A short synthesis of the taxotere side chain through dilithiation of boc-benzylamine. J Org Chem 58: 255

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · JANUARY 1993

Impact Factor: 4.72 · DOI: 10.1021/jo00053a048

5 AUTHORS, INCLUDING:

Arlene Correa
Universidade Federal de São Carlos
107 PUBLICATIONS **1,130** CITATIONS

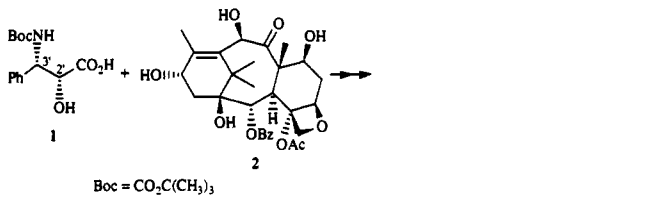
A Short Synthesis of the Taxotere Side Chain through Dilithiation of Boc-benzylamine

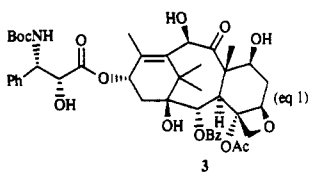
Alice M. Kanazawa, Arlene Correa, Jean-Noël Denis, Marie-Jacqueline Luche, and Andrew E. Greene*

Université Joseph Fourier de Grenoble, Chimie Recherche (LEDSS), Domaine Universitaire, BP 53X, 38041 Grenoble Cedex, France

Received August 25, 1992

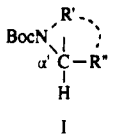
Taxotere (3, eq 1), a taxol analogue obtainable from 10-desacetyl baccatin III (2),[1] is emerging as the most promising cancer chemotherapeutic agent among the known natural and semisynthetic taxanes.[2] Having already developed an effective procedure for esterifying 10-desacetyl baccatin III with the taxotere side chain 1 (both



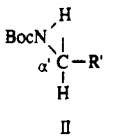


in suitably protected form) for the preparation of taxotere,[1b-e] we have recently been examining various alternative approaches for obtaining the enantiomerically pure 2′*R*,3′*S* acid.[3] We now report a novel synthesis of this side chain based on the use of the dianion of *tert*-butoxycarbonyl (Boc)-benzylamine.

While Boc N,N-disubstituted amine derivatives (I)[4] and similar compounds[5] have been found by several groups



I



II

over the last few years to undergo clean α′-lithiation in the presence of organometallic reagents, the corresponding N-monosubstituted derivatives (II) have received remarkably little study in this context.[6] Nevertheless, it seemed reasonable to expect that Boc-benzylamine would suffer lithiation at the benzyl position (and on nitrogen), in that *N*-benzylbenzamide was known to experience this conversion.[7] In this event, the addition of an unsaturated aldehyde might then lead to a predominantly syn amino alcohol derivative that could be manipulated to provide the requisite side chain. The realization of this sequence of transformations, *which has resulted in a synthesis of the taxotere side chain in esterification-ready form in only three chemical steps from Boc-benzylamine*, is described below.

Boc-benzylamine (4, Scheme I) in the presence of 3.0 equiv of *sec*-butyllithium and 2.1 equiv of tetramethylethylenediamine in THF at −78 °C is, in fact, converted to the desired dianion: the addition of 2.2 equiv of freshly distilled acrolein to the relatively stable,[8] deep-red intermediate produces the syn and anti amino alcohol derivatives 5 in 49% combined yield and in a 6:1 ratio. This syn preference (consistent with a chelated transition state in which steric interactions are minimized) and the yield, taken together, were most satisfactory under these conditions. Several other base–solvent combinations (*sec*-butyllithium in diglyme or ether–TMEDA; LDA in diglyme)[7] and electrophiles (benzaldehyde, crotonaldehyde, cyclohexyl glyoxylate, furfural) were also tested in this reaction, but led to significantly poorer diastereoselection and/or lower yield.

Initially, the syn isomer, separated from the mixture by silica gel chromatography, was converted to its ethoxyethyl ether (87% yield), which was then oxidized under slightly modified Sharpless conditions[3] to provide in 77% yield the racemic syn acid (Scheme I). (+)-Ephedrine was found to be the best of several resolving agents examined and provided the ethoxyethyl-protected side chain (+)-6,[3] which had previously been used for the esterification of 10-desacetyl baccatin III.[1b] Unfortunately, however, the resolution yielded only 50% of the theoretical amount of the 2′*R*,3′*S* acid. In that it seemed likely the presence of methyl epimers (55:45 ratio) was having a deleterious effect on the efficiency of this resolution, the (trichloroethoxy)-methyl group, which had been used with considerable success in our earlier taxotere–taxol work,[1c] was next examined in this approach.

The (trichloroethoxy)methyl-protected *syn*-5 could be readily prepared in 70% yield by reaction of purified *syn*-5 with (2,2,2-trichloroethoxy)methyl bromide in acetonitrile in the presence of proton sponge.[9] On oxidative cleavage, as before, this material was smoothly converted to the pure racemic acid in 80% yield. As had been expected, the resolution of this acid was facile and furnished the enantiomerically pure (≥99%)[10] protected taxotere side chain 7 in 83% of the theoretical yield. Even more satisfying, however, was the discovery that the racemic

(1) (a) Mangatal, L.; Adeline, M.-T.; Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Tetrahedron* **1989**, *45*, 4177–4190. (b) Colin, M.; Guénard, D., Guéritte-Voegelein, F.; Potier, P. U.S. Patent (Rhône-Poulenc Santé) 4924012, May 8, 1990. (c) Denis, J-N.; Greene, A. E., Fr. Appl. (Rhône-Poulenc Rorer S.A.) 91/10,398, Aug 19, 1991. (d) See also: Denis, J-N.; Greene, A. E.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917–5919. (e) Denis, J-N., Greene, A. E.; Guénard, D.; Guéritte-Voegelein, F. U.S. Patent (Centre National de la Recherche Scientifique) 4924011, May 8, 1990.

(2) Bissery, M-C.; Guénard, D.; Guéritte-Voegelein, F.; Lavelle, F. *Cancer Res.* **1991**, *51*, 4845–4852. Guéritte-Voegelein, F.; Guénard, D.; Lavelle, F.; Le Goff, M-T.; Mangatal, L.; Potier, P. *J. Med. Chem.* **1991**, *34*, 992–998.

(3) For previous methods of preparation see: Denis, J-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1991**, *56*, 6939–6942, and references cited therein.

(4) Beak, P.; Lee, W. K. *J. Org. Chem.* **1990**, *55*, 2578–2580. Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708–9710.

(5) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471–523.

(6) For examples of ortho lithiation of Boc-anilines, see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933. For dilithiation of Boc-2-alkylanilines, see: Clark, R. D.; Muchowski, J. M.; Fisher, L. E.; Flippin, L. A.; Repke, D. B.; Souchet, M. *Synthesis* **1991**, 871–878.

(7) Tischler, A. N.; Tischler, M. H. *Tetrahedron Lett.* **1978**, 3–4. See also: Simig, G.; Schlosser, M. *Ibid.* **1988**, *29*, 4277–4280.

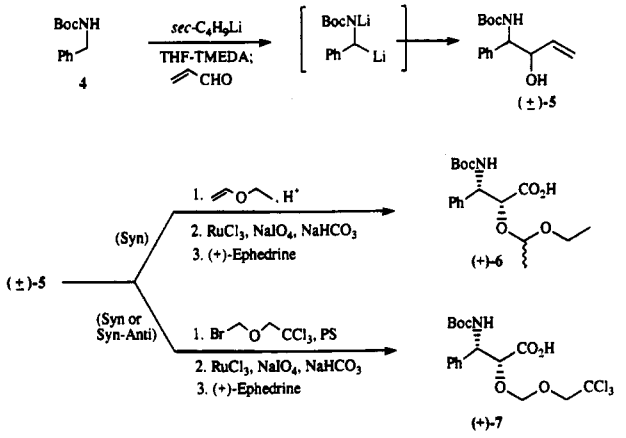
(8) Boc-benzylamine is recovered in 95% yield on protonation of the dianion after 2 h at −78 °C.

(9) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031.

(10) Determined by ^{19}F NMR analysis of the Mosher ester of the alcohol derived from the methyl ester (CH_2N_2; Zn–Cu, CH_3CO_2H–CH_3OH). See: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

0022-3263/93/1958-0255$04.00/0

Scheme I[a]



[a] Boc = $CO_2C(CH_3)_3$; PS = proton sponge.

mixture of syn and anti diastereomers **5**, on subjection to the above reaction sequence, also provided diastereomerically and enantiomerically pure **7**, and in comparable overall yield. This alternative, in which the removal of the racemic anti derivative is effected simultaneously with the resolution of the syn compound, is distinctly advantageous in that it obviates a tedious chromatographic separation of the syn and anti diastereomers of **5**.

In summary, a novel and exceptionally direct synthesis of the pure, esterification-ready taxotere side chain has been effected from Boc-benzylamine.[11] The approach, easily and rapidly carried out (no chromatography separations), may prove to be the most practical for obtaining this highly important compound.

Experimental Section[12]

1,1-Dimethylethyl (*N*-Benzylamino)methanoate (4). To a stirred solution of 20.9 mL (20.5 g, 191 mmol) of benzylamine and 39.8 mL (28.9 g, 286 mmol) of triethylamine in 500 mL of CH_2Cl_2 was added portion-wise 50.0 g (229 mmol) of di-*tert*-butyl dicarbonate. After being stirred for 2 h at 20 °C, the reaction mixture was processed in the usual manner and the crude product was purified by crystallization from hexane and by silica gel chromatography of the resulting mother liquors with 5% ethyl acetate in CH_2Cl_2 to give 37.8 g (96%) of **4**: mp 55.5–56.5 °C (hexane); ^{1}H NMR (300 MHz) δ 7.34–7.22 (m, 5 H), 4.84 (br s, 1 H), 4.30 (d, J = 5.7 Hz, 2 H), 1.46 (s, 9 H); ^{13}C NMR (50.3 MHz) δ 155.84 (C), 138.93 (C), 128.54 (CH), 127.41 (CH), 127.27 (CH), 79.43 (C), 44.69 (CH_2), 28.38 (CH_3); IR 3350, 3315, 1680, 1550, 1450, 1290, 1255, 1180 cm^{-1}. Anal. Calcd for $C_{12}H_{17}O_2N$: C, 69.54; H, 8.27. Found: C, 69.44; H, 8.50.

(±)-1,1-Dimethylethyl [*N*-[(1*RS*,2*RS*)-2-Hydroxy-1-phenyl-3-butenyl]amino]methanoate ((±)-*syn*-5) and (±)-1,1-Dimethylethyl [*N*-[(1*RS*,2*SR*)-2-Hydroxy-1-phenyl-3-butenyl]amino]methanoate ((±)-*anti*-5). A stirred solution of 4.20 g (20.3 mmol) of carbamate **4** and 6.50 mL (5.01 g, 43.1 mmol) of tetramethylethylenediamine in 40 mL of THF at −78 °C was treated dropwise with 60.0 mL (60.0 mmol) of a 1 M solution of *sec*-butyllithium in hexane. After being stirred for 3 h at this temperature, the reaction mixture was cooled to −100 °C and treated with 3.0 mL (2.5 g, 44.9 mmol) of freshly distilled acrolein. The resulting mixture was stirred for 3 min at −100 °C and then for 3 h at −78 °C. The crude product was isolated with ether in the usual way and purified by filtration over silica gel with 5% ether in CH_2Cl_2 to provide 2.61 g (49%) of a ca. 6:1 mixture (^{1}H NMR) of (±)-*syn*-**5** and (±)-*anti*-**5**. Separation of these diastereomers could be effected by silica gel chromatography with ether–hexane–dichloromethane (5:45:50). (±)-*syn*-**5**: mp 86.5–88 °C (hexane); ^{1}H NMR (300 MHz) δ 7.37–7.24 (m, 5 H), 5.86 (ddd, J = 5.4, 10.5, 17.2 Hz, 1 H), 5.34 (dt, J = 1.4, 17.2 Hz, 1 H), 5.26 (br s, 1 H), 5.20 (dt, J = 1.4, 10.5 Hz, 1 H), 4.70 (br s, 1 H), 4.38 (pseudo t, J = 4.6, 4.8 Hz, 1 H), 1.90 (br s, 1 H), 1.40 (s, 9 H); ^{13}C NMR (50.3 MHz) δ 155.89 (C), 139.96 (C), 137.17 (CH), 128.32 (CH), 127.26 (CH), 126.69 (CH), 116.36 (CH_2), 79.58 (C), 75.33 (CH), 58.74 (CH), 28.12 (CH_3); IR 3400, 1690, 1500, 1365, 1175 cm^{-1}; mass spectrum (CI) m/z 321 (M^+ + isobutane), 281 (MH^+ + NH_3), 264 (MH^+, 100%), 246, 225, 208, 190, 164, 124, 106. Anal. Calcd for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.15; H, 7.98; N, 5.34. (±)-*anti*-**5**: mp 150–151 °C; ^{1}H NMR (300 MHz) δ 7.36–7.24 (m, 5 H), 5.71 (ddd, J = 5.5, 10.5, 17 Hz, 1 H), 5.26 (dt, J = 1.2, 17 Hz, 1 H), 5.24 (br s, 1 H), 5.18 (dt, J = 1.2, 10.5 Hz, 1 H), 4.78 (br s, 1 H), 4.43 (pseudo q, J = 0.9, 4.4 Hz, 1 H), 1.8 (br s, 1 H), 1.41 (s, 9 H); ^{13}C NMR (50.3 MHz) δ 155.61 (C), 138.14 (C), 136.27 (CH), 128.33 (CH), 127.56 (CH), 127.29 (CH), 117.06 (CH_2), 79.85 (C), 75.33 (CH), 59.22 (CH), 28.23 (CH_3); IR 3370, 1680, 1530, 1290, 1250, 1170 cm^{-1}. Anal. Calcd for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.43, H, 8.14; N, 5.08.

(2*R*,3*S*)-(+)-3-[[*N*-(1,1-Dimethylethoxy)carbonyl]amino]-2-(1-ethoxyethoxy)-3-phenylpropanoic Acid ((+)-6). A solution of 526 mg (2.00 mmol) of (±)-*syn*-**5** and 50.2 mg (0.20 mmol) of pyridinium *p*-toluenesulfonate in 1.90 mL (1.43 g, 19.9 mmol) of ethyl vinyl ether and 20 mL of CH_2Cl_2 was stirred at 20 °C for 4 h. One drop of pyridine was added to the reaction mixture, which was then processed with CH_2Cl_2 in the usual way. The crude product was purified by silica gel chromatography with 20% ether in hexane to afford 580 mg (87%) of a 55:45 mixture of epimeric racemic acetals: mp 66–72 °C; ^{1}H NMR (300 MHz) δ 7.37–7.17 (m, 5 H), 5.91 and 5.77 (2 ddd, J = 7, 10.5, 17.4 Hz, 1 H), 5.44 and 5.37 (2 m, 1 H), 5.30 and 5.25 (2 dt, J = 1.2, 17.4 Hz, 1 H), 5.23 and 5.22 (2 dt, J = 1.2, 10.5 Hz, 1 H), 4.73 and 4.71 (2 m, 1 H), 4.62 and 4.31 (2 q, J = 5.3 and 5.4 Hz, 1 H), 4.23 and 4.16 (2 pseudo dd, J = 6.6, 7 Hz, 1 H), 3.51–3.05 and 2.98–2.90 (2 m, 2 H), 1.40 (s, 9 H), 1.22 and 1.05 (2 d, J = 5.3 and 5.4 Hz, 3 H), 1.07 and 0.90 (2 t, J = 7 Hz, 3 H); IR 3370, 1680, 1520, 1495, 1365, 1170 cm^{-1}. Anal. Calcd for $C_{19}H_{29}O_4N$: C, 68.03; H, 8.71; N, 4.18. Found: C, 68.00; H, 8.78; N, 4.13.

To a stirred mixture of the above epimeric acetals (251 mg, 0.75 mmol) in 1.50 mL of CCl_4, 1.50 mL of CH_3CN, and 2.25 mL of H_2O at 20 °C were added 409.5 mg (4.88 mmol) of $NaHCO_3$ and, in small portions, 882 mg (4.13 mmol) of $NaIO_4$. After being stirred for 5 min following completion of the addition, the mixture was treated with 25.1 mg (0.12 mmol) of $RuCl_3$ and stirring was allowed to continue for 48 h at 20 °C. The reaction mixture was extracted with ether and then carefully acidified with aqueous HCl, and the product was isolated with CH_2Cl_2 to provide 205 mg (77%) of pure racemic acid (as a mixture of acetals).

A 1.74-g (4.92 mmol) sample of the racemic acid dissolved in 12 mL of hot acetone was treated with a solution of 847 mg (5.13 mmol) of (+)-ephedrine in 12 mL of acetone. The solvent was allowed to evaporate slowly from the resulting solution at 20 °C until the onset of crystallization, at which time the temperature was lowered to 0 °C. The resulting crystals were filtered and washed twice with 1 mL of cold acetone to give 634 mg of the salt, which was then recrystallized from 10 mL of acetone to afford 301 mg of white crystals. Several recrystallizations of the residues from the mother liquors provided an additional 346 mg of crystals. Treatment of the salt with 1 N HCl in the presence of CH_2Cl_2 gave 441 mg (25%) of the corresponding free acid (+)-**6**: mp 33–37 °C; $[\alpha]^{25}_D$ + 17.6° (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.52 (br s, 1 H), 7.38–7.13 (m, 5 H), 5.72 (br s, 1 H), 5.29 (br s, 1 H), 4.80–4.65 and 4.50–4.35 (2 m, 2 H), 3.52–3.15 and 2.88–2.60 (2 m, 2 H), 1.42 (s, 9 H), 1.20 and 1.18 (2 d, J = 5.4 Hz, 3 H), 1.04 and 0.81 (2 t, J = 7 Hz, 3 H); IR 3700–2200, 1720, 1660, 1500, 1370, 1280, 1170 cm^{-1}. Anal. Calcd for $C_{19}H_{29}O_6N$ (methyl ester): C, 62.10; H, 7.96. Found: C, 62.01; H, 7.97. The methyl ester of (+)-**6** (CH_2N_2) was identical spectroscopically with material previously prepared by an alternative synthesis.[3] ^{1}H and ^{19}F NMR analysis of the Mosher esters of the alcohols derived from the methyl esters of (±)-**6** and (+)-**6** (aqueous HCl; (*R*)-

(11) The protected taxol side chain ((2*R*,3*S*)-(−)-3-phenyl-3-(phenylmethanamido)-2-(2,2,2-trichloroethoxy)methoxypropanoic acid) can be prepared from *N*-benzylbenzamide, albeit less effectively, in an analogous way ((−)-pseudoephedrine replaces (+)-ephedrine).

(12) For general experimental procedures, see: Denis, J-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957–1959.

(−)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl chloride, pyridine) indicated the enantiomeric purity of (+)-6 to be ca. 93%.

(2*R*,3*S*)-(+)-3-[[*N*-(1,1-Dimethylethoxy)carbonyl]amino]-3-phenyl-2-(2,2,2-trichloroethoxy)methoxypropanoic Acid ((+)-7). A mixture of 263 mg (1.00 mmol) of (±)-*syn*-**5**, 2.12 mL (1.40 g, 20.0 mmol) of 2-methyl-2-butene, 643 mg (3.00 mmol) of proton sponge (1,8-bis(dimethylamino)naphthalene), 485 mg (2.00 mmol) of (2,2,2-trichloroethoxy)methyl bromide, and 10 4-Å molecular sieve beads in 3.60 mL of CH_3CN was stirred at 20 °C for 24 h and then treated with additional proton sponge (643 mg, 3.00 mmol) and bromide (485 mg, 2.00 mmol). After an additional 24 h, the mixture was again treated with the bromide (242.4 mg, 1.00 mmol) and then stirred for 24 h, whereupon aqueous $NaHCO_3$ was added. The crude product was isolated with CH_2Cl_2 in the usual fashion and purified by silica gel chromatography with 10% ether in hexane to give 298 mg (70%) of the racemic acetal: mp 75 °C (hexane); ^{1}H NMR (200 MHz) δ 7.40–7.26 (m, 5 H), 5.83 (ddd, J = 7, 11, 17 Hz, 1 H), 5.41–5.32 (m, 1 H), 5.36 (d, J = 17 Hz, 1 H), 5.35 (d, J = 11 Hz, 1 H), 4.86 (br s, 1 H), 4.74 (AB q, J_{AB} = 7 Hz, $\delta_A - \delta_B$ = 17.7 Hz, 2 H), 4.37 (deformed dd, J = 2.5, 7 Hz, 1 H), 3.42 (AB q, J_{AB} = 11.8 Hz, $\delta_A - \delta_B$ = 74 Hz, 2 H), 1.43 (s, 9 H); ^{13}C NMR (75.5 MHz) 155.48 (C), 140.31 (C), 134.25 (CH), 128.40 (CH), 127.43 (CH), 126.65 (CH), 119.67 (CH_2), 96.60 (C), 92.76 (CH_2), 79.98 (CH), 79.68 (C), 79.16 (CH_2), 57.64 (CH), 28.34 (CH_3); IR 3460, 1720, 1500, 1370, 1020 cm^{-1}; mass spectrum (CI) m/z 430.5 (M^+ + 6, 3.4%), 428.5 (M^+ + 4, 31.7%), 426.5 (M^+ + 2, 97.5%), 424.5 (M^+, 100%). Anal. Calcd for $C_{18}H_{24}O_4NCl_3$: C, 50.90; H, 5.69; N, 3.30. Found: C, 50.81; H, 5.80; N, 3.29.

To a stirred mixture of the above acetal (245 mg, 0.58 mmol) in 1.20 mL of CCl_4, 1.20 mL of CH_3CN, and 1.80 mL of H_2O at 20 °C were added 315 mg (3.75 mmol) of $NaHCO_3$ and, in small portions, 679 mg (3.18 mmol) of sodium periodate. After being stirred for 5 min following the completion of the addition, the mixture was treated with 24.5 mg (0.12 mmol) of $RuCl_3$ and stirring was allowed to continue for 29 h at 20 °C. The reaction mixture was extracted with ether and then carefully acidified with aqueous HCl, and the product was isolated with CH_2Cl_2 to give 204 mg (80%) of pure racemic acid.

A 215-mg (0.48 mmol) sample of the racemic acid dissolved in 1.2 mL of warm acetone was treated with a solution of 85 mg (0.51 mmol) of (+)-ephedrine in 1.2 mL of acetone. The crystals obtained at 20 °C were washed with ether and then recrystallized from methanol–ethyl acetate (4:1) to yield 88 mg of the salt. Several recrystallizations from methanol–ethyl acetate of the residues from the mother liquors gave an additional 33.5 mg of the salt. Treatment of the salt with 1 N HCl in the presence of CH_2Cl_2 afforded 88.5 mg (83% of the theoretical yield) of the free acid (+)-7: $[\alpha]^{25}_D$ + 62° (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz) δ 7.38–7.29 (m, 5 H), 5.59 (deformed d, J = 9 Hz, 1 H), 5.43 (deformed d, J = 9.5 Hz, 1 H), 4.83 (AB q, J_{AB} = 7.3 Hz, $\delta_A - \delta_B$ = 30 Hz, 2 H), 4.60 (br s, 1 H), 3.44 (AB q, J_{AB} = 11.7 Hz, $\delta_A - \delta_B$ = 91 Hz, 2 H), 2.73 (br s, 1 H), 1.43 (s, 9 H); ^{13}C NMR (75.5 MHz) δ 171.91 (C), 155.69 (C), 138.92 (C), 128.66 (CH), 127.89 (CH), 126.39 (CH), 96.22 (C), 94.81 (CH_2), 80.84 (C), 79.43 (CH_2), 57.88 (CH), 55.78 (CH), 28.25 (CH_3); IR 3500–2300, 1730, 1500, 1375, 1180, 1090, 1020 cm^{-1}; mass spectrum (CI) m/z 448.5 (M^+ + 6, 3.4%), 446.5 (M^+ + 4, 31.7%), 444.5 (M^+ + 2, 97.5%), 442.5 (M^+, 100%). Anal. Calcd for $C_{17}H_{22}O_6NCl_3 \cdot H_2O$: C, 44.32; H, 5.25; N, 3.04. Found: C, 44.49; H, 5.26; N, 3.06. When the mixture of (±)-*syn*-**5** and (±)-*anti*-**5** (ca. 6:1) was subjected to the above sequence of reactions, pure (+)-**7** was obtained in comparable overall yield.

Treatment of (+)-**7** with CH_2N_2 in ether provided the methyl ester: mp 90–91 °C (cyclohexane); $[\alpha]^{25}_D$ + 42° (*c* 1.3, $CHCl_3$); ^{1}H NMR (200 MHz) δ 7.41–7.23 (m, 5 H), 5.46 (br s, 1 H), 5.36 (br s, 1 H), 4.79 (AB q, J_{AB} = 7.3 Hz, $\delta_A - \delta_B$ = 26 Hz, 2 H), 4.54 (deformed s, 1 H), 3.80 (s, 3 H), 3.42 (AB q, J_{AB} = 11.5 Hz, $\delta_A - \delta_B$ = 91.3 Hz, 2 H), 1.41 (s, 9 H); ^{13}C NMR (75.5 MHz) δ 169.98 (C), 155.04 (C), 139.01 (C), 128.63 (CH), 127.82 (CH), 126.43 (CH), 96.21 (C), 94.75 (CH_2), 80.02 (C), 79.40 (CH_2), 77.44 (CH), 55.89 (CH), 52.47 (CH_3), 28.25 (CH_3); IR 3450, 1760, 1720, 1500, 1370, 1175, 1020 cm^{-1}; mass spectrum (CI) m/z 462.5 (M^+ + 6, 3.4%), 460.5 (M^+ + 4, 31.7%), 458.5 (M^+ + 2, 97.5%); 456.5 (M^+, 100%). Anal. Calcd for $C_{18}H_{24}O_6NCl_3$: C, 47.33; H, 5.30; N, 3.07. Found: C, 47.45; H, 5.15; N, 3.19. ^{1}H and ^{19}F NMR analysis of the Mosher esters of the alcohols derived from the methyl esters of (±)-**7** and (+)-**7** (Zn–Cu, CH_3CO_2H–CH_3OH; (*R*)-(−)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl chloride, pyridine) indicated the enantiomeric purity of (+)-**7** to be ≥99%.

Acknowledgment. We thank Prof. J. Lhomme for his interest in our work. Financial support from the CNRS (URA 332) and Rhône-Poulenc Rorer and fellowship awards from the CAPES (Brazil) to A.C. and the CNPq (Brazil) to A.M.K. are gratefully acknowledged.