Asymmetric Synthesis of Homochiral *syn*- and *anti*-3-Phenylisoserine Derivatives: A Practical Strategy for the Synthesis of the Taxol C-13 Side Chain

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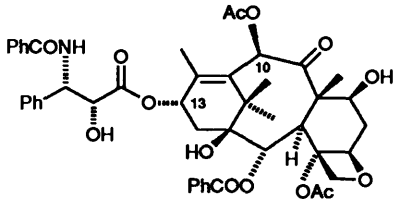
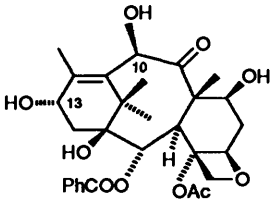
A tandem lithium amide conjugate addition–electrophilic hydroxylation approach to the synthesis of *N*-benzoyl-3-phenylisoserine methyl esters affords a strategy for the practical synthesis of the taxol side chain.

The synthesis of homochiral 3-phenylisoserine derivatives has become of major interest in recent years particularly with respect to the total and semi-synthetic approaches to taxol **1**[1] (Fig. 1). Taxol, a complex diterpene isolated in limited quantities from the bark of the Western Yew (*Taxus brevifolia*),[2] exhibits strong antitumour/antileukaemic activity and is currently considered a major lead in cancer chemotherapy.[3] The more readily available taxol precursor 10-deacetylbaccatin III **2** (Fig. 1) can be obtained (1 g kg^{-1}) by extraction from the leaves of *T. baccata* and has been converted into **1** *via* coupling with the appropriately protected C-13 side chain.[4] This 3-phenylisoserine derived side chain, which is essential for antitumour activity,[5] has consequently attracted significant synthetic attention.[6–9] In this communication we report a tandem lithium amide conjugate addition–electrophilic hydroxylation strategy which provides a practical synthesis of both the *anti*-(2*R*,3*R*) and *syn*-(2*S*,3*R*)-*N*-benzoyl-3-phenylisoserine methyl esters **7** and **10**. In this context, it is interesting to note that biological activity has been observed in taxol derivatives bearing both *syn* and *anti* C-13 side chains.[5]



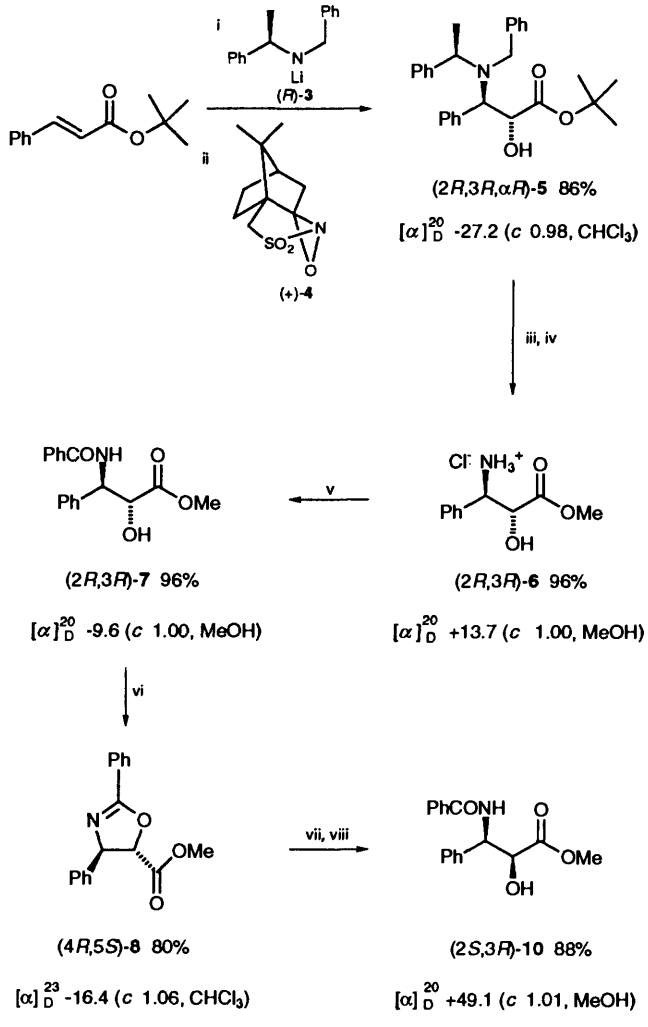
Taxol **1**



10-Deacetylbaccatin III **2**

Fig. 1

We have previously shown that the conjugate addition of homochiral lithium (*R*)-(α-methylbenzyl)benzylamide (*R*)-**3** to *tert*-butyl cinnamate proceeds with a diastereoisomeric excess (d.e.) of 95%.[10] However, attempts to alkylate the intermediate enolate in this reaction resulted in low stereoselectivity in the formation of the α-centre.[10] In contrast, we report herein that the hydroxylation of the intermediate enolate with (+)-(camphorsulfonyl)oxaziridine[11] **4** leads to the formation of **5** (92% d.e.) in 86% yield as a single diastereoisomer after column chromatography (Scheme 1).† Preliminary experiments[12] suggest that this is, in fact, the mismatched reaction since



Scheme 1 *Reagents:* i (*R*)-**3**; ii, (+)-**4**; iii, 7 atm H_2, Pd/C, AcOH; iv, HCl (g), MeOH; v, PhCOCl (1 equiv.), Et_3N; vi, diethyl azodicarboxylate, Ph_3P; vii, HCl (0.5 mol dm^{-3}), MeOH; viii, aq. $NaHCO_3$

examination of the ^{1}H NMR spectrum of the crude product for the complementary pairing did not indicate the presence of the *syn* diastereoisomer (> 98% d.e.). The relative stereochemistry within **5** was confirmed by single crystal X-ray diffraction[12]

† All new compounds were fully characterised.

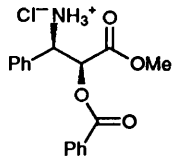


Fig. 2 Dihydrooxazole hydrolysis intermediate **9**

while the absolute configuration follows from that of (*R*)-(α-methylbenzyl)benzylamine.

Debenzylation of **5** *via* hydrogenolysis (7 atm H_2, Pd/C, AcOH) followed by transesterification and ion-exchange of the intermediate acetate salt led to the formation of **6** in 96% yield as a single diastereoisomer. Interestingly, no products resulting from the hydrogenolysis of the final *N*-benzyl moiety were observed. Finally, benzoylation of **6** with one equivalent of benzoyl chloride gave the *anti* diastereoisomer[8,9] (−)-(2*R*,3*R*)-*N*-benzoyl-3-phenylisoserine methyl ester **7** in 96% yield (79% overall, three steps): m.p. 153 °C; $[\alpha]_D^{20}$ −9.6 (*c* 1.00, MeOH) {lit.,[8] (+)-(2*S*,3*S*)-**7**, m.p. 158–159 °C; $[\alpha]_D^{20}$ +8.7 (*c* 1.03, MeOH)}.

In order to obtain the *syn* relative stereochemistry, an inversion of the alcohol stereocentre was required. Thus, treatment of homochiral **7** under Mitsunobu conditions[13] gave the *trans*-dihydrooxazole[9] **8** in 80% yield *via* intramolecular nucleophilic displacement of the alcohol. Hydrolysis of dihydrooxazole **8** was achieved *via* initial treatment with HCl (0.5 mol dm^{-3}) in methanol (1 h) yielding the intermediate **9** (Fig. 2) which was treated *in situ* with an excess of base ($NaHCO_3$) to allow O to N benzoyl transfer.[14] This led to the formation of the *syn* diastereoisomer (+)-(2*S*,3*R*)-*N*-benzoyl-3-phenylisoserine methyl ester **10** as a single diastereoisomer in 88% yield (56% overall, five steps): m.p. 185–187 °C {lit.,[2,7] (−)-(2*R*,3*S*)-**10**, m.p. 183–185, 184–185 °C}; $[\alpha]_D^{20}$ +49.1 (*c* 1.01, MeOH) {lit.,[2,7] (−)-(2*R*,3*S*)-**10**, $[\alpha]_D^{23}$ −49.6 (MeOH), $[\alpha]_D^{24}$ −48 (*c* 1.0, MeOH)}.

Although the above chemistry relates to the asymmetric synthesis of the unnatural enantiomer of **7**, the fact that both enantiomers of (α-methylbenzyl)benzylamine are readily available on a large scale allows direct access to all four stereoisomers of the taxol side chain methyl ester in high selectivity and excellent overall yields (79% for *anti* and 56% for *syn* from *tert*-butyl cinnamate). We believe that this approach represents the most practical and efficient synthesis of these important intermediates reported to date.

Experimental

(2R,3R,αR)-tert-*Butyl* 3-(*N-Benzyl*-N-α-*methylbenzyl*)-*amino*-2-*hydroxy*-3-*phenylpropionate* **5**.—A solution of (*R*)-(α-methylbenzyl)benzylamine (3.31 g, 15.69 mmol) in anhydrous tetrahydrofuran (thf) (50 cm^{-3}) was degassed under nitrogen, cooled to −78° C and butyllithium (8.81 cm^3, 14.71 mmol, 1.67 mol dm^{-3} in hexane) was added dropwise *via* syringe. The resultant pink lithium amide solution was stirred for 1 h whereupon *tert*-butyl cinnamate (2 g, 9.80 mmol) was added as a solution in anhydrous thf (5 cm^3). The resultant yellow enolate solution was stirred for a further 2 h before solid (+)-(camphorsulfonyl)oxaziridine **4** (3.59 g, 15.69 mmol) was added. After stirring for 1.5 h at −78° C, the mixture was warmed to 0° C for 15 min and quenched by the addition of saturated aq. ammonium chloride. The thf was removed under reduced pressure and the residue was diluted with water (50 cm^3) and extracted with dichloromethane (3 × 80 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to give the crude product **5** from which the diastereoselectivity of the reaction was assessed (92% d.e.). The camphor residues could be precipitated from the crude material with a small amount of diethyl ether and were readily recycled. Purification of the supernatant diethyl ether solution by column chromatography on silica gel [light petroleum–diethyl ether (5:1) as eluent] gave the single diastereoisomer **5** as a colourless oil (3.61 g, 86%) which could be crystallised from hexane; $[\alpha]_D^{20}$ −27.2 (*c* 0.98, $CHCl_3$); δ_H(300 MHz, $CDCl_3$) 7.50–7.22 (15 H, m, Ph), 4.39 [1 H, br s, C*H*(OH)], 4.22 [2 H, m, CH(OH)C*H*N, NC*H*CH_3], 4.14, 3.84 (2 H, AB system, J_{AB} 15.0, NCH_2Ph), 2.77 [1 H, br s, CH(O*H*)], 1.22 (3 H, d, obscured, NCHCH_3) and 1.21 [9 H, s, $CO_2C(CH_3)_3$] (Found: C, 78.15; H, 7.75; N, 3.05. $C_{28}H_{33}NO_3$ requires: C, 77.93; H, 7.71; N, 3.25%).

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