Enantioselective Synthesis of the Taxol and Taxotere Side Chains

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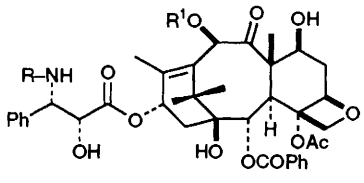
A new route to Taxol and Taxotere side chains *via* asymmetric dihydroxylation of both *cis* and *trans* methyl cinnamates is described.

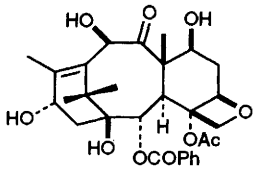
Taxol[1–3] is a diterpene with anticancer activity isolated in low yields from the bark of the Pacific yew tree (*Taxus brevifolia*). Its total synthesis remains elusive. Thus, semisynthesis *via* 10-deacetyl baccatin III and a properly protected 3-phenyl isoserine is possible.[4] The semisynthetic Taxol derivative Taxotere,[5] is also accessible from 10-deacetyl baccatin III and *N-tert* butoxycarbonyl-3-phenyl isoserine.[6] A number of methods for the synthesis of the side chain derivatives have been published.[6,7] In this communication, we report the enantioselective synthesis of Taxol and Taxotere side chains starting from both *cis*- and *trans*-methyl cinnamate, (Scheme 1).†

Asymmetric dihydroxylation with AD-mix-β[8] of *cis*-methyl cinnamate gave the diol **2** in 36% yield (7% optical purity). The diol was then allowed to react with thionyl chloride in CCl_4 to give a diastereoisomeric mixture of cyclic sulfites, which were oxidised immediately to the corresponding sulfate **3** using a catalytic amount of $RuCl_3$ with sodium periodate as the stoichiometric oxidant.[9] Treatment of the sulfate **3** with sodium azide in acetone–water[9a] for 2–3 h at room temp. gave the desired azido alcohol **4** after hydrolysis in 81% yield. Based on ^1H NMR, only traces (<5%) of the regioisomeric alcohol could have been present in the crude product. Catalytic reduction (10% Pd/C) of **4** in the presence of two equivalents of di-*tert*-butyl dicarbonate in methanol gave the Taxotere side chain methyl ester **5** in 78% yield after flash chromatography. Benzoylation of the azido alcohol **4** with benzoyl chloride in dichloromethane in the presence of DMAP[7d] gave the benzoate **6** in 77% yield. Reduction of the azide in methanol with concomitant acyl migration[7a] from oxygen to nitrogen gave the Taxol side chain methyl ester **7** in good yield. Asymmetric dihydroxylatrion of *Z*-alkenes is known to proceed with only modest enantioselectivity,[8,10] and thus the enantiopurity achieved with this sequence was unacceptably low. This fact together with the known difficulties in the preparation of *cis*-cinnamic esters[11] prompted us to search for an alternative route.

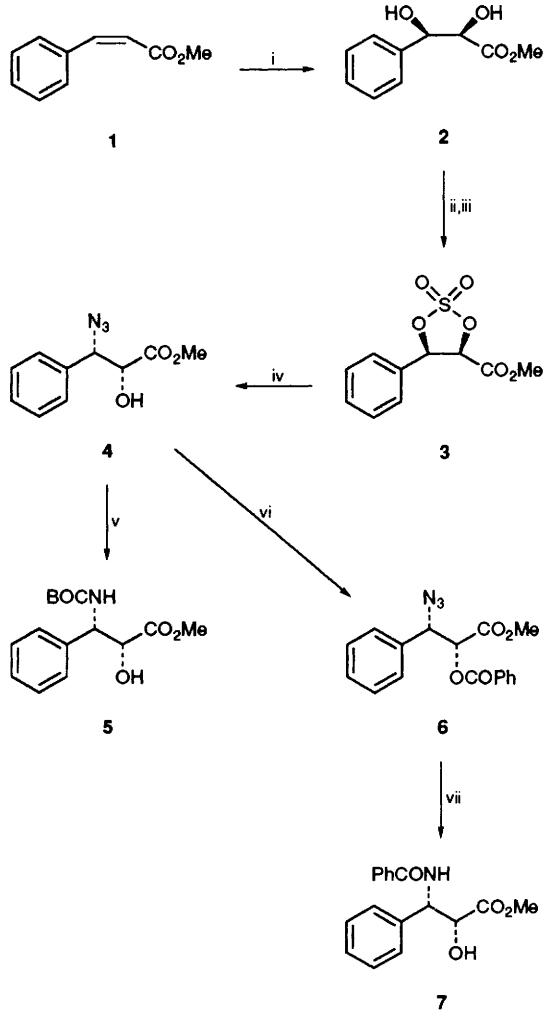
The commercially available and inexpensive *trans*-methyl cinnamate **8** was subjected to asymmetric dihydroxylation as above with AD-mix-α and the diol **9**[12]‡ thus obtained was transformed to the corresponding sulfate **10** as described above (Scheme 2). The sulfate **10** was treated with ammonium bromide in acetone overnight at room temp. to give a *ca* 9 : 1 mixture of regioisomeric hydroxy bromides with the desired **11** predominating. The mixture of bromides was treated with sodium azide in dimethylformamide (DMF) at 65–75 °C to furnish the azido alcohol **4** in 80% yield as a 4 : 1 mixture of diastereoisomers after flash chromatography.[7d] This mixture could be purified on normal phase HPLC to give pure **4**.§ It was more convenient to transform this diastereoisomer mixture to the Taxol and Taxotere side chains as described above, and separate the diastereoisomers at the final stage by crystallization.¶ In this context it is worth mentioning that the (2*S*, 3*S*) azido alcohol has recently been transformed to the Taxol side chain by Gou *et al.*[7d] This diastereoisomeric azide is accessible by our method in three steps through AD of



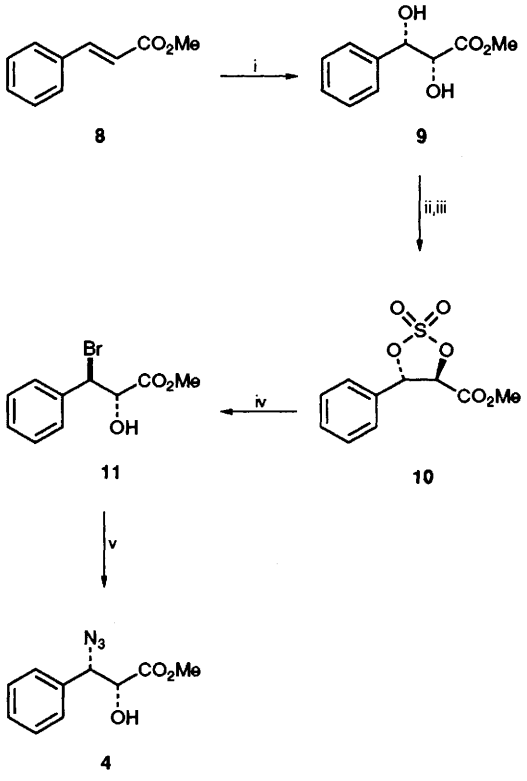
R = PhCO; R^1 = Ac Taxol
R = BOC; R^1 = H Taxotere



10-Deacetyl Baccatin III



Scheme 1 Synthesis of the Taxol and Taxotere side chains from *Z*-cinnamate; *Reagents and conditions*: i, AD-mix-β[8] (36%); ii, $SOCl_2$, CCl_4; iii, $RuCl_3$, $NaIO_4$, MeCN, CCl_4 (60%); iv, NaN_3, Me_2CO, H_2O (81%); v, H_2, Pd/C, $(Boc)_2O$, MeOH (78%); vi, PhCOCl, DMAP, CH_2Cl_2 (77%); vii, H_2, Pd/C, MeOH (77%)



Scheme 2 Synthesis of the Taxol and Taxotere side chains from *E*-cinnamate; *Reagents and conditions*: i, AD-mix-α[8] (72%); ii, $SOCl_2$, CCl_4; iii, $RuCl_3$, $NaIO_4$, MeCN, CCl_4 (61%); iv, NH_4Br, Me_2Co (86%); v, NaN_3, DMF (80%); For **9**, $[\alpha]_D$ + 12.2 (0.213, $CHCl_3$)

trans-methyl cinnamate with AD-mix-β followed by sulfate formation and opening of the sulfate with sodium azide as described above.

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Footnotes

† All compounds exhibited satisfactory analytical and spectral data.

‡ The enantiopurity of compound **9** was determined to be 92% ee by chiral phase GLC (β-cyclodextrin column, isothermal, 150 °C).

§ $[\alpha]_D$ + 144.7 (*c* 0.44, $CHCl_3$), lit.[7c] $[\alpha]_D$ + 142 (*c* 1.1, $CHCl_3$). This material was determined to be > 97% ee (DAICEL-OD, 5% Pr^iOH in hexanes).

¶ Crystallised Taxotere side chain **5** gave $[\alpha]_D$ −7.3 (*c* 0.60, $CHCl_3$). lit.[7c] $[\alpha]_D$ −7 (*c* 1.2, $CHCl_3$). Crystallised Taxol side chain **7** gave $[\alpha]_D$ −46.8 (*c* 1.0, MeOH), lit.[7c] $[\alpha]_D$ −48 (*c* 1.0, MeOH).

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