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Taxotere® by Esterification with Stereochemically "Wrong" (2*S*,3*S*)-Phenylisoserine Derivatives

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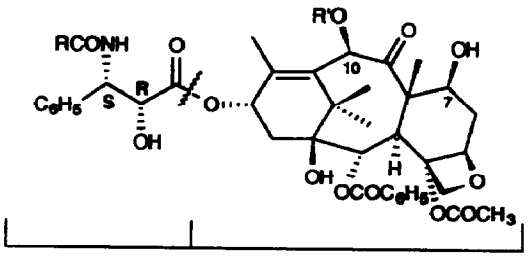
Abstract: Cyclically protected anti (2*S*, 3*S*) phenylisoserines on esterification with baccatin III derivatives afford Taxotere® and taxol precursors with the syn (2'*R*, 3'*S*) side chain.

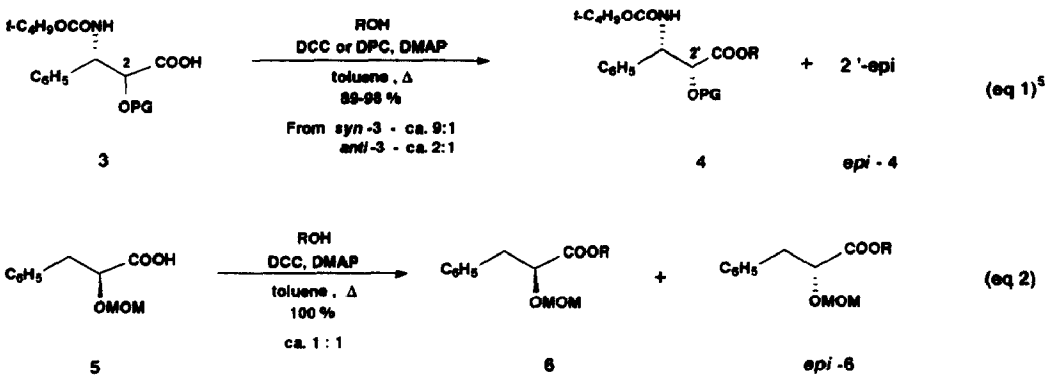
Taxol (paclitaxel) and its analogue Taxotere® (docetaxel)[1] are remarkable, broad-spectrum cancer chemotherapeutic agents[2] that offer considerable promise. Semi-synthetically, these two important compounds have to date been obtained by esterification of baccatin III derivatives with forms of the phenylisoserine side chains possessing only the 2*R*, 3*S* stereochemistry.[1] While fostering many imaginative syn(2*R*,3*S*)-selective phenylisoserine syntheses,[1,3] this focus on matching the phenylisoserine and taxol--Taxotere® side chain stereocenters has resulted in the elimination of many other possible approaches from consideration. We now report the potentially useful discovery that *anti (2S,3S) phenylisoserine side chain derivatives, available through a variety of procedures,[4] can also be directly used for this crucial esterification.*



1 R = C_6H_5 ; R' = CH_3CO (Taxol)

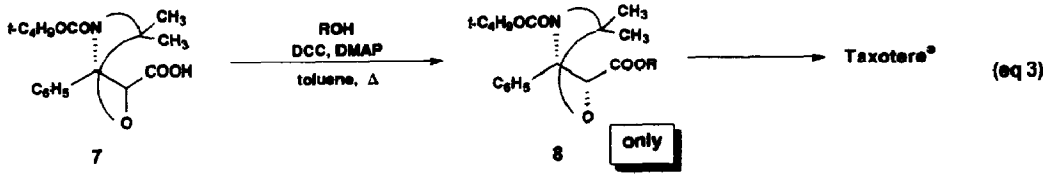
2 R = t-C_4H_9O ; R' = H (Taxotere®)

That epimerization can attend esterification under certain conditions was noticed in our early work with acyclically protected Taxotere® and taxol side chains, as well as with other side chains (e.g., eqs 1,2):



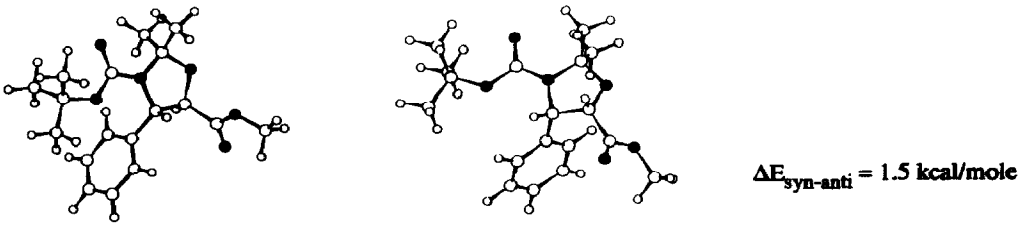
ROH = 7, 10-bis-trichloroethoxycarbonyl derivative of 10-desacetyl baccatin III

These results[6] suggested that a protected form of the anti side chain with a markedly higher energy content than that of the corresponding syn might lead to the natural syn relationship on esterification. In that the isopropylidene-protected Taxotere® derivative **8**, obtained from *syn*-**7** (in which the phenyl and carboxyl groups



ROH = 7, 10-bis-trichloroethoxycarbonyl derivative of 10-desacetyl baccatin III

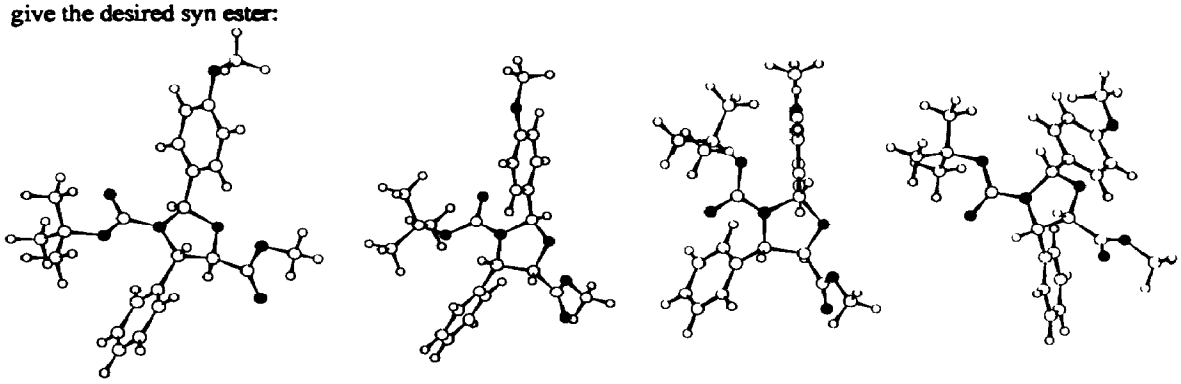
enjoy a trans disposition), had been shown by Commerçon and co-workers[7] to be useful for the preparation of Taxotere®, *anti*-**7** (cis disposition) appeared to be of potential interest. Molecular mechanics calculations[8] indicated, as expected, a significant ΔE for the syn (trans) and anti (cis) forms of the isopropylidene-protected side chain (CH_3 esters):



syn-**7** (CH_3 ester) *anti*-**7** (CH_3 ester) $\Delta E_{syn\text{-}anti}$ = 1.5 kcal/mole

Gratifyingly, *esterification of the 7,10-bis-trichloroethoxycarbonyl derivative of 10-desacetyl baccatin III with anti-7 under the usual conditions[9] also produced exclusively (400 MHz ^1H NMR) the Taxotere® precursor 8 in 86% yield after purification* (eq 3).[10]

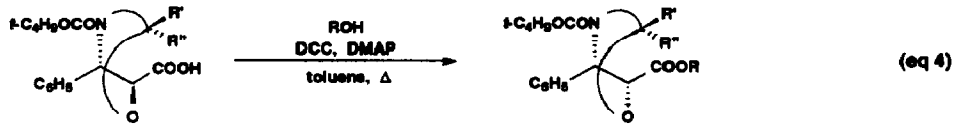
That this phenomenon is not limited to the isopropylidene derivative is seen by the reactions of the *p*-methoxybenzylidene-protected anti (cis) side chains **9** and **10**. Molecular mechanics calculations (CH_3 esters) indicated that each is appreciably less stable than the corresponding syn (trans) isomer,[11] and thus might readily give the desired syn ester:



syn-9 (CH_3 ester) *anti-9* (CH_3 ester) *syn-10* (CH_3 ester) *anti-10* (CH_3 ester)

$\Delta E_{syn\text{-}anti}$ = 4.9 kcal/mole $\Delta E_{syn\text{-}anti}$ = 2.0 kcal/mole

On esterification, anti acid **9** in fact generated the syn ester **11**, together with a minor amount of the anti (85:15), in 95% yield after purification. The related anti acid **10** gave *only* the syn ester **12** in 90% yield after silica gel chromatography (eq 4).



(eq 4)

9 R' = *p*-$C_6H_4OCH_3$; R" = H

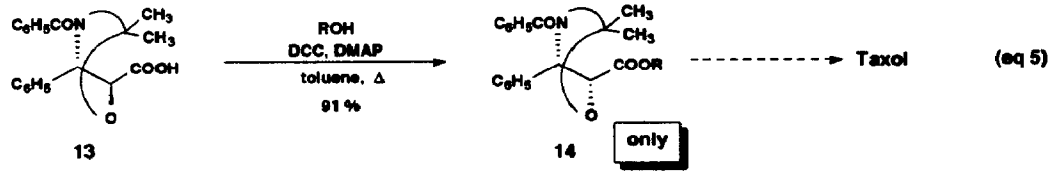
10 R' = H; R" = *p*-$C_6H_4OCH_3$

11 R' = *p*-$C_6H_4OCH_3$; R" = H

12 R' = H; R" = *p*-$C_6H_4OCH_3$

ROH = 7, 10-bis-trichloroethoxycarbonyl derivative of 10-desacetyl baccatin III

Significantly, complete epimerization has also been found to accompany the esterification of **13** in the taxol series (eq 5).



13 **14**

(eq 5)

ROH = 7-triethylsilyl derivative of baccatin III

The epimerization strategy disclosed in this paper for obtaining syn esters from anti (2*S*,3*S*) phenylisoserine derivatives thus provides an alternative approach to the important esterifications that lead to Taxotere® and taxol.

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References and Notes

1. For reviews, see: Blechert, S.; Guénard, D. In *The Alkaloids, Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: San Diego, 1990; Vol. 39, p 195. Kingston, D. G. I.; Samaranayake, G.; Ivey, C. A. *J. Nat. Prod.* **1990**, *53*, 1. Kingston, D. G. I. *Pharmac. Ther.* **1991**, *52*, 1. Swindell, C. S. *Org. Prep. Proc. Int.* **1991**, *23*, 465. Borman, S. *Chem. Eng. News* **1991**, *69*(35), 11; **1992**, *70*(41), 30. Potier, P.; Guénard, D.; Guéritte-Voegelein, F. *Acc. Chem. Res.* **1993**, *26*, 160. Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1.

2. Slichenmyer, W. J.; Van Hoff, D. D.; *Anti-Cancer Drugs* **1991**, *2*, 519. Rowinsky, E. K.; Donehower, R. C. *J. Natl. Cancer Inst.* **1991**, *83*, 1778; *Pharmac. Ther.* **1991**, *52*, 35. Holmes, F. A.; Walters, R. S.; Theriault, R. L.; Forman, A. D.; Newton, L. K.; Raber, M. N.; Buzdar, A. U.; Frye, D. K.; Hortobagyi, G. N. *Ibid.* **1991**, *83*, 1797. Einzig, A.; Wiernik, P.; Schwartz, E. *Cancer Treat. Res.* **1991**, *58*, 89. Bissery, M.-C.; Guénard, D.; Guéritte-Voegelein, F.; Lavelle, F. *Cancer Res.* **1991**, *51*, 4845. Guéritte-Voegelein, F.; Guénard, D.; Lavelle, F.; Le Goff, M.-T.; Mangatal, L.; Potier, P. *J. Med. Chem.* **1991**, *34*, 992. Lavelle, F.; Guéritte-Voegelein, F.; Guénard, D. *Bull. Cancer* **1993**, *80*, 326.

3. For previous work from our laboratory, see: Denis, J.-N.; Greene, A. E.; Serra, A. A.; Luche, M.-J. *J. Org. Chem.* **1986**, *51*, 46. Denis, J.-N.; Greene, A. E.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917. Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957; **1990**, *55*, 5538; **1991**, *56*, 6936. Denis, J.-N.; Greene, A. E.; Kanazawa, A., Fr Appl (Rhône-Poulenc Rorer S.A.) 92/11,740, June 10, 1992. Kanazawa, A. M.; Correa, A.; Denis, J.-N.; Luche, M.-J.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 255.

4. See, for example: Harada, K. *J. Org. Chem.* **1966**, *31*, 1407. Bunnage, M. E.: Davies, S. G.; Goodwin, C. J. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1375. For recent chemoenzymatic methods of preparation, see: Hönig, H.; Seufer-Wasserthal, P.; Weber, H. *Tetrahedron* **1990**, *46*, 3841. Gou, D.-M.; Liu, Y.-C.; Chen, C.-S. *J. Org. Chem.* **1993**, *58*, 1287.

5. The esters are stable to epimerization under the reaction conditions. From *syn*-**3** with PG = trichloroethoxymethyl, in the absence of ROH a 1:1 mixture of the syn and anti acids **3** was recovered after hydrolysis.

6. For other examples of epimerization accompanying DCC-DMAP promoted esterification, see: Trost, B. M.; McDougal, P. G. *Tetrahedron Lett.* **1982**, *23*, 5497. Herold, P.; Mohr, P.; Tamm, C. *Helv. Chim. Acta* **1983**, *66*, 1983.

7. Commerçon, A.; Bézard, D.; Bernard, F.; Bourzat, J. D. *Tetrahedron Lett.* **1992**, *33*, 5185. For related examples, see: Bourzat, J. D.; Commerçon, A.; Paris, J.-M. Int Appl (Rhône-Poulenc Rorer S.A.) PCT/WO 92/09589, June 11, 1992.

8. Insight II Discover, version 2.1.2 (Biosym Technologies).

9. 3 equiv of *anti*-**7**, 3 equiv of DCC, 1 equiv of DMAP, toluene (52 mL/ mmol ROH), argon, 72 °C, 16 h.

10. Identified by comparison with an authentic sample and by transformation to Taxotere®. Acid *anti*-**7**, in the absence of ROH, afforded an 82:18 mixture of *syn*- and *anti*-**7** after hydrolysis. The corresponding methyl ester, in the absence of ROH, and the acid, in the presence of DMAP alone, were found to be stable to epimerization under the reaction conditions.

11. The preparation and use of *p*-methoxybenzylidene-protected syn derivatives will soon be reported by Dr. E. Didier and co-workers (Rhône-Poulenc Rorer S.A.).

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