Highly Stereocontrolled and Efficient Preparation of the Protected, Esterification-Ready Docetaxel (Taxotere) Side Chain

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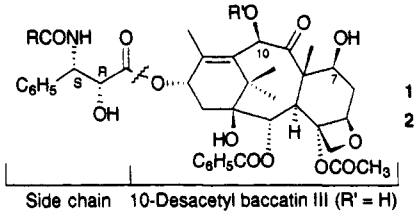
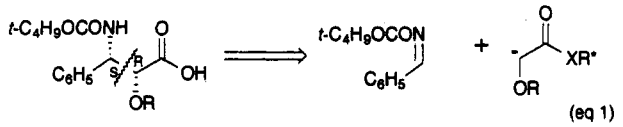
Summary: A high-yield synthesis of the *p*-methoxybenzylidene-protected docetaxel (Taxotere) side chain, a useful derivative for efficient, epimerization-free esterification of the 7,10-bis[(trichloroethoxy)carbonyl] derivative of 10-desacetylbaccatin III for the preparation of docetaxel, has been effected; the C-4 and C-5 stereocenters of the 1,3-oxazolidine are generated with complete (≥99%) stereocontrol whereas that at C-2 is produced with 96% selectivity.

Docetaxel (**1**, Taxotere) and paclitaxel (**2**, Taxol) are arguably the most outstanding cancer chemotherapeutic substances discovered in recent times.[1] While paclitaxel can today be secured from the yew tree or semisynthetically, only the latter option is currently available for the preparation of non-natural docetaxel. The partial synthesis of this important substance has generally been accomplished through esterification of a derivative of the (2*R*,3*S*)-phenylisoserine side chain with a protected form of 10-desacetylbaccatin III, a comparatively abundant natural product also obtained from the yew tree, followed by deprotection.[2]



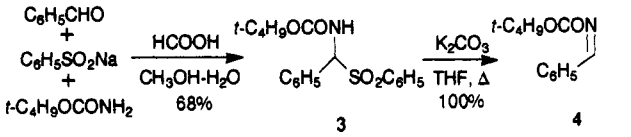
1 R = *t*-C_4H_9O ; R' = H
2 R = C_6H_5 ; R' = CH_3CO

The recognized chemotherapeutic importance of these complex diterpenes has fostered an impressive array of imaginative, albeit not always highly practical, side-chain approaches.[1] In this paper, we report a new approach to the *protected, esterification-ready* docetaxel side chain that combines unusually high levels of stereocontrol, directness, and efficiency. Embodied in this work are (1) a convenient new method for the generation of imine derivatives, (2) a potentially general approach to enantiopure β-arylisoserine derivatives, and (3) new, mild procedures for preparing 1,3-oxazolidines. The approach is based on π-face differentiation in chiral enolate–imine condensation,[3] which translates into a particularly direct strategy for the construction of this important side chain (eq 1).



(eq 1)

Although benzaldehyde *N*-(*tert*-butoxycarbonyl)imine was known, its preparation proceeded in only modest yield and required successive distillations.[4] As known alternative approaches to this type of easily hydrolyzed compound also proved unsatisfactory, effort was directed toward the development of a new method of preparation. This has resulted in a convenient procedure for obtaining the imine in pure form that is efficient and amenable to scaleup: *N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)benzylamine (**3**), which is prepared[5] from benzaldehyde, sodium benzenesulfinate, and *tert*-butyl carbamate and crystallizes during formation (68% yield), is simply refluxed in THF in the presence of potassium carbonate (eq 2). After filtration of the reaction mixture (K_2CO_3, $KHCO_3$, and $C_6H_5SO_2K$ are insoluble), the pure imine **4** can be isolated by evaporation of the solvent or used directly in solution. The yield is quantitative.[6,7]



(eq 2)

The best chiral controller in terms of yield and diastereoselection (2*R*,3*S* vs 2*S*,3*R* and vs 2*R*,3*R* and 2*S*,3*S*) proved clearly to be Oppolzer's L-(+)-camphorsultam (**5a**, Scheme 1).[8] This easily prepared,[8a] commercially available

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(1) For reviews on the occurrence, biological properties, and syntheses of these compounds, see: Blechert, S.; Guénard, D. In *The Alkaloids, Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: San Diego, 1990; Vol. 39, pp 195–238. Kingston, D. G. I.; Samaranayake, G.; Ivey, C. A. *J. Nat. Prod.* **1990**, *53*, 1–12. Kingston, D. G. I. *Pharmac. Ther.* **1991**, *52*, 1–34. Swindell, C. S. *Org. Prep. Proc. Int.* **1991**, *23*, 465–543. Borman, S. *Chem. Eng. News* **1991**, *69*(35), 11–18; **1992**, *70*(41), 30–32. Potier, P.; Guénard, D.; Guéritte-Voegelein, F. *Acc. Chem. Res.* **1993**, *26*, 160–167. Lavelle, F.; Guéritte-Voegelein, F.; Guénard, D. *Bull. Cancer* **1993**, *80*, 326–338. Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1–188. Suffness, M. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, 1993; Vol. 28, pp 305–314.

(2) (a) Colin, M.; Guénard, D.; Guéritte-Voegelein, F.; Potier, P. US Patent (Rhône-Poulenc Santé) 4924012, 8 May 1990. (b) Denis, J.-N.; Greene, A. E. Fr. Appl. (Rhône-Poulenc Rorer S.A.) 91/10,398, 19 Aug 1991. (c) Commerçon, A.; Bézard, D.; Bernard, F.; Bourzat, J. D. *Tetrahedron Lett.* **1992**, *33*, 5185–5189. (d) Bourzat, J. D.; Commerçon, A.; Paris, J.-M. Int. Appl. (Rhône-Poulenc Rorer S. A.) PCT/WO 92/09589, 11 June 1992. (e) Ojima, I.; Sun, C. M.; Zucco, M.; Park, Y. H.; Duclos, O.; Kuduk, S. *Tetrahedron Lett.* **1993**, *34*, 4149–4152. (f) 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. Denis, J.-N.; Greene, A. E.; Guénard, D.; Guéritte-Voegelein, F. US Patent (Centre National de la Recherche Scientifique) 4924011, 8 May 1990.

(3) Denis, J.-N.; Greene, A. E.; Kanazawa, A. Fr Appl (Rhône-Poulenc Rorer S. A.) 92/11,740, 5 Oct 1992. Cf. Swindell, C. S.; Tao, M. *J. Org. Chem.* **1993**, *58*, 5889–5891.

(4) See: Kupfer, R.; Meier, S.; Würthwein, E.-U. *Synthesis* **1984**, 688–690. Vidal, J.; Drouin, J.; Collet, A. *J. Chem. Soc., Chem. Commun.* **1991**, 435–437. For an improved method of preparation, see: Vidal, J.; Guy, L.; Stérin, S.; Collet, A. *J. Org. Chem.* **1993**, *58*, 4791–4793. We thank Prof. Collet and Dr. Vidal for useful information.

(5) See: Engberts, J. B. F. N.; Strating, J. *Rec. Trav. Chim.* **1965**, *84*, 942–950. See also: Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622–2636. Sulfone **3**, previously unknown, was obtained through a procedure analogous to that described by Engberts and Strating and kindly furnished by Drs. P. Léon and D. Bernard (CRC, Rhône-Poulenc Rorer).[6]

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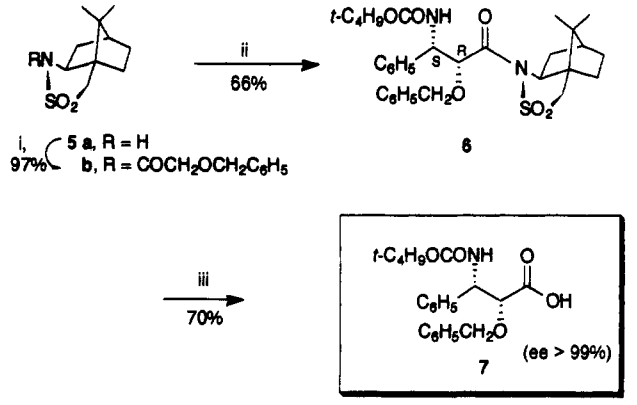
Scheme 1[a]



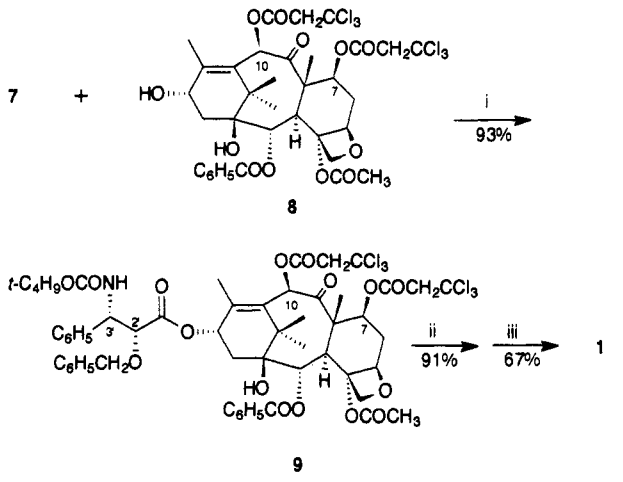
[a] Conditions: (i) NaH, $C_6H_5CH_3$, O °C, 30 min, then $C_6H_5CH_2OCH_2COCl$, 20 °C, 2 h; (ii) $LiN(Si(CH_3)_3)_2$, THF, −78 °C, 1 h, then **4**, −78 °C, 15 min; (iii) LiOH, H_2O_2, THF, H_2O, 20 °C, 15 h, then Na_2SO_3, H_2O, O °C, 5 min.

auxiliary on acylation with (benzyloxy)acetyl chloride was converted to amide **5b** in 97% yield.[9] Treatment of this derivative in THF at −78 °C with lithium bis(trimethylsilyl)amide and then benzaldehyde *N*-(*tert*-butoxycarbonyl)imine (**4**) *generated exclusively* (≥99%) *the desired, 2R,3S diastereomer 6 in 66% yield*![10] The stereochemical outcome of this remarkable transformation is consistent with Oppolzer's published model involving a *Z* enolate in a well-organized, Li-chelated transition state.[8b]

The preparation of the esterification-ready side chain **7** was then completed in 70% yield through hydrogen peroxide assisted hydrolysis of **6**. In this reaction, unfortunately, the alternative cleavage mode apparently was also operative, which diminished the yield of **7**.

Docetaxel could be prepared from this free acid with reasonably high efficiency (Scheme 2). Its esterification with 7,10-bis[(2,2,2-trichloroethoxy)carbonyl]-10-desacetylbaccatin III (**8**) was effected in toluene with DCC and DMAP[2b,f] to provide in 93% yield after purification the

Scheme 2[a]



[a] Conditions: (i) **7**, DCC, $C_6H_5CH_3$, 20 °C, 5 min, then **8**, DMAP, 20 °C, 20 h; (ii) Zn–Cu, CH_3COOH, CH_3OH, 65 °C, 30 min; (iii) H_2, Pd, CH_3COOH, 40 °C, 6 h.

triply protected docetaxel derivative **9**. Docetaxel could be liberated from **9** through treatment first with zinc–copper couple in acetic acid–methanol and then with hydrogen in the presence of palladium black. However, docetaxel so produced was found to be contaminated with up to 15% of the corresponding 2′*S* derivative. The formation of this epimer, which occurs during esterification, is apparently unavoidable with open forms of the side chain.[11] In that removal of this diastereomeric

(6) Sulfone **3** was prepared as follows: a mixture of benzaldehyde (10.6 g, 100 mmol), *tert*-butyl carbamate (5.86 g, 50 mmol), sodium benzenesulfinate (20.3 g, 124 mmol), and formic acid (4.6 g, 100 mmol) in 50 mL of methanol and 100 mL of water was stirred at 20 °C for 21 h. The solid material was filtered, washed with water and diisopropyl ether, and then dried under reduced pressure to give 11.8 g (68%) of sulfone **3**: mp 170 °C; ^{1}H NMR (200 MHz) δ 8.00–7.80 (m, 2 H), 7.75–7.20 (m, 8 H), 5.93 (deformed d, J = 10 Hz, 1 H), 5.80 (deformed d, J = 10 Hz, 1 H), 1.26 (s, 9 H); ^{13}C NMR (50.3 MHz) δ 153.5 (C), 136.8 (C), 133.9 (CH), 129.8 (C), 129.7 (CH), 129.4 (CH), 128.9 (CH), 128.6 (CH), 81.1 (C), 73.9 (CH), 27.9 (CH_3); IR (Nujol) 3370, 3280, 1700, 1540, 1520, 1320, 1160, 1090 cm^{-1}; mass spectrum (CI) m/z 365 ($MH^+ + NH_3$), 348 (MH^+), 311, 263, 236, 225, 206, 169, 160, 150, 106. Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.51; H, 6.24; N, 3.97. Preparation of imine **4**: a stirred mixture of 2.00 g (5.76 mmol) of sulfone **3** and 4.70 g (34.0 mmol) of dry potassium carbonate in 67 mL of THF under argon was refluxed for 12 h. The mixture was then allowed to cool to room temperature and filtered through Celite, and the filtrate was concentrated to leave 1.18 g (100%) of imine **4**: ^{1}H NMR (200 MHz) δ 8.90 (s, 1H), 8.00–7.90 (m, 2 H), 7.60–7.44 (m, 3 H), 1.59 (s, 9 H); ^{13}C NMR (50.3 MHz) δ 169.4 (CH), 162.5 (C), 134.1 (C), 133.4 (CH), 130.1 (CH), 128.8 (CH), 82.1 (C), 27.8 (CH_3); IR 2970, 2925, 1730, 1650, 1605, 1590, 1485, 1460, 1400, 1375, 1275, 1260, 1220, 1155 cm^{-1}; mass spectrum (CI) m/z 206 (MH^+), 166, 150, 146, 132, 122, 118, 106. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.25; H, 7.57; N, 6.99.

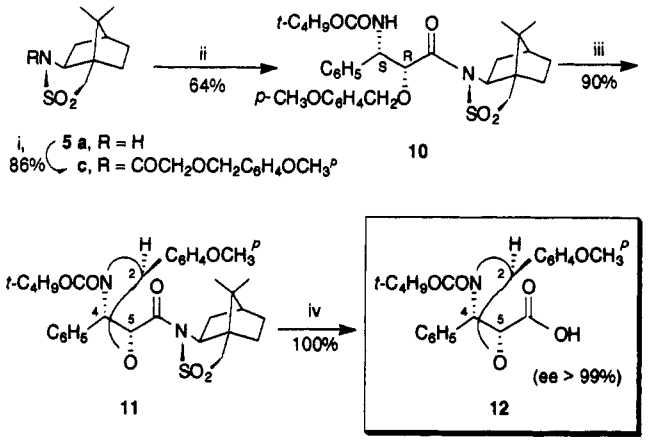
(7) Benzaldehyde *N*-benzoylimine can also be prepared in high yield through an analogous procedure. For the use of this imine with chiral enolates, see ref 3.

(8) For reviews, see: Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969–2004; *Pure Appl. Chem.* **1990**, *62*, 1241–1250. See also: (a) Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477–8482. (b) Oppolzer, W.; Blagg, I.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767–2772. (c) Oppolzer, W.; Tamura, O. *Tetrahedron Lett.* **1990**, *31*, 991–994. (d) Oppolzer, W.; Lienard, P. *Helv. Chim. Acta* **1992**, *75*, 2572–2582.

(9) Spectroscopic (NMR, IR, MS) data are in full accord with the proposed structures in this paper, and satisfactory combustion analyses have obtained for all new compounds. The stated yields are for the purified, chromatographically homogeneous substances. Data for key compounds: **10**: mp 85–86 °C; $[\alpha]^{25}_D$ 55° (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.43–7.20 (m, 5 H), 6.95–6.89 (m, 2 H), 6.74–6.68 (m, 2 H), 5.57 (d, J = 9.3 Hz, 1 H), 5.31 (d, J = 9.3 Hz, 1H), 4.83 (s, 1 H), 4.29 (ABq, J_{AB} = 11.3 Hz, $\delta_A - \delta_B$ = 123.3 Hz, 2 H), 4.00 (m, 1 H), 3.76 (s, 3 H), 3.51 (ABq, J_{AB} = 13.6 Hz, $\delta_A - \delta_B$ = 21.7 Hz, 2 H), 2.30–1.89 (m, 5 H), 1.39 (s, 9 H), 1.60–1.20 (m, 2 H), 1.27 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (50.3 MHz) δ 169.9 (C), 159.1 (C), 154.9 (C), 139.6 (C), 129.5 (CH), 128.8 (C), 128.0 (CH), 127.0 (CH), 126.7 (CH), 113.4 (CH), 80.9 (CH), 79.2 (C), 72.1 (CH_2), 65.0 (CH), 55.6 (CH), 55.1 (CH_3), 53.0 (CH_2), 48.8 (C), 47.9 (C), 44.4 (CH), 37.5 (CH_2), 32.7 (CH_2), 28.2 (CH_3), 26.5 (CH_2), 20.6 (CH_3), 19.9 (CH_3); IR 3425, 2950, 2920, 2850, 1720, 1710, 1610, 1580, 1510, 1490, 1385, 1360, 1325, 1270, 1240, 1210, 1160, 1130, 1100, 1055, 1030, 1005, 980 cm^{-1}; mass spectrum (CI) m/z 600 (MH_2^+), 538, 499, 345, 233, 216, 206, 197, 180, 154, 150, 137, 121, 106. Anal. Calcd for $C_{32}H_{42}N_2O_7S$: C, 64.19; H, 7.07; N, 4.68. Found: C, 64.10; H, 7.19; N, 4.71. **11**: mp 147–148 °C; $[\alpha]^{25}_D$ 53° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.53–7.50 (m, 2 H), 7.40–7.20 (m, 5 H), 6.92–6.89 (m, 2 H), 6.28 (s, 1 H), 5.29–5.16 (m, 2 H), 3.81 (s, 3 H), 3.88–3.75 (m, 1 H), 3.33 (s, 2 H), 2.10–2.07 (m, 2 H), 1.87–1.84 (m, 3 H), 1.52–1.26 (m, 2 H), 1.01 (s, 9 H), 0.90 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR (50.3 MHz) δ 167.9 (C), 159.9 (C), 151.3 (C), 138.2 (C), 130.8 (C), 129.0 (CH), 128.4 (CH), 127.9 (CH), 126.6 (CH), 113.3 (CH), 92.4 (CH), 82.1 (CH), 80.2 (C), 65.3 (CH), 64.7 (CH), 55.1 (CH_3), 52.5 (CH_2), 48.4 (C), 47.5 (C), 44.4 (CH), 37.9 (CH_2), 32.4 (CH_2), 27.6 (CH_3), 26.1 (CH_2), 20.4 (CH_3), 19.5 (CH_3); IR 2970, 1710, 1620, 1595, 1520, 1460, 1395, 1375, 1280, 1250, 1170, 1140, 1095, 1070, 1030, 830 cm^{-1}; mass spectrum (CI) m/z 597 (MH^+), 533, 497, 477, 433, 399, 360, 346, 299, 254, 233, 224, 216, 196, 180, 151, 137. Anal. Calcd for $C_{32}H_{40}N_2O_7S$: C, 64.41; H, 6.76; N, 4.69. Found: C, 64.15; H, 6.85; N, 4.80. **12**: mp 140–141 °C (hexane–dichloromethane); ^{1}H NMR (200 MHz) δ 7.42–7.26 (m, 7H), 6.95–6.89 (m, 2 H), 6.38 (s, 1 H), 5.54 (br s, 1 H), 5.40 (deformed d, J = 4.7 Hz, 1 H), 4.61 (d, J = 4.2 Hz, 1 H), 3.81 (s, 3 H), 1.06 (s, 9 H); ^{13}C NMR (75.5 MHz) δ 172.7 (C), 160.4 (C), 151.7 (C), 140.4 (C), 130.5 (C), 128.8 (CH), 128.4 (CH), 128.1 (CH), 126.3 (CH), 113.9 (CH), 92.4 (CH), 82.7 (CH), 81.0 (C), 63.7 (CH), 55.3 (CH_3), 27.8 (CH_3); IR 3700–2300, 2985, 2925, 1770, 1710, 1615, 1520, 1410, 1370, 1250, 1170, 1090, 1035, 920, 830, 730, 700 cm^{-1}; mass spectrum (CI) m/z 417 ($MH^+ + NH_3$), 400 (MH^+), 361, 356, 344, 317, 300, 264, 256, 236, 213, 199, 180, 154, 137, 124, 110. Anal. Calcd for $C_{22}H_{28}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.01; H, 6.35; N, 3.56.

(10) The *R,S*+*S,R*/*R,R*+*S,S* diasteroselection was established by NMR comparison of **7** (methyl ester, obtained from *crude* **6**) with independently prepared syn and anti samples. The *R,S*/*S,R* diastereoselection was determined by application of the Mosher ester technique to the above derivative after debenzylation (H_2, Pd/C, $HClO_4$(cat), C_2H_5OH).

Scheme 3[a]

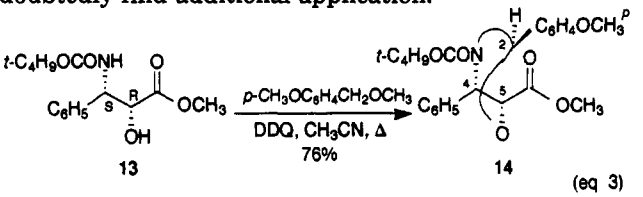


[a] Conditions: (i) NaH, $C_6H_5CH_3$, 20 °C, 30 min, then *p*-$CH_3OC_6H_4CH_2OCH_2COCl$, 20 °C, 3 h; (ii) $LiN(Si(CH_3)_3)_2$, THF, −78 °C, 30 min, then **4**, −78 °C, 15 min; (iii) DDQ, 4-Å MS, CH_2Cl_2, 20 °C, 14 h; (iv) LiOH, H_2O_2, THF, H_2O, 0 °C, 30 min, 20 °C, 2 h, then Na_2SO_3, H_2O, 0 °C, 5 min.

contaminant required a tedious, impractical chromatography, and inspired by Commerçon and co-workers' important finding that the side chain in a cyclic oxazolidine form is effectively protected and suffers no epimerization during the crucial esterification,[2c,d] we elected to examine a modification of our approach, which proved eminently successful.

N-[[(*p*-Methoxybenzyl)oxy]acetyl]-2,10-camphorsultam (**5c**, Scheme 3), formed in 86% yield from [(*p*-methoxybenzyl)oxy]acetic acid, under reaction conditions similar to those used above produced in 64% yield *and once again exclusively* (≥99%) the desired 2*R*,3*S* diastereomer (**10**). With the expectation that a (*tert*-butoxycarbonyl)amino group might readily intercept a neighboring cation in analogy with Oikawa and co-workers' finding[12] with a hydroxyl substituent, the vicinal hydroxy amine derivative **10** was exposed to dichlorodicyanobenzoquinone (DDQ) in dichloromethane at ambient temperature. Pleasingly, a smooth, highly stereoselective (96%) cyclization ensued under these nearly neutral conditions and gave in 90% yield after purification the (2*R*, 4*S*, 5*R*)oxazolidine **11**, which on hydrolysis provided the esterification-ready, pure free acid **12**, now in quantitative yield.[13,14]

Interestingly, this product (methyl ester) could also be secured intermolecularly and under kinetic control from ester **13**, albeit slightly less effectively (96% diastereoselection, 76% yield of **14**), by using *p*-methoxybenzyl methyl ether and DDQ in refluxing acetonitrile.[15] These new, exceptionally mild oxazolidine syntheses will undoubtedly find additional application.



As expected, esterification of 7,10-bis[(2,2,2-trichloroethoxy)carbonyl]-10-desacetylbaccatin III (**8**) with a small excess of acid **12**[14] delivered in high yield the protected docetaxel precursor, now devoid of epimeric impurities, which could be readily converted to docetaxel by mild acid treatment followed by Zn reduction.

In summary, a new, highly stereocontrolled and exceptionally direct preparation of the esterification-ready docetaxel side chain in an effective protected form has been developed. Additional applications of this approach are now under study and will be discussed in a future publication.

Acknowledgment. We thank Prof. J. Lhomme for his interest in our work and Drs. D. Bernard, E. Didier, P. Leon, and J.-M. Mas for several helpful discussions. Financial support from the CNRS (URA 332) and Rhône-Poulenc Rorer and a fellowship award from the CNPq (Brazil) to A.M.K. are gratefully acknowledged.

Supplementary Material Available: Complete experimental procedures with spectral and analytical data for the synthesis of the side chain **12** and the conversion of **13** to **14** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) Denis, J.-N.; Kanazawa, A. M.; Greene, A. E. *Tetrahedron Lett.* **1994**, *35*, 105–108.

(12) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889–892.

(13) The intact inductor was recovered in quantitative yield at this point.

(14) This free acid was first prepared (through an entirely different procedure) and used for conversion to docetaxel, which proceeds in >90% yield, by Dr. E. Didier and co-workers at Rhône-Poulenc Rorer. We are grateful to Dr. Didier for information relating to this work, which will soon be published.

(15) Oikawa, Y.; Nishi, T.; Yonemitsu, O. *Tetrahedron Lett.* **1983**, *24*, 4037–4040.