119.7, 75.5, 69.2, 63.5, 53.9, 51.6, 38.5. Anal. Calcd for $C_{25}H_{23}NO_5S$: C, 66.8; H, 5.2; N, 3.1. Found: C, 66.4; H, 5.0; N, 3.3.

Methyl (2*S*,3*R*)-3-*p*-Toluensulfonyloxymethyl-1-(9′-phenylfluoren-9′-yl)aziridine Carboxylate (7). The same procedure as above was used, starting from ditosylate **5** (126 mg, 0.138 mmol). Reaction time was 5 h. Compound **7** (64 mg, 67%) was obtained as a white solid: mp 173 °C; $[\alpha]^{20}_D = -105.5°$ (*c* 0.55, $CHCl_3$); IR (KBr, cm^{-1}) 1750, 1365; ^1H NMR δ 7.47−7.16 (m, 13H), 4.4 (m, 1H), 4.13 (m, 2H) 3.67 (s, 3H), 2.68 (s, 3H), 2.44 (d, $J = 6.3$ Hz, 1H); ^{13}C NMR δ 169.4, 147.6, 145.2, 145.0, 142.6, 141.8, 140.3, 133.3, 130.2, 129.6, 129.4, 128.8, 128.5, 128.3, 128.0, 127.7, 127.2, 126.6, 126.2, 120.6, 120.5, 75.8, 68.2, 52.6, 38.0, 37.8, 30.1, 21.1. Anal. Calcd for $C_{31}H_{27}NO_5S$: C, 70.8; H, 5.2; N, 2.7. Found: C, 70.6; H, 5.5; N,3.0.

Methyl (2*S*,3*S*)-3-Methanosulfonyloxy-1-(9′-phenylfluoren-9′-yl)azetidine Carboxylate (11). A solution of dimesylate **10** (40 mg, 0.073 mmol) and Et_3N (51 μL, 0,37 mmol, 500 mol %) in DMF (0.24 mL) was stirred at 110 °C for 7 h. The reaction mixture was allowed to reach room temperature, and then it was partitioned between EtOAc (30 mL) and 5% aqueous HCl (25 mL). The aqueous layer was back extracted with EtOAc (10 mL), and the combined organic layer was washed with H_2O (3 × 15 mL) and brine (20 mL), dried, and concentrated. The residue was purified by column chromatography (silica gel, EtOAc/hexanes 1/2.5) to give **11** (24 mg, 73%) as an oil, which crystallized on standing: mp 169 °C; $[\alpha]^{20}_D = -106.5°$ (*c* 0.55, $CHCl_3$); IR (KBr, cm^{-1}) 1747, 1355; ^1H NMR δ 7.77 (d, $J = 7.5$ Hz, 1H), 7.68 (d, $J = 7.5$ Hz, 1H), 7.47−7.16 (m, 11H), 5.07 (q, $J = 6.2$ Hz, 1H), 3.68 (t, $J = 7.3$ Hz, 1H), 3.47 (d, $J = 5.5$ Hz, 1H), 3.29 (s, 3H), 3.23 (t, $J = 6.9$ Hz, 1H), 2.84 (s, 3H); ^{13}C NMR δ 170.3, 145.4, 144.4, 141.6, 140.5, 140.4, 129.1, 128.9, 128.4, 127.7, 127.6, 127.5, 127.2, 126.7, 126.4, 120.4, 120.1, 75.7, 69.0, 66.6, 53.4, 51.8, 37.7. Anal. Calcd for $C_{25}H_{23}NO_5S$: C, 66.8; H, 5.2; N, 3.1. Found: C, 66.9; H, 5.1; N,3.0.

Methyl (2*S*,3*R*)-3-Methanosulfonyloxymethyl-1-(*tert*-butoxycarbonyl)aziridine Carboxylate (13). A suspension of **6** (63 mg, 0.14 mmol), Boc_2O (122 mg, 0.56 mmol, 400 mol %), and Pd/C (10 w%, 10 mg) in deoxygenated CH_3OH (4 mL) was shaken under a pressure of 50 psi of H_2 for 15 h. The reaction mixture was filtered through a pad of Celite. The filtrate and the washings were concentrated to a residue, which was purified by column chromatography (silica gel, EtOAc/hexanes 1/4) to give **13** (41 mg, quant.) an oil: $[\alpha]^{20}_D = -122.3°$ (*c* 1.32, $CHCl_3$); IR (KBr, cm^{-1}) 2935, 1752, 1525; ^1H NMR (2 rotamers in a 1/1.8 ratio) δ 4.75 (dd, $J = 6.0$ Hz, $J = 11.6$ Hz, 1H), 4.29 (dd, $J = 6.6$ Hz, $J = 11.6$ Hz, 1H), 4.30−4.22 (m, 1 H), 3.74 and 3.64 (s, 3H), 3.00 and 2.97 (s, 3H), 3.17 and 2.60 (d, $J = 6.28$, $J = 5.65$, 1H), 1.39 and 1.37 (s, 9H); ^{13}C NMR δ 167.5, 159.4, 83.7, 66.3, 53.2, 40.1, 39.0, 38.2, 28.1. Anal. Calcd for $C_{11}H_{19}NO_7S$: C, 42.7; H, 6.2; N, 4.5. Found: C, 42.6; H, 6.0; N,4.9.

Acknowledgment. Financial support from the CICYT (Spain, grant SAF99-0127) and the *Xunta de Galicia* (grant XUGA 20912B96) is gratefully acknowledged, as well as fellowships from the *Xunta de Galicia* and the Universidad de Santiago de Compostela (to E.F.-M.). We also thank Prof. Rafael Suau (Universidad de Málaga, Spain) for the elemental analyses.

JO000732+