Asymmetric Synthesis of the Taxol and Taxotère C-13 Side Chains

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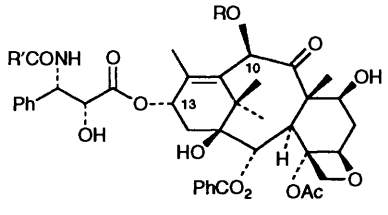
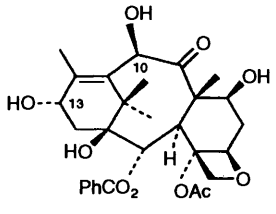
A practical and efficient asymmetric synthesis of the 3-benzoylamino-2-hydroxy-3-phenylpropionic acid derived side chain of the important anticancer agent taxol is described. The pivotal synthetic transformation relies upon the highly diastereoselective tandem lithium amide conjugate addition–electrophilic hydroxylation of *tert*-butyl cinnamate **4**. The resultant *anti* β-amino-α-hydroxy acid derivative is readily converted to the *anti* diastereoisomer of the taxol side chain methyl ester, from which the naturally occurring *syn* configuration is secured by a simple Mitsunobu inversion sequence *via* a dihydrooxazole intermediate. Under optimal conditions, this straightforward approach provides the taxol side chain methyl ester (−)-**15** (natural enantiomer) in four steps and 60% yield from *tert*-butyl cinnamate **4**. The protocol is applied to the preparation of all four taxol side chain stereoisomers and is extended to allow for the synthesis of the side chain of taxotère, a potent taxol analogue.

Taxol **1**,[1] first isolated in 1971 by extraction from the trunk bark of *Taxus brevifolia* (Western Yew),[2] exhibits strong anti-tumour/antileukaemic activity and is currently considered a major lead in cancer chemotherapy. Indeed, the exceptional



Taxol **1** R = Ac R' = Ph
Taxotère **3** R = H R' = Bu^{t}O



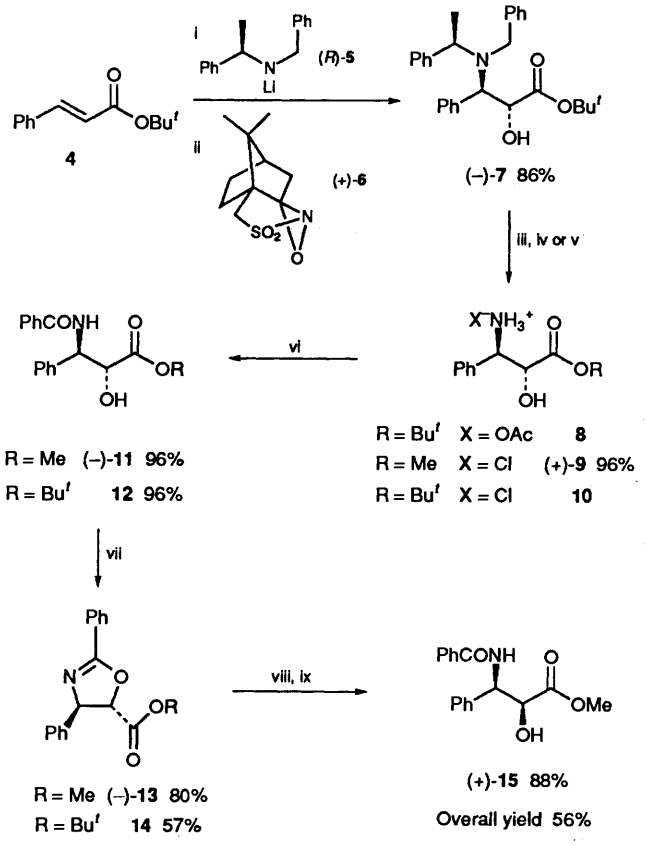
10-Deacetyl baccatin III **2**

efficacy of taxol has recently led to its approval by the FDA for the treatment of refractory ovarian cancer.[3] Unfortunately, attempts to address the ever-increasing demand for taxol are rendered problematic by its isolation process which is tedious and low-yielding (0.1–0.2 g kg^{-1} of yew bark).[2,4] Furthermore, such a procedure presents a serious ecological problem since stripping of the bark kills the yew and such trees are particularly slow-growing.[4] It appears that the major obstacle facing the routine clinical use of taxol is its extreme scarcity and consequently there has been a prodigious effort in recent years directed towards the synthesis of this important molecule.[5]

The structural complexity of taxol renders a total synthesis particularly challenging[5] and it is unlikely that such an approach will alleviate its paucity of supply. Fortunately, however, a semi-synthetic approach to taxol has been devised which allows the generation of significant quantities of material without serious ecological ramifications.[4,6] Thus, the taxol precursor 10-deacetyl baccatin III **2** can be obtained in good yield (1 g kg^{-1}) by extraction from the leaves of *T. baccata* (European Yew) and consequently, through prudent harvesting, a continual source of the diterpenoid taxol sub-structure is available.[4] The advent of an efficient procedure for the preparation of taxol from compound **2** relies upon the ready availability of the residual side-chain component and significant attention has thus been devoted towards the asymmetric synthesis of this important intermediate.[7,8,9,10] Furthermore, studies on a number of side-chain analogues[11,12] have helped delineate the structural requirements for anticancer activity and have led to the identification of taxotère **3**,[12] a potent taxol analogue which is currently undergoing clinical trials in France. Taxotère **3**, which also possesses a 3-amino-2-hydroxy-3-phenylpropionic acid derived side chain, appears to exhibit even greater activity than taxol and offers superior bioavailability.[12] Evidently, the efficient asymmetric synthesis of such side-chain derivatives is of timely importance and we describe herein full details of our efforts in this area.[13]

Results and Discussion

We have previously shown that the tandem conjugate addition–enolate hydroxylation of *tert*-butyl cinnamate **4** using homochiral lithium (*R*)-benzyl(α-methylbenzyl)amide (*R*)-**5** and the oxaziridine (+)-**6** affords the *anti* diastereoisomer (−)-**7** with excellent diastereoselectivity (92% d.e.) (Scheme 1).[14] Interestingly, despite the excellent level of asymmetric induction in the enolate hydroxylation, it transpires that this pairing of reagents constitutes the 'mismatched pair' and generation of the corresponding *syn* diastereoisomer can be curtailed by utilisation of the complementary pairing (*vide infra*).[14] Debenzylation of compound (−)-**7** could be readily achieved by the catalytic hydrogenolysis over palladium on activated carbon in acetic acid under 7 atm of hydrogen. The resultant acetate salt **8** underwent concomitant transesterification and ion-exchange upon treatment with a saturated solution of HCl in methanol. Importantly, no products resulting from cleavage of the final *N*-benzyl moiety in compound (−)-**7** were observed and the methyl ester salt (+)-**9** was secured in excellent yield



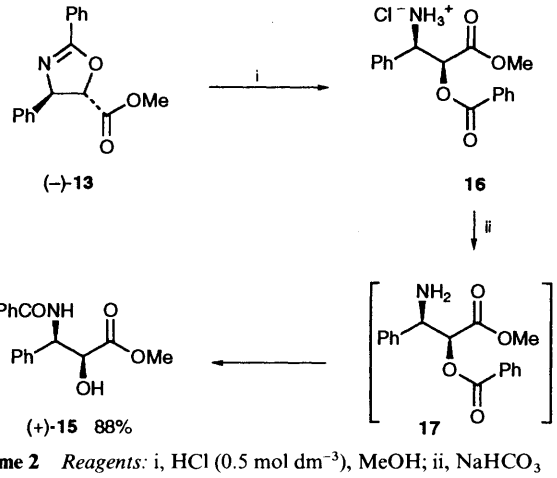
Scheme 1 *Reagents:* i, (*R*)-**5**, THF, −78 °C; ii, (+)-**6**; iii, 7 atm H_2, Pd–C, AcOH; iv, HCl, MeOH; v, HCl, Bu'OH–THF; vi, PhCOCl (1 equiv.), Et_3N; vii, DEAD Ph_3P, THF, 0 °C; viii, HCl (0.5 mol dm^{-3}), MeOH; ix, $NaHCO_3$

(96%). Although, the methyl ester series could also have been accessed by an original addition–hydroxylation sequence using methyl cinnamate as acceptor, this was avoided on account of the lower yield in this reaction and the difficulty involved in product isolation.[14] Finally, benzoylation of this salt (+)-**9** with 1 equiv. of benzoyl chloride afforded the *anti* diastereoisomer of the taxol side-chain methyl ester, methyl (2*R*,3*R*)-3-benzoylamino-2-hydroxy-3-phenylpropionate (−)-**11**, in 96% yield (79% overall, three steps): m.p. 153 °C $[\alpha]_D^{20}$ −9.6 (*c* 1.00, MeOH) {lit.,[9] (+)-**11**, m.p. 158–9 °C; $[\alpha]_D^{20}$ +8.7 (*c* 1.03, MeOH)}. It is noteworthy that taxol derivatives equipped with either enantiomer of the *anti* side chain have been found to be almost as active as taxol itself.[11]

In order to obtain the *syn* relative stereochemistry, an inversion of the alcohol stereogenic centre was required. It was anticipated that suitable activation of the hydroxyl moiety in the hydroxy ester (−)-**11** would afford the corresponding dihydrooxazole *via* intramolecular alcohol displacement. Formation of dihydrooxazoles from such substrates using Mitsunobu conditions[15] has literature precedent[16] and such a mild procedure appeared especially attractive. Indeed, treatment of the hydroxyester (−)-**11** with an excess of triphenylphosphine and diethylazodicarboxylate (DEAD) in tetrahydrofuran (THF) led to the formation of the *trans*-dihydrooxazole (−)-**13** in 80% isolated yield: $[\alpha]_D^{23}$ −16.4 (*c* 1.06, $CHCl_3$) {lit.,[8] (+)-**13**, $[\alpha]_D^{20}$ + 13 (*c* 1, $CHCl_3$)}. The coupling constant for the ring protons in compound (−)-**13** (*J* 6.4) was indicative of the *trans* ring stereochemistry[17] and this observation was consistent with the proposed intramolecular displacement with attendant stereochemical inversion. After the completion of these studies it was reported that such a transformation could also be achieved in comparable yield (73%) using thionyl chloride hydroxyl group activation.[8]

We have also investigated the analogous reaction sequence in the *tert*-butyl ester series. Thus, the acetate **8** could be converted to the hydrochloride **10** with retention of the *tert*-butyl ester moiety if the ion-exchange was performed in a saturated solution of HCl in 2,2-dimethyl propanol and THF (Scheme 1). Without isolation, the hydrochloride was readily benzoylated and compound **12** was secured in excellent yield (85%) from the hydroxylated adduct (−)-**7**. Unfortunately, it was not possible to achieve complete reaction conversion in the corresponding dihydrooxazole formation and the dihydrooxazole **14** was only isolated in moderate yield (57%). The poor conversion in this reaction may well be a consequence of the bulky *tert*-butyl ester substituent retarding the cyclisation process and the aforementioned transesterification to the methyl ester series was thus preferred.

With the appropriate relative stereochemistry successfully embedded in the dihydrooxazole (−)-**13** it was now necessary to effect the hydrolysis to yield the desired *syn* diastereoisomer. The strongly acidic hydrolysis conditions routinely employed[18] for dihydrooxazole hydrolysis were not suitable here since it was desirable to retain both the ester and amide moieties in the product. Consequently, cognisant of the possibility for intramolecular *O* to *N* benzoyl transfer,[19] a mild hydrolysis procedure was devised. Thus, initial treatment of (−)-**13** with HCl (0.5 mol dm^{-3}) in methanol (1 h) afforded the hydrochloride intermediate **16** (Scheme 2) which was then treated *in*



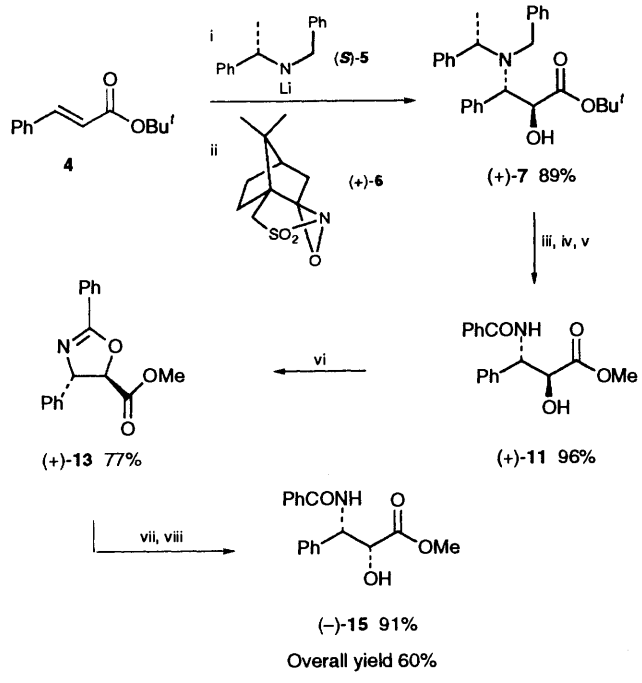
Scheme 2 *Reagents:* i, HCl (0.5 mol dm^{-3}), MeOH; ii, $NaHCO_3$

situ with an excess of base ($NaHCO_3$) to generate the intermediate **17**, and thus allow rearrangement to occur (48 h). This procedure furnished the desired *syn* diastereoisomer methyl (2*S*,3*R*)-3-benzoylamino-2-hydroxy-3-phenylpropionate (+)-**15** as a single diastereoisomer in 88% yield (56% overall, five steps) (Scheme 1): m.p. 185–187 °C {lit.,[2,7] (−)-**15**, m.p. 183–185, 184–185 °C}; $[\alpha]_D^{20}$ +49.1 (*c* 1.01, MeOH) {lit.,[2,7] (−)-**15**, $[\alpha]_D^{23}$ −49.6 (MeOH), $[\alpha]_D^{24}$ −48 (*c* 1.0, MeOH)}.

In order to unequivocally confirm the proposed mechanism of hydrolysis, it was of interest to ascertain whether the intermediate **17** could be identified before benzoyl migration had occurred. Consequently, the above hydrolysis of (−)-**13** was repeated except that product isolation was attempted *immediately* after basification with $NaHCO_3$. Analysis of the crude product by ^1H NMR spectroscopy confirmed that the dihydrooxazole had been successfully consumed and indicated the generation of two reaction products in a ratio of 4:1. The minor product was readily identified as (+)-**15**, thus confirming that partial rearrangement had occurred, and the remaining resonances were consistent with the major product being the free amino intermediate **17**. Confirmation that the amine **17** was a transient intermediate which led to the formation of (+)-**15** was obtained by dissolving the 4:1 mixture of products in

dichloromethane and stirring overnight: subsequent analysis of the mixture by ^{1}H NMR spectroscopy now indicated a 1:1 mixture of compounds (+)-**15** and **17**. The hydrochloride salt **16** would not be expected to undergo rearrangement and its isolation was consequently attempted. Thus, the hydrolysis of (−)-**13** was performed in the standard manner using HCl (0.5 mol dm^{-3}) in methanol (2 H). The solvent was then evaporated under reduced pressure to reveal a brilliant white solid in quantitative yield. Full characterisation, including elemental analysis, confirmed this material as the hydrochloride salt **16**.

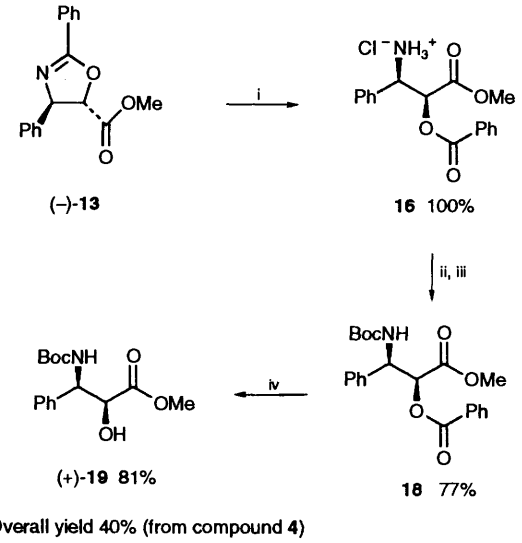
The above chemistry relates to the asymmetric synthesis of the unnatural enantiomer of **15**; however, since both enantiomers of the lithium amide **5** are readily available from the appropriate homochiral parent amine, the natural enantiomeric series is equally accessible using this methodology. Thus, the above synthetic procedure was repeated starting with lithium (*S*)-benzyl(α-methylbenzyl)amide (*S*)-**5** (Scheme 3). It



Scheme 3 *Reagents:* i, (*S*)-**5**, THF, −78 °C; ii, (+)-**6**; iii, 7 atm H_2, Pd–C, AcOH; iv, HCl, MeOH; v, PhCOCl (1 equiv.), Et_3N; vi, DEAD, Ph_3P, THF, 0 °C; vii, HCl (0.5 mol dm^{-3}), MeOH; viii, $NaHCO_3$

is noteworthy that the utilisation of the oxaziridine (+)-**6** in this tandem addition–hydroxylation procedure resulted in the formation of the hydroxylated amino ester (+)-**7** as a single diastereoisomer (>98% d.e.): none of the corresponding *syn* diastereoisomer could be detected.[13,14] Consequently, this reaction constituted the 'matched' pairing of reagents and led to a commensurate improvement in yield for this transformation (89%, *cf.* 86% for aforementioned 'mismatched' pair). The transformation of compound (+)-**7** to the methyl ester (+)-**11** was conducted without isolation of the intermediate hydrochloride salt and the product (+)-**11** was secured in excellent overall yield (96%). The yields for the remaining two steps were similar to those obtained in the previous series and the overall yield of the *syn* product (−)-**15** was improved to 60%. The specific rotations for the isolated intermediates were, within experimental error, equal in magnitude to those previously recorded in the alternative enantiomeric series. The specific rotation of the final product (−)-**15**, the natural enantiomer of the taxol side chain methyl ester, though still congruent with the literature values, was found to be slightly lower than that obtained previously for its enantiomer: $[\alpha]_D^{20}$ −48.4 (*c* 0.98, MeOH) {lit.,[2,7] $[\alpha]_D^{23}$ −49.6 (MeOH), $[\alpha]_D^{24}$ −48 (*c* 1.0, MeOH); (+)-**15** (*vide supra*), $[\alpha]_D^{20}$ +49.1 (*c* 1.01, MeOH)}. The origin of this difference appears to be related to the use of (hygroscopic) methanol as solvent for these measurements. The specific rotation for (−)-**15** was found to be identical to that previously secured for its enantiomer if chloroform solutions were employed: $[\alpha]_D^{20}$ −31.4 (*c* 0.53, $CHCl_3$) {(+)-**15**, $[\alpha]_D^{20}$ +31.4 (*c* 0.51, $CHCl_3$)}. Consequently, the use of chloroform for measurement of these specific rotations appears to be more accurate and is henceforth recommended. It should, however, be stressed that the stereochemical homogeneity of the above products is secure since only single diastereoisomers were employed in all the transformations and the homochirality of the precursor secondary amines, and thus the lithium amides (*R*)- and (*S*)-**5**, was rigorously established.[14] It is noteworthy that the above sequence has been performed on a large-scale in our laboratory (starting from 70g of *tert*-butyl cinnamate **4**) with little compromise in overall yield, and this procedure consequently appears well-suited for use in semi-synthetic approaches to taxol.

In view of the increasing interest in the taxol analogue taxotère,[12,20] it was desirable to extend the present methodology to include the *N*-*tert*-butoxycarbonyl (Boc) analogue of **15**. It was anticipated that the *anti* Boc analogue of, say, compound (−)-**11** could not be converted into the corresponding *syn* diastereoisomer using the dihydrooxazole inversion protocol, since the hypothetical dihydrooxazole intermediate might be expected to collapse to the corresponding oxazolidinone *via* elimination of 2-methylprop-1-ene. Consequently, a preparation of the *syn* diastereoisomer starting from the stable dihydrooxazole (−)-**13** was designed. As described above, hydrolysis of (−)-**13** to the hydrochloride **16** could be achieved in quantitative yield (Scheme 4) and it was of interest to investigate whether, upon liberation of the free amine, derivatisation of the amino moiety could be effected before intramolecular rearrangement had occurred. Thus, a mixture of (−)-**11** and Boc_2O in dichloromethane was treated with triethylamine and the resultant solution stirred for 2 h. Analysis of the product by ^{1}H NMR spectroscopy indicated the generation of two products in a ratio of 18:1. The minor product was readily identified as the benzoyl transfer product (+)-**15**, however the major product transpired to be the desired *N*-Boc derivative **18** which was isolated in 77% yield by flash chromatography on silica gel (Scheme 4). Surprisingly, the rate of intramolecular benzoyl migration was thus significantly



Scheme 4 *Reagents:* i, HCl (0.5 mol dm^{-3}), MeOH, 2 h; ii, $(Boc)_2O$; iii, Et_3N; iv, NaOMe, MeOH

slower than the alternative intermolecular reaction under these conditions. Finally, selective removal of the benzoyl group in compound **18** by treatment with sodium methoxide in methanol afforded the desired *syn* diastereoisomer (+)-**19** as a single diastereoisomer in excellent yield (81%): $[\alpha]_D^{22}$ +6.8 (*c* 0.24, $CHCl_3$) {lit.,[7] (−)-**19**, $[\alpha]_D^{24}$ −7 (*c* 1.2, $CHCl_3$)}. The overall yield of compound (+)-**19** from *tert*-butyl cinnamate **4** was thus 40% and, since the chemistry is straightforward, the large-scale synthesis of compound (+)-**19** (and its enantiomer) could certainly be contemplated.

In conclusion, the newly developed methodology for the asymmetric synthesis of β-amino-α-hydroxy acid derivatives has been applied to the synthesis of all four stereoisomers of the taxol side chain methyl ester. Using this approach, the naturally occurring taxol side-chain methyl ester (+)-**15** can be prepared as a single diastereoisomer in excellent overall yield (60%) from *tert*-butyl cinnamate **4**. The directness of the approach, ready availability of the homochiral starting reagents, experimental simplicity, suitability for large-scale production, together with the excellent yields and stereoselectivities secured, renders the procedure described herein the most efficient described to date for the preparation of this important homochiral fragment. Furthermore, the synthetic strategy has been extended to allow for the synthesis of the taxotère side-chain methyl ester and this may also be of value should taxotère prevail as the taxol analogue of choice for clinical use.

Experimental

General.—Details are the same as those reported previously.[14]

Unnatural Taxol Side Chain Enantiomeric Series

tert-*Butyl* (2R,3R,αR)-3-[(N-*Benzyl*-N-(α-*methylbenzyl*)-*amino*]-2-*hydroxy*-3-*phenylpropionate* (−)-**7**.—The experimental details for the synthesis of (−)-**7** have been previously reported.[13,14]

(2R,3R)-2-*Hydroxy*-3-*methoxycarbonyl*-1-*phenylpropyl-ammonium Hydrochloride* (+)-**9**.—A solution of the tertiary amine (−)-**7** (1.09 g, 2.53 mmol) in acetic acid (12 cm^3) was treated with 10% palladium on activated carbon (300 mg) and stirred at room temp. under 7 atm of hydrogen overnight. After the mixture had been filtered to remove the catalyst, the filtrate was evaporated under reduced pressure to afford the acetate salt **8**. This salt was dissolved in anhydrous methanol saturated with HCl gas, and the solution stirred for 5 min after which it was evaporated under reduced pressure. The residue was again dissolved in methanolic HCl and the solution stirred at room temp. overnight. It was then evaporated under reduced pressure and the residue dried *in vacuo* to afford the title compound as a white hygroscopic solid (564 mg, 96%). An analytical sample was prepared by crystallisation from methanol–diethyl ether; $[\alpha]_D^{20}$ +13.7 (*c* 1.00, MeOH); ν_{max}(KBr)/cm^{-1} 1746s (C=O); δ_H(300 MHz; CD_3OD) 7.51–7.40 (5 H, m, Ph), 4.76, 4.72 [2 H, AB, J_{AB} 4.1, C*H*(OH)C*H*N] and 3.62 (3 H, s, CO_2Me); δ_C(125 MHz; CD_3OD) 172.1 (CO_2), 133.9 (Ph: C_{ipso}), 130.7 (Ph: C_{para}), 129.9 and 129.6 (Ph: C_{ortho} and C_{meta}), 72.2 [*C*H(OH)], 57.7 [CH(OH)*C*HN] and 52.8 (CO_2Me); *m*/*z*(CI) 196 (M^+, 100%) and 106 (54) (Found: C, 51.7; H, 6.4; N, 6.3. $C_{10}H_{14}ClNO_3$ requires C, 51.84; H, 6.09; N, 6.05%).

Methyl (2R,3R)-3-*Benzoylamino*-2-*hydroxy*-3-*phenyl-propionate* (−)-**11**.—Triethylamine (2.77 g, 27.4 mmol) was added dropwise to a suspension of the hydrochloride salt (+)-**9** (1.27 g, 5.49 mmol) in dichloromethane (20 cm^3) and the mixture stirred for 15 min at room temp. Freshly distilled benzoyl chloride (771 mg, 5.49 mmol) in dichloromethane (2 cm^3) was added dropwise to the resultant solution and stirring was continued at room temp. overnight. The solution was then diluted with dichloromethane (20 cm^3) and water (20 cm^3) was added. The organic layer was separated and the aqueous layer extracted with further dichloromethane (2 × 20 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the title compound as a white solid which was dried *in vacuo* overnight (1.58 g, 96%); m.p. 153 °C (from chloroform) {lit.,[9] (+)-**11**, m.p. 158–9 °C}; $[\alpha]_D^{20}$ −9.6 (*c* 1.00, MeOH) {lit.,[9] (+)-**11**, $[\alpha]_D^{20}$ +8.7 (*c* 1.03, MeOH)}; ν_{max}($CHCl_3$)/cm^{-1} 1742s (ester C=O) and 1662s (amide C=O); δ_H(300 MHz; $CDCl_3$) 7.84–7.81 (2 H, m, Ph), 7.53–7.30 (8 H, m, Ph), 7.17 (1 H, br d, *J* 8.6, PhCON*H*), 5.64 [1 H, dd, *J* 8.6 and 3.5, CH(OH)C*H*NH], 4.73 [1 H, d, *J* 3.5, C*H*(OH)CHN] and 3.75 (3 H, s, CO_2Me); δ_C(50 MHz; $CDCl_3$) 172.7 (CO_2), 167.1 (Ph*C*ONH), 136.8 and 134.3 (Ph: C_{ipso}), 131.9 and 128.5 (Ph: C_{para}), 128.8, 127.7 and 127.3 (Ph: C_{ortho} and C_{meta}), 73.1 [CH(OH)], 55.6 [CH(OH)*C*HN] and 52.6 (CO_2Me); *m*/*z*(CI) 300 (MH^+, 78%), 210 (29) and 105 (100) (Found: C, 68.2; H, 5.8; N, 4.8. $C_{17}H_{17}NO_4$ requires C, 68.22; H, 5.72; N, 4.68%).

Methyl (4R,5S)-2,4-*Diphenyl*-4,5-*dihydrooxazole*-5-*carboxylate* (−)-**13**.—A solution of the ester (−)-**11** (500 mg, 1.67 mmol) and triphenylphosphine (877 mg, 3.34 mmol) in anhydrous THF (12 cm^3) was cooled to 0 °C. The stirred solution was then treated dropwise with a solution of diethyl azodicarboxylate (DEAD) (582 mg, 3.34 mmol) in anhydrous THF (6 cm^3). Upon complete addition of the DEAD, the resultant yellow solution was allowed to warm to room temp. After the mixture had been stirred overnight, it was evaporated under reduced pressure and purification of the residue by flash chromatography on silica gel (petroleum–diethyl ether 2:1) afforded the title compound as a colourless oil (377 mg, 80%); $[\alpha]_D^{23}$ −16.4 (*c* 1.06, $CHCl_3$) {lit.,[8] (+)-**13**, $[\alpha]_D^{20}$ +13 (*c* 1, $CHCl_3$)}; ν_{max}($CHCl_3$)/cm^{-1} 1758vs (C=O) and 1656vs (N=C–O); δ_H(300 MHz; $CDCl_3$) 8.12–8.09 (2 H, m, Ph), 7.56–7.34 (8 H, m, Ph), 5.46 (1 H, d, *J* 6.4, CHC*H*CO_2), 4.93 (1 H, d, *J* 6.4, C*H*CHCO$_2$) and 3.88 (3 H, s, CO_2Me); δ_C(50 MHz; $CDCl_3$) 171.0 (CO_2), 164.3 [N*C*(Ph)O], 141.4 and 127.0 (Ph: C_{ipso}), 132.2 and 128.3 (Ph: C_{para}), 129.1, 129.0, 128.7 and 126.7 (Ph: C_{ortho} and C_{meta}), 83.2 (CH*C*HCO$_2$), 74.7 (*C*HCHCO$_2$) and 52.8 (CO_2Me); *m*/*z*(CI) 300 (MNH_4^+, 22%), 282 (MH^+, 100), 222 (28) and 105 (34) (Found: C, 72.4; H, 5.3; N, 5.2. $C_{17}H_{15}NO_3$ requires C, 72.58; H, 5.37; N, 4.98%).

Methyl (2S,3R)-3-*Benzoylamino*-2-*hydroxy*-3-*phenyl-propionate* (+)-**15**.—The dihydrooxazole (−)-**13** (119 mg, 0.423 mmol) was treated with a solution of 0.5 mol dm^{-3} hydrochloric acid (5 cm^3, 2.50 mmol) in methanol (5 cm^3) and the resultant mixture stirred at room temp. until TLC analysis indicated complete hydrolysis of the starting material (1 h). Sodium hydrogen carbonate (210 mg, 2.50 mmol) was then cautiously added to the mixture in portions until an alkaline pH was obtained. The resultant solution was stirred at room temp. for 48 h and subsequently extracted with dichloromethane (3 × 30 cm^3). The combined organic extracts were then dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the pure title compound as a white solid, which was crystallised from chloroform (112 mg, 88%); m.p. 185–187 °C {lit.,[2,7] (−)-**15**, m.p. 183–185 °C, 184–185 °C}; $[\alpha]_D^{20}$ +49.1 (*c* 1.01, MeOH) {lit.,[2,7] (−)-**15**, $[\alpha]_D^{23}$ −49.6 (MeOH), $[\alpha]_D^{24}$ −48 (*c* 1.0, MeOH)}; $[\alpha]_D^{20}$ +31.4 (*c* 0.51, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1738s (ester C=O) and 1666s (amide C=O); δ_H(300 MHz; $CDCl_3$) 7.79–7.77 (2 H, m, Ph), 7.54–7.30 (8 H, m, Ph), 6.97 (1 H, br d, *J* 9.0, PhCON*H*), 5.76 [1 H, dd, *J* 9.0 and 2.0, CH(OH)C*H*NH], 4.65 [1 H, dd, *J* 3.9 and 2.0, C*H*(OH)CHN], 3.86 (3 H, s, CO_2Me) and 3.26 [1 H, d, *J* 3.9, CH(O*H*)]; D_2O

shake: *inter alia* δ_H(300 MHz; $CDCl_3$) 4.65 [1 H, d, *J* 2.1, C*H*(OH)CHN]; δ_C(125 MHz; $CDCl_3$) 173.4 (CO_2), 166.8 (PhCONH), 138.8 and 134.2 (Ph: C_{ipso}), 131.8 and 128.0 (Ph: C_{para}), 128.8, 128.7, 127.1 and 126.9 (Ph: C_{ortho} and C_{meta}), 73.2 [*C*H(OH)], 54.9 [CH(OH)*C*HN] and 53.3 (CO_2*Me*); *m/z*(CI) 300 (MH^+, 100%), 210 (17) and 105 (27) (Found: C, 68.0; H, 5.7; N, 4.8. $C_{17}H_{17}NO_4$ requires C, 68.22; H, 5.72; N, 4.68%).

Studies on Dihydrooxazole Hydrolysis

Identification of the Hydrolysis Intermediate (2S,3R)-*Methyl* 3-Amino-2-*benzoyloxy*-3-*phenylpropionate* **17**.—The dihydrooxazole (−)-**13** (60 mg, 0.214 mmol) was treated with a solution of 0.5 mol dm^{-3} hydrochloric acid (3 cm^3, 2.50 mmol) in methanol (3 cm^3) and the resultant mixture stirred at room temp. until TLC analysis indicated complete hydrolysis of the starting material (1 h). The solvent was evaporated under reduced pressure and the residue was treated with sat. aq. sodium hydrogen carbonate and immediately extracted with ethyl acetate (3 × 15 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Analysis of the crude product by ^1H NMR spectroscopy indicated a 4:1 mixture of the free amine **17** and the benzoyl transfer product (+)-**15**. This mixture of compounds was dissolved in dichloromethane (5 cm^3) and the solution stirred overnight at room temp. Evaporation of the solvent and analysis of the product by ^1H NMR spectroscopy now indicated a 1:1 mixture of compounds **17** and (+)-**15**, thus confirming the intermediacy of compound **17** in the benzoyl transfer. Isolation of the title compound was not attempted due to its evident instability, however the ^1H NMR spectrum could be partially assigned from the crude product mixture; δ_H(300 MHz; $CDCl_3$) 5.40 [1 H, d, *J* 4.4, C*H*(OCOPh)], 4.62 [1 H, br m, CH(OCOPh)C*H*NH_2] and 3.71 (3 H, s, CO_2Me).

(2S,3R)-*Methyl* 3-*Amino*-2-*benzoyloxy*-3-*phenylpropionate Hydrochloride* **16**.—The dihydrooxazole (−)-**13** (150 mg, 0.534 mmol) was treated with a solution of 0.5 mol dm^{-3} hydrochloric acid (10 cm^3, 5.00 mmol) in methanol (10 cm^3) and the resultant mixture stirred at room temp. for 2 h. The solvent was evaporated under reduced pressure and the residue dried *in vacuo* overnight to afford the title compound as a brilliant white solid in quantitative yield; m.p. 185 °C (decomp.); $[\alpha]_D^{20}$ −21.7 (*c* 0.54, MeOH); ν_{max}(KBr)/cm^{-1} 1746vs (ester C=O) and 1727vs (ester C=O); δ_H(300 MHz; CD_3OD) 8.19–8.16 (2 H, m, Ph), 7.73–7.48 (8 H, m, Ph), 5.64 [1 H, d, *J* 6.4, C*H*(OCOPh)], 5.02 (1 H, d, *J* 6.4, CHC*H*N) and 3.66 (3 H, s, CO_2Me); δ_C(50 MHz; CD_3OD) 167.5 and 165.4 (Ph*C*O_2, *C*O_2Me), 134.1 and 132.7 (Ph: C_{ipso}), 130.0–127.6 (Ph: C_{ortho}, C_{meta} and C_{para}), 73.6 [*C*H(OCOPh)], 55.1 (CH*C*HN) and 52.0 (CO_2*Me*); *m/z*(CI) 300 (MH^+, 94%), 106 (100) and 105 (50) (Found: C, 60.7; H, 5.5; N, 4.35. $C_{17}H_{18}ClNO_4$ requires C, 60.81; H, 5.40; N, 4.17%).

Studies on tert-*Butyl Ester Series*

tert-*Butyl* (2R,3R)-3-*Benzoyloxy*-2-*hydroxy*-3-*phenylpropionate* **12**.—An acetic acid solution of the hydroxylated adduct (−)-**7** (2.50 g, 5.80 mmol) was debenzylated in an analogous manner to that described above in the preparation of compound (+)-**9**. The resultant acetate salt was dissolved in a mixture of anhydrous THF and *tert*-butyl alcohol (1:1) which had previously been saturated with HCl(g). The mixture was stirred for 5 min and the solvent evaporated under reduced pressure to afford the intermediate hydrochloride salt **10**. Triethylamine (2.77 g, 27.4 mmol) was then added dropwise to a suspension of the hydrochloride salt in dichloromethane (30 cm^3) and the mixture stirred for 30 min at room temp. Freshly distilled benzoyl chloride (652 mg, 4.64 mmol) in dichloromethane (2 cm^3) was added dropwise to the resultant solution and stirring was continued at room temp. overnight. The solution was then diluted with dichloromethane (50 cm^3) and water (30 cm^3). The organic layer was separated, the aqueous layer extracted with further dichloromethane (2 × 60 cm^3) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum–ethyl acetate, 2:1) afforded the title compound as a colourless oil (1.35 g, 85% based on benzoyl chloride); $[\alpha]_D^{23}$ +21.5 (*c* 0.98 $CHCl_3$); ν_{max}(CH_2Cl_2)/cm^{-1} 1729s (ester C=O) and 1665s (amide C=O); δ_H(300 MHz; $CDCl_3$) 7.83–7.80 (2 H, m, Ph), 7.52–7.29 (8 H, m, Ph), 7.19 (1 H, br d, *J* 8.7, PhCON*H*), 5.58 [1 H, dd, *J* 8.7 and 3.6, CH(OH)C*H*NH], 4.59 [1 H, dd, *J* 5.7 and 3.6, C*H*(OH)CHNH], 3.21 [1 H, d, *J* 5.7, CH(O*H*)] and 1.38 (9 H, s, CO_2CMe); D_2O shake: *inter alia* δ_H(300 MHz; $CDCl_3$) 4.59 [1 H, d, *J* 3.6, C*H*(OH)CHN]; δ_C(125 MHz; $CDCl_3$) 170.8 (CO_2), 166.5 (Ph*C*ONH), 137.0 and 134.3 (Ph: C_{ipso}), 131.6 and 128.2 (Ph: C_{para}), 128.5, 128.4, 128.1 and 127.1 (Ph: C_{ortho} and C_{meta}), 83.7 (CO_2*C*Me_3), 72.8 [*C*H(OH)], 55.3 [CH(OH)*C*HN] and 27.9 (CO_2C*Me*$_3$); *m/z* (CI) 342 (MH^+, 42%), 286 (100), 210 (36) and 105 (53) (Found: C, 70.2; H, 6.8; N, 4.2. $C_{20}H_{23}NO_4$ requires C, 70.36; H, 6.79; N, 4.10%).

tert-*Butyl* (4R,5S)-2,4-*Diphenyl*-4,5-*dihydrooxazole*-5-*carboxylate* (−)-**14**.—A solution of (−)-**11** (500 mg, 1.67 mmol) and triphenylphosphine (877 mg, 3.34 mmol) in anhydrous THF (12 cm^3) was cooled to 0 °C. The stirred solution was then treated dropwise with a solution of diethyl azodicarboxylate (DEAD) (469 mg, 2.69 mmol) in anhydrous THF (6 cm^3). Upon complete addition of the DEAD, the resultant yellow solution was allowed to warm to room temp. After the mixture had been stirred overnight, it was evaporated under reduced pressure whereupon analysis of the residue by ^1H NMR spectroscopy indicated only 60% conversion. Purification of the residue by flash chromatography on silica gel (petroleum–diethyl ether, 4:1) afforded the title compound as a colourless oil, which crystallised upon storage (249 mg, 57%); m.p. 66–67 °C; $[\alpha]_D^{23}$ −15.8 (*c* 0.99, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1748vs (C=O) and 1655vs (N=C–O); δ_H(300 MHz; $CDCl_3$) 8.14–8.11 (2 H, m, Ph), 7.55–7.35 (8 H, m, Ph), 5.40 (1 H, d, *J* 6.4, CHC*H*CO_2),4.81 (1 H, d, *J* 6.4, C*H*CHCO_2) and 1.56 (9 H, s, CO_2CMe_3); δ_C(125 MHz; $CDCl_3$) 169.0 (CO_2), 164.2 [N*C*(Ph)O], 141.5 and 127.0 (Ph: C_{ipso}), 131.8, 128.8, 128.7, 128.4, 127.9 and 126.4 (Ph: C_{ortho}, C_{meta} and C_{para}), 83.5 (CH*C*HCO_2), 82.8 (CO_2*C*Me_3), 74.7 (*C*HCHCO_2) and 28.0 (CO_2C*Me*$_3$); *m/z* (CI) 324 (MH^+, 100%) and 222 (28) (Found: C, 74.3; H, 6.8; N, 4.3. $C_{20}H_{21}NO_3$ requires C, 74.28; H, 6.54; N, 4.33%).

Natural Taxol Side-chain Enantiomeric Series

tert-*Butyl* (2S,3S,αS)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)-*amino*]-2-*hydroxy*-3-*phenylpropionate* (−)-**7**.—The experimental details for the synthesis of the hydroxy ester (−)-**7** have been previously reported.[14]

Methyl (2S,3S)-3-*Benzoylamino*-2-*hydroxy*-3-*phenylpropionate* (+)-**11**.—An acetic acid solution of the ester (−)-**7** (2.50 g, 5.80 mmol) was debenzylated in an analogous manner to that described above in the preparation of compound (+)-**9**. The resultant acetate salt was dissolved in a saturated solution of HCl(g) in anhydrous methanol (50 cm^3), the solution stirred for 5 min; the mixture was then evaporated under reduced pressure. The residue was again dissolved in methanolic HCl (50 cm^3) and the solution stirred at room temp. overnight. The solvent was subsequently evaporated under reduced pressure and the residue dried *in vacuo* to afford the crude intermediate

hydrochloride salt which was used in the next step without purification.

Triethylamine (2.92 g, 28.9 mmol) was added dropwise to a suspension of the hydrochloride salt in dichloromethane (30 cm^3) and the mixture stirred for 20 min at room temp. Freshly distilled benzoyl chloride (773 mg, 5.51 mmol) in dichloromethane (2 cm^3) was added dropwise to the resultant solution and stirring was continued at room temp. overnight. The solution was then diluted with dichloromethane (20 cm^3) and 1.0 mol dm^{-3} hydrochloric acid (30 cm^3) was added to it. After thorough mixing of the mixture, the organic layer was separated and the aqueous layer extracted with further dichloromethane (2 × 40 cm^3). The combined organic extracts were then dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the title compound as a white solid (1.57 g, 96%); $[\alpha]_D^{20}$ +9.5 (*c* 1.01, MeOH) {lit.,[9] $[\alpha]_D^{20}$ +8.7 (*c* 1.03, MeOH); (−)-**11** (*vide supra*), $[\alpha]_D^{20}$ −9.6 (*c* 1.00, MeOH)}.

Methyl (4S,5R)-2,4-*Diphenyl*-4,5-*dihydrooxazole*-5-*carboxylate* (+)-**13**.—A solution of the hydroxy ester (+)-**11** (500 mg, 1.67 mmol) was treated with DEAD and triphenylphosphine in the manner described above for compound (−)-**11**. Purification of the product by flash chromatography on silica gel (petroleum–diethyl ether, 2:1) afforded the title compound as a colourless oil (361 mg, 77%); $[\alpha]_D^{20}$ +16.8 (*c* 1.04, $CHCl_3$) {lit.,[8] $[\alpha]_D^{20}$ +13 (*c* 1, $CHCl_3$); (−)-**13** (*vide supra*), $[\alpha]_D^{23}$ −16.4 (*c* 1.06, $CHCl_3$)}.

Methyl (2R,3S)-3-*Benzoylamino*-2-*hydroxy*-3-*phenylpropionate* (−)-**15**.—The dihydrooxazole (+)-**13** (235 mg, 0.836 mmol) was treated with a solution of 0.5 mol dm^{-3} hydrochloric acid (10 cm^3, 2.50 mmol) in methanol (10 cm^3) and the resultant mixture stirred at room temp. until TLC analysis indicated complete hydrolysis of the starting material (1.5 h). Sat. aq. sodium hydrogen carbonate was then cautiously added to the mixture in portions until an alkaline pH was obtained. The resultant solution was stirred at room temp. for 16 h and subsequently extracted with dichloromethane (3 × 30 cm^3). The combined organic extracts were then dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the pure title compound as a white solid (228 mg, 91%) which was crystallised from chloroform; m.p. 185–187.5 °C {lit.,[2,7] m.p. 183–185 °C, 184–185 °C}; $[\alpha]_D^{20}$ −48.4 (*c* 0.98, MeOH) {lit.,[2,7] $[\alpha]_D^{23}$ −49.6 (MeOHOH), $[\alpha]_D^{24}$ −48 (*c* 1.0, MeOH); (+)-**15** (*vide supra*), $[\alpha]_D^{20}$ +49.1 (*c* 1.01, MeOH)}; $[\alpha]_D^{20}$ −31.4 (*c* 0.53, $CHCl_3$) {(+)-**15** (*vide supra*), $[\alpha]_D^{20}$ +31.4 (*c* 0.51, $CHCl_3$)}; $\nu_{max}(CHCl_3)/cm^{-1}$ 1737s (ester C=O) and 1666s (amide C=O); δ_H(300 MHz; $CDCl_3$) 7.79–7.77 (2 H, m, Ph), 7.54–7.30 (8 H, m, Ph), 7.00 (1 H, br d, *J* 9.0, PhCONH), 5.76 [1 H, dd, *J* 9.0 and 2.0, CH(OH)CHNH], 4.65 [1 H, dd, *J* 3.9 and 2.1, CH(OH)CHN], 3.85 (3 H, s, CO_2Me) and 3.33 (1 H, d, *J* 3.9, CH(OH)]; δ_C(125 MHz; $CDCl_3$) 173.4 (CO_2), 166.9 (PhCONH), 138.9 and 134.3 (Ph: C_{ipso}), 131.7 and 128.0 (Ph: C_{para}), 128.8, 128.7, 127.1 and 127.0 (Ph: C_{ortho} and C_{meta}), 73.3 [CH(OH)], 55.0 [CH(OH)CHN] and 53.2 (CO_2Me); *m*/*z*(CI) 300 (MH^+, 100%), 210 (24) and 105 (41) (Found: C, 68.45; H, 5.75; N, 4.5. $C_{17}H_{17}NO_4$ requires C, 68.22; H, 5.72; N, 4.68%).

Studies on Taxotère Side Chain

Methyl (2S,3R)-3-(N-tert-*Butoxycarbonylamino*)-2-*benzoyloxy*-3-*phenylpropionate* **18**.—A suspension of the hydrochloride salt **16** (179 mg, 0.534 mmol) in dichloromethane (15 cm^3) was treated with di-*tert*-butyl dicarbonate (233 mg, 1.07 mmol) and the mixture vigorously stirred at room temp. Dropwise addition of a solution of triethylamine (108 mg, 1.07 mmol) in dichloromethane (4 cm^3) to the mixture resulted in the generation of a homogeneous solution. This was stirred for a further 2 h after which it was diluted with water (15 cm^3) and extracted with dichloromethane (2 × 20 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Analysis of the crude product by ^1H NMR spectroscopy indicated an 18:1 mixture of the desired product **18** and the *O* to *N* benzoyl transfer product (+)-**15**. Purification by flash chromatography on silica gel (petroleum–diethyl ether, 3:1) afforded the title compound as a white solid (165 mg, 77%); m.p. 106–107 °C (from diethyl ether–hexane); $[\alpha]_D^{21}$ −9.1 (*c* 0.86, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1768s (ester C=O), 1749s (ester C=O), 1719vs (ester C=O), 1707s (amide C=O) and 1683s (amide C=O); δ_H(300 MHz; $CDCl_3$) 8.02–7.98 (2 H, m, Ph), 7.62–7.30 (8 H, m, Ph), 5.52 [3 H, br s, CH(OCOPh)CHNH], 3.79 (3 H, s, CO_2Me) and 1.45 (9 H, s, Me_3CO); δ_C(125 MHz; $CHCl_3$) 168.2 and 165.4 (PhCO$_2$ and CO_2Me), 154.9 (Me_3COCO), 138.0 and 129.0 (Ph: C_{ipso}), 133.5 and 127.9 (Ph: C_{para}), 129.8, 128.7, 128.5 and 126.5 (Ph: C_{ortho} and C_{meta}), 80.2 (Me_3COCO), 75.3 [CH(OCOPh)], 54.9 (CHCHN), 52.6 (CO_2Me) and 28.2 (Me_3COCO); *m*/*z*(CI) 400 (MH^+, 7%), 361 (20), 300 (43), 106 (100) and 105 (41) (Found: C, 66.1; H, 6.1; N, 3.6. $C_{22}H_{25}NO_6$ requires C, 66.15; H, 6.31; N, 3.51%).

Methyl (2S,3R)-3-(N-tert-*Butoxycarbonylamino*)-2-*hydroxy*-3-*phenylpropionate* (+)-**19**.—A solution of compound **18** (30 mg, 0.0752 mmol) in methanol (2 cm^3) was treated with sodium methoxide (5 mg, 0.0926 mmol) and the mixture stirred at room temp. overnight. Subsequent evaporation of the mixture under reduced pressure gave a residue which was diluted with sat. aq. ammonium chloride (10 cm^3) and extracted with dichloromethane (3 × 15 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was triturated with cyclohexane to afford the title compound as a white solid which was recrystallised from dichloromethane–cyclohexane (18 mg, 81%); m.p. 125 °C {lit.,[7] (−)-**19**, m.p. 130.5–131.5 °C}; $[\alpha]_D^{22}$ +6.8 (*c* 0.24, $CHCl_3$) {lit.,[7] (−)-**19**, $[\alpha]_D^{24}$ −7 (*c* 1.2, $CHCl_3$)}; $\nu_{max}(CHCl_3)/cm^{-1}$ 1736s (ester C=O) and 1712s (amide C=O); ν_{max}(Nujol film)/cm^{-1} 1733m (ester C=O) and 1689m (amide C=O); δ_H(300 MHz; $CDCl_3$) 7.38–7.28 (5 H, m, Ph). 5.40 [1 H, br d, *J* 9.1, CH(OH)CHN], 5.23 [1 H, br d, *J* 9.1, CH(OH)CHN], 4.48 (1 H, br s, OCONH), 3.86 (3 H, s, CO_2Me), 3.14 [1 H, br s, CH(OH)] and 1.43 (9 H, s, Me_3CO); δ_C(125 MHz; $CDCl_3$) 173.4 (CO_2), 155.1 (Me_3COCO], 139.1 (Ph: C_{ipso}), 128.6, 127.7 and 126.7 (Ph: C_{para}, C_{ortho} and C_{meta}), 79.9 (Me_3COCO), 73.5 [CH(OH)], 56.1 [CH(OH)CHN], 53.1 (CO_2Me) and 28.2 [Me_3COCO]; *m*/*z* (CI) 296 (25), 257 (35), 240 (66), 222 (22), 206 (27), 196 (49), 106 (100), 91 (17) and 57 (13) (Found: C, 60.9; H, 6.90; N, 4.7. $C_{15}H_{21}NO_5$ requires C, 61.00; H, 7.17; N, 4.74%).

Note added in proof. It has recently been shown that the dihydrooxazole (+)-**13** can be coupled efficiently, *via* the corresponding acid, to 7-(trimethylsilyl)baccatin III and the product hydrolysed to give taxol: D. G. I. Kingston, A. G. Chaudhary, A. A. L. Gunatilata and M. L. Middleton, *Tetrahedron Lett.*, 1994, **35**, 4483.

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