Direct, Stereoselective Synthesis of the Protected Paclitaxel (Taxol) Side Chain and High-yield Transformation to Paclitaxel

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A short, efficient approach to the *p*-methoxybenzylidene-protected paclitaxel (Taxol) side chain through benzaldehyde benzoylimine-chiral enolate condensation, followed by DDQ-mediated oxazolidine formation and hydrolysis is described; the C-7-triethylsilyl derivative of baccatin III undergoes esterification with this side chain in the presence of DCC and DMAP to provide after acid hydrolysis paclitaxel in excellent overall yield.

The potential of paclitaxel (Taxol) in cancer chemotherapy combined with its unique mode of action, unusual structure, and rich functionality has made it one of the most targeted compounds for total synthesis within recent memory.[1]

The elegant total syntheses of this yew tree natural product recently accomplished by the research groups of Nicolaou[2] and Holton[3] represent landmark achievements in organic synthesis. Both approaches are relatively short in view of the complexity of paclitaxel and of potential value for accessing analogues that might otherwise be difficult to obtain; however, they are clearly not suitable for a large-scale preparation of paclitaxel. In fact, it is quite possible, if not probable, that total synthesis will never be able to rival in efficiency the 10-desacetylbaccatin III-based partial synthesis [eqn. (1)].

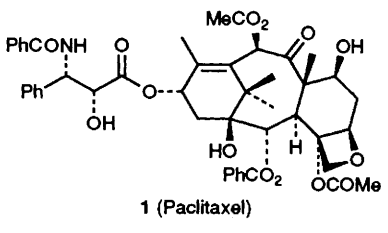
The first such synthesis of paclitaxel from 10-desacetylbaccatin III we disclosed in 1988.[4] We now report a substantially improved approach to paclitaxel based on a new peparation of the enantiopure side chain in a protected form that leads to a particularly efficient coupling. This approach would appear to be competitive with the very best means currently available for obtaining this highly important natural product.[1]

The first key reaction in the approach[5] was the chiral enolate–imine condensation shown in eqn. (2). Oppolzer's L-(+)-2,10-camphorsultam (**2a**, Scheme 1), which is readily prepared and commercially available,[6] was found at the outset to be an excellent chiral controller for this conversion in terms of both π-face selectivity and yield. Treatment of *N*-(*p*-methoxybenzyloxyacetyl)-2,10-camphorsultam **2b**, obtained in 86% yield from *p*-methoxybenzyloxyacetic acid through the acid chloride, in THF at −78 °C first with lithium bis(trimethylsilyl)amide and then with benzaldehyde *N*-benzoylimine[7]† stereoselectively delivered the desired 2*R*,3*S syn* diastereomer **3** in 68% yield after purification.‡ *None* (≤0.5%) of the 2*S*,3*R* isomer was formed.§ The stereochemical sense of this transformation is that expected from Oppolzer's published model in which the *Z*-enolate is involved in a highly organized, Li-chelated transition state.[6]

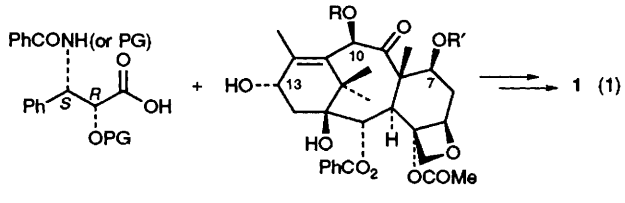
In that the docetaxel and paclitaxel side chains protected as 1,3-oxazolidines had earlier been shown to undergo the crucial esterification reaction with baccatin III derivatives without discernible epimerization,[8] the *p*-methoxybenzylidene derivative **4** was the next targeted intermediate.[9] Pleasingly, exposure of **3** to DDQ not only effected cyclization but also provided excellent selectivity (>99%) at the new diastereogenic centre to give the desired 1,3-oxazolidine **4** in 94% yield.[10] Interestingly, the related oxazolidine **7** could be secured through an intermolecular reaction with approximately equal efficiency [eqn. (3)].[11] It is noteworthy that the particularly mild, essentially neutral conditions of these novel oxazolidine forming methods result in the production of the less stable C-2 diastereomer, indicating overall kinetic control.[9–11]¶

Hydrogen peroxide assisted hydrolysis of the sultam amide **4** cleanly effected release of the intact sultam auxiliary and afforded the *p*-methoxybenzylidene-protected paclitaxel side chain **5** in nearly quantitative yield. The protected, esterification-ready free acid can thus be stereoselectively secured in only four steps from Oppolzer's camphorsultam **2a** in 52% overall yield.

The preparation of paclitaxel from this side chain derivative and the C-7 triethylsilyl derivative of baccatin III **8**[4] was also highly efficient (Scheme 2). The critical esterification, carried out in warm toluene in the presence of DCC and DMAP,[4] smoothly afforded the protected paclitaxel derivative **9** in 94% yield after purification. Most significant was that no trace of any diastereomeric material was formed, which avoided a tedious chromatographic separation. As we had hoped, dilute ethanolic hydrochloric acid[4] served to remove in one operation both the triethylsilyl and *p*-methoxybenzylidene protect-



1 (Paclitaxel)



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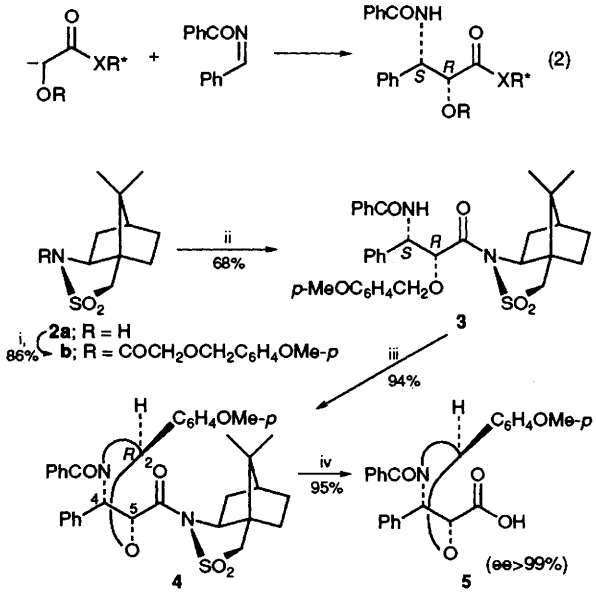
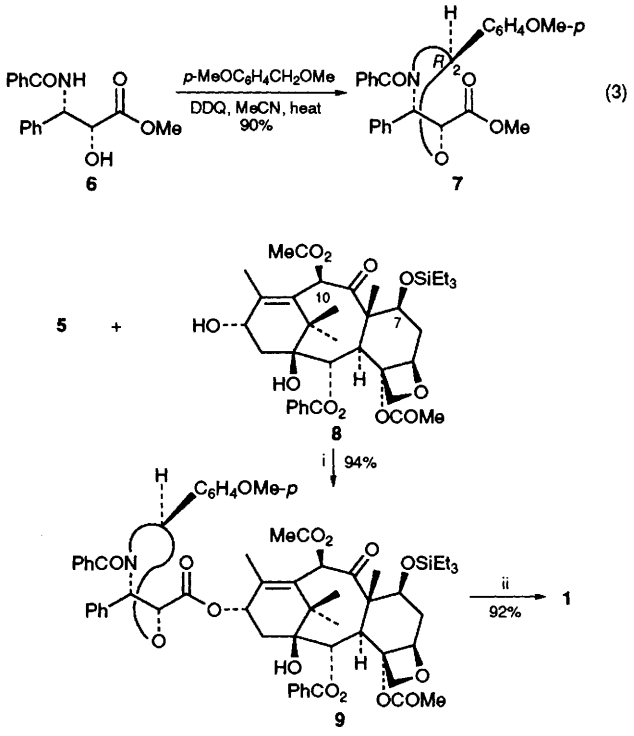


Scheme 1 *Reagents and conditions*; i, NaH, toluene, 20 °C, 30 min, then *p*-$MeOC_6H_4CH_2OCH_2COCl$, 20 °C, 3 h; ii, $LiN(SiMe_3)_2$, THF, −78 °C, 20 min, then benzaldehyde *N*-benzoylimine, −78 °C, 30 min; iii, DDQ, 3 Å molecular sieves, MeCN, 20 °C, 51 h; iv, LiOH, H_2O_2, THF, H_2O, 0 °C, 25 min, then Na_2SO_3, H_2O, 0 °C, 5 min



Scheme 2 *Reagents and conditions*: i, **5**, DCC, toluene, 20 °C, 5 min, then **8**, DMAP, 75 °C, 18 h; ii, 0.5% HCl–EtOH, 0 °C, 15 h

ing groups in this derivative and delivered pure paclitaxel in excellent yield.

In summary, the Taxol side chain derivative **5** possessing the requisite chirality at all three stereogenic centres has been directly prepared through π-face selective chiral amide enolate–imine condensation, followed by kinetically controlled oxazolidine ring formation and amide hydrolysis. This derivative is an outstanding baccatin III coupling partner for efficient, epimerization-free production of paclitaxel. Additional applications of this approach are currently under investigation.

We thank Drs D. Bernard, E. Didier, E. Fouque, P. Léon and I. Taillepied for fruitful discussions and Professor J. Lhomme for his interest in our work. 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.

Received, 18th August 1994; Com. 4/05077K

Footnotes

† This imine was also readily and conveniently prepared through a new procedure[5] that involved the α-amino sulfone derivative (J. B. F. N. Engberts and J. Strating, *Rec. Trav. Chim. Pays-Bas*, 1965, **84**, 942), which was kindly furnished by Drs P.Léon and D. Bernard (CRC, Rhône-Poulenc Rorer).

‡ The stated yields are for the purified, chromatographically homogeneous substances. All new compounds provided satisfactory combustion analyses. *Selected physical data for key compounds*: **3**: $[\alpha]_D^{25}$ + 41 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz) δ 7.77 (m, 2 H), 7.5–7.2 (m, 8 H), 7.07 (d, *J* 9 Hz, 1 H), 6.96 (d, *J* 8.6 Hz, 2 H), 6.73 (d, *J* 8.6 Hz, 2 H), 5.74 (pseudo d, *J* 9 Hz, 1 H), 5.02 (pseudo s, 1 H), 4.35 (ABq, J_{AB} 11 Hz, δ_A–δ_B 116 Hz, 2 H), 4.0 (m, 1 H), 3.77 (s, 3 H), 3.53 (ABq, J_{AB} 13.8 Hz, δ_A–δ_B 24.2 Hz, 2 H), 2.1–1.8 (m, 5 H), 1.65–1.20 (m, 2 H), 1.28 (s, 3 H), 0.97 (s, 3 H); mass spectrum (CI) *m/z* 620 ($MH^+ + NH_3$), 603 (MH^+), 517, 466, 233, 210, 154, 137, 121, 105. **4**: $[\alpha]_D^{25}$ + 60 (*c* 0.8, $CHCl_3$); ^1H NMR (200 MHz) δ 7.40–6.40 (m, 15 H), 5.47 (br s, 1 H), 5.30–5.20 (m, 1 H), 3.90–3.70 (m, 1 H), 3.73 (s, 3 H), 3.30 (s, 2 H), 2.20–1.60 (m, 5 H), 1.45–1.07 (m, 2 H), 0.84 (s, 3 H), 0.71 (s, 3 H); mass spectrum (CI) *m/z* 601 (MH^+), 539, 482, 465, 426, 403, 300, 255, 240, 231. **5**: mp 93–95 °C; $[\alpha]_D^{25}$ + 116 (*c* 0.6, $CHCl_3$); ^1H NMR (200 MHz) δ 7.40–7.10 (m, 12 H), 6.84 (d, *J* 8.6 Hz, 2 H), 6.68 (s, 1 H), 5.63 (d, *J* 5.1 Hz, 1 H), 4.73 (d, *J* 5.1 Hz, 1 H), 3.78 (s, 3 H). **9**: mp 174–177 °C; $[\alpha]_D^{25}$ − 40 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz) δ 8.03–8.00 (m, 2 H), 7.64–7.58 (m, 1 H), 7.49–7.44 (m, 2 H), 7.40–7.13 (m, 12 H), 6.80 (deformed d, *J* 6.5 Hz, 2 H), 6.65 (s, 1 H), 6.38 (s, 1 H), 6.15 (t, *J* 8.2, 9.6 Hz, 1 H), 5.62 (d, *J* 7.1 Hz, 1 H), 4.85 (d, *J* 8.2 Hz, 1 H), 4.67 (d, *J* 6.3 Hz, 1 H), 4.41 (dd, *J* 6.6, 10.5 Hz, 1 H), 4.15 (ABq, J_{AB} 8.3 Hz, δ_A–δ_B 38.7 Hz, 2 H), 3.71 (d, *J* 7.1 Hz, 1 H), 2.52–2.42 (m, 1 H), 2.17 (s, 3 H), 2.21–2.04 (m, 2 H), 1.90–1.70 (m, 1 H), 1.79 (s, 3 H), 1.75 (s, 3 H), 1.67 (s, 1 H), 1.64 (s, 3 H), 1.20 (s, 3 H), 1.19 (s, 3 H), 0.91 (deformed t, *J* 7.8, 8.0 Hz, 9 H), 0.60–0.50 (m, 6 H).

§ The *R,S* + *S,R*/*R,R* + *S,S* diastereoselection (9 : 1) was established by ^1H NMR spectral comparison of the methyl ester obtained from crude **3** with independently prepared *syn* and *anti* samples. The *R,S*/*S,R* diastereoselection (≥99.5 : 0.5) was determined by application of the Mosher ester technique to the above derivative after debenzylation (H_2, Pd/C, $HClO_4$ (cat.), EtOH).

¶ These products on acid treatment are largely isomerized to the C-2 *S* isomers, which are also predicted by molecular mechanics calculations to be thermodynamically the more stable. It is important to point out that *p*-methoxybenzylidene-protected side chain esters with the *R* configuration at C-2 undergo deprotection considerably more rapidly and cleanly than those with the *S*.

References

1 For recent reviews on the occurrence, biological properties, and partial syntheses of paclitaxel and congeners, see M. Suffness, *Ann. Rep. Med. Chem.*, 1993, **28**, 305; K. C. Nicolaou, W.-M. Dai and R. K. Guy, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 15; G. I. Georg, S. M. Ali, J. Zygmunt and L. R. Jayasinghe, *Exp. Opin. Ther. Pat.*, 1994, **4**, 109.

2 K. C. Nicolaou, Z. Yang, J. J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Claiborne, J. Renaud, E. A. Couladouros, K. Paulvannan and E. J. Sorensen, *Nature*, 1994, **367**, 630.

3 R. A. Holton, H.-B. Kim, C. Somoza, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile and J. H. Liu, *J. Am. Chem. Soc.*, 1994, **116**, 1599.

4 J.-N. Denis, A. E. Greene, D. Guénard, F. Guéritte-Voegelein, L. Mangatal and P. Potier, *J. Am. Chem. Soc.*, 1988, **110**, 5917; J.-N. Denis, A. E. Greene, D. Guénard and F. Guéritte-Voegelein, *US Pat.* (Centre National de la Recherche Scientifique) 4924011, 1990.

5 See J.-N. Denis, A. E. Greene and A. Kanazawa, *Fr Appl.* (Rhône-Poulenc Rorer S.A.) 92/11740, 1992; see also A. Kanazawa, J.-N. Denis and A. E. Greene, *J. Org. Chem.*, 1994, **59**, 1238; C. S. Swindell and M. Tao, *J. Org. Chem.*, 1993, **58**, 5889.

6 For reviews, see W. Oppolzer, *Tetrahedron*, 1987, **43**, 1969; *Pure Appl. Chem.*, 1990, **62**, 12; see also: F. A. Davis, J. C. Towson, M. C. Weismiller, S. Lal and P. J. Carroll, *J. Am. Chem. Soc.*, 1988, **110**, 8477; W. Oppolzer, I. Blagg, I. Rodriguez and E. Walther, *J. Am. Chem. Soc.*, 1990, **112**, 2767.

7 R. Kupfer, S. Meier and E.-U. Würthwein, *Synthesis*, 1984, 688.

8 A. Commerçon, D. Bézard, F. Bernard and J. D. Bourzat, *Tetrahedron Lett.*, 1992, **33**, 5185; see also: J. D. Bourzat, A. Commerçon and J.-M. Paris, *Int. Appl.* (Rhône-Poulenc Rorer S.A.) PCT/WO 92/09589, 1992; J.-N. Denis, A. Kanazawa and A. E. Greene, *Tetrahedron Lett.*, 1994, **35**, 105.

9 *p*-Methoxybenzylidene protection has been used for the docetaxel side chain, see E. Didier, E. Fouque, I. Taillepied and A. Commerçon, *Tetrahedron Lett.*, 1994, **35**, 2349, and ref. 5.

10 For a similar transformation of mono *p*-methoxybenzyl-substituted vicinal diols, see Y. Oikawa, T. Yoshioka and O. Yonemitsu, *Tetrahedron Lett.*, 1982, **23**, 889.

11 For the analogous conversion of vicinal diols, see Y. Oikawa, T. Nishi and O. Yonemitsu, *Tetrahedron Lett.*, 1983, **24**, 4037.