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Utilization of a Benzoyl Migration To Effect an Expeditious Synthesis of the Paclitaxel C-13 Side Chain

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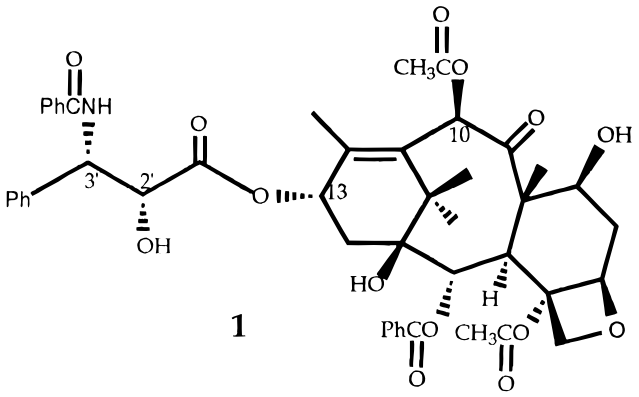
Abstract:

A benzoyl migration has been used to remove two steps during the asymmetric dihydroxylation literature route to (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine, the C-13 position side chain of paclitaxel. The modification provides the product as its more desirable methyl ester in similar overall yields with no loss of enantiomeric purity when scaled up to multigram quantities.

Paclitaxel (**1**) is a complex natural product used clinically because of its ability to stabilize microtubules, interrupt the cell cycle, and ultimately, cause apoptosis within cancer cells.[2] Initially available from yew tree bark by a process which killed the trees,[3] another option for the manufacture of paclitaxel involves taking advantage of the more plentiful and renewable supply of the 10,13-dihydroxy intermediate 10-deacetylbaccatin III in a coupling scheme that then necessitates incorporating the (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine side chain located at position C-13.[4,5] Thus, chemical methodologies pertaining to the production of paclitaxel's C-13 side chain are potentially of major economic significance.



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As part of a medicinal chemistry program to prepare simplified analogs of **1**, we also needed multigram quantities of paclitaxel's C-13 position side chain. Of the reported routes to this substituent, the Sharpless et al. asymmetric dihydroxylation method (Scheme 1) seemed to be the most promising.[6] However, during this procedure the alcohol located at position 2 is protected as an acetyl ester and, when the 3-position is elaborated to an amine, the acetyl group spontaneously migrates to form the acetamide. This necessitates removal of the amide acetyl group as a distinct step so that the resulting amine can be subsequently reconverted to the desired benzamide. In addition, hydrolysis of the acetamide is accompanied by cleavage of the methyl ester such that the final product is in the form of its α-hydroxy carboxylic acid. The latter represents a less than ideal arrangement which can be awkward to manipulate during subsequent coupling reactions.

Alternatively, we have utilized a benzoyl group to protect the 2-position hydroxyl functionality and, after effecting a similar migration, have obtained the product more directly and in the form of its methyl ester (Scheme 2). Although this possibility has been alluded to by others,[7] no experimental details for the overall process or specific physical properties for the novel intermediate **3** have been reported.

Conversion of methyl cinnamate to the (2*R*,3*S*)-diol **2** in high enantiomeric excess was accomplished by using the catalytic asymmetric dihydroxylation method elaborated by Sharpless et al.[8] Analogous to the case of acetylation,[6] regioselective benzoylation was then effected at the more acidic hydroxyl group located α to the cinnamate carbonyl[9,10] by using trimethyl orthobenzoate.[11] Thus, subsequent treatment with acetyl bromide selectively displaced the β-alcohol to produce the new key intermediate (2*S*,3*R*)-**3**, which has an inverted configuration at position 3. This intermediate was then subjected to an S_N2 reaction with sodium azide to introduce a nitrogen system while restoring the requisite 2*R*,3*S* stereochemistry. Reduction of the azide was accompanied by efficient migration of the benzoyl moiety to directly provide the desired C-13 side chain as its methyl ester.

Evidence supporting an intramolecular migration of the benzoyl moiety (path a in Scheme 3) includes the observation that TLC and NMR examination of the crude reaction mixture revealed that only the desired product **i** was formed rather than the variety of potential products, **i** along with

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(11) Using catalog (*Aldrich Catalog Handbook of Fine Chemicals*; Aldrich Chemical Co.: Milwaukee, WI, 1996−1997; p 148, 1487) list prices to compare the cost of trimethyl orthobenzoate (TMOB) to that of trimethyl orthoacetate plus benzoyl chloride indicates that the latter pair is slightly more expensive than TMOB for millimolar quantities of reagents but is less expensive for molar quantities of reagents. Thus, it seems reasonable to assume that the lower cost of TMOB could be obtained on a contract basis for larger quantities if, indeed, this particular reagent continued to be employed for the benzoylation step.

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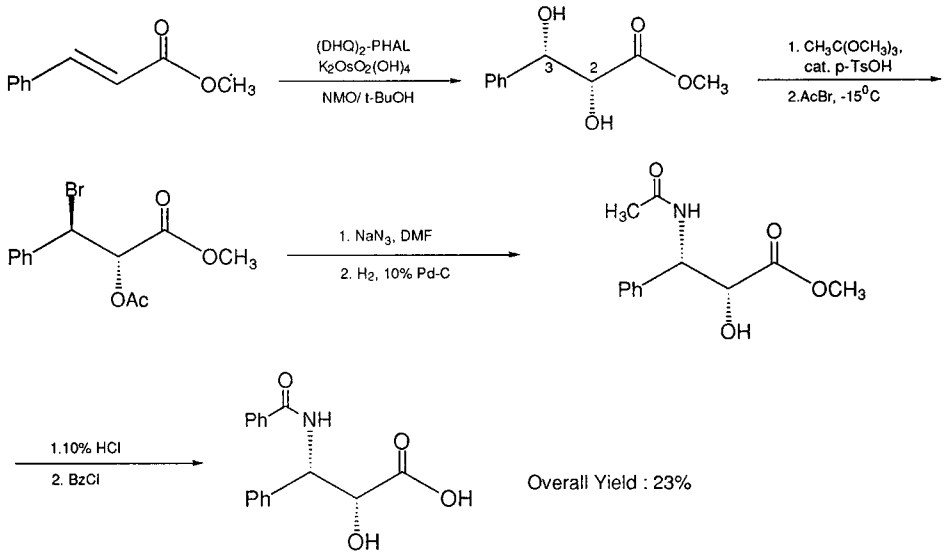
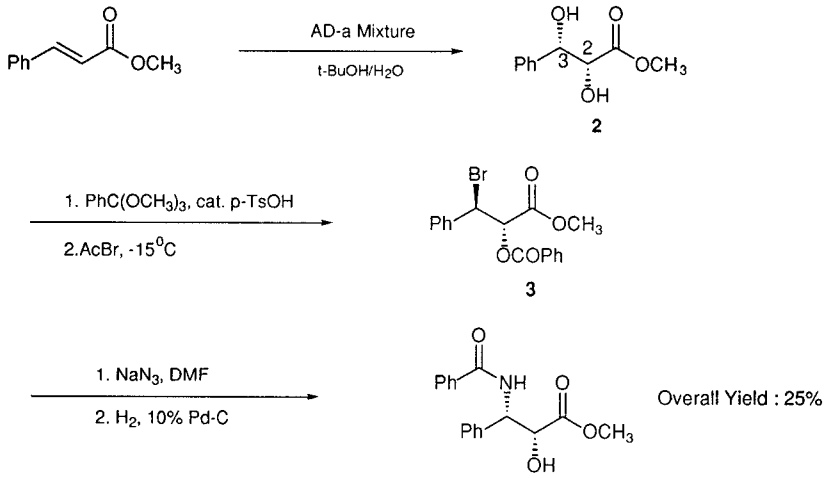
Scheme 1. **The Sharpless dihydroxylation route to the paclitaxel C-13 side chain[6]**



Scheme 2. **Synthesis of the paclitaxel C-13 side chain as its methyl ester utilizing a benzoyl migration**



iv−**vi**, which are likely to result during an intermolecular acyl-transfer mechanism (path b). Furthermore, when the azide intermediate is stirred with an equimolar amount of benzylamine at room temperature under conditions which simulate those in which the benzoyl moiety undergoes intramolecular migration (Scheme 4), there is no evidence for intermolecular acyl transfer of the benzoyl group to the benzylamine when the mixture is subsequently evaporated and assessed by TLC and NMR. Apparent intermolecular acyl-transfer-type products are observed only upon forcing this donor−acceptor mixture (Scheme 4) at conditions well above those employed to effect the intramolecular migration observed in Schemes 1 and 2.

Table 1 summarizes the results from scale-up of the benzoyl migration method from 5 to 100 mmol and also provides some comparative data to the original Sharpless method.

In our hands, subsequent coupling and hydroxy-group-protecting reactions employing the α-hydroxy acid have proven to be problematic, generally producing complex reaction product mixtures. Alternatively, using approaches similar to those described by others,[12] we find that the α-hydroxy methyl ester material can be readily protected as the MOM derivative, quantitatively hydrolyzed to the acid, and then conveniently employed in a variety of coupling reaction protocols, e.g., Scheme 5. Likewise, the MOM group can be selectively removed under gentle conditions which allow retention of the labile esters present within the overall paclitaxel framework **1**.[12]

Conclusions

The benzoyl modification represents an improvement in that it removes two steps while providing the more desirable methyl ester version of the product in about the same overall percent yield with no significant diminution of enantiomeric purity. The migration may be able to be exploited in combination with more recent approaches such as Sharpless's amino-hydroxylation method[16] or, as has already been accomplished in some cases,[12,17] with certain of the other literature routes which have additionally become available to prepare the C-13 side chain of paclitaxel.[18,19] Finally, our

(12) Epoxide route: Denis, J.-N.; Greene, A. E.; Serra, A. A.; Luche, M.-J. *J. Org. Chem.* **1986**, *51*, 46.
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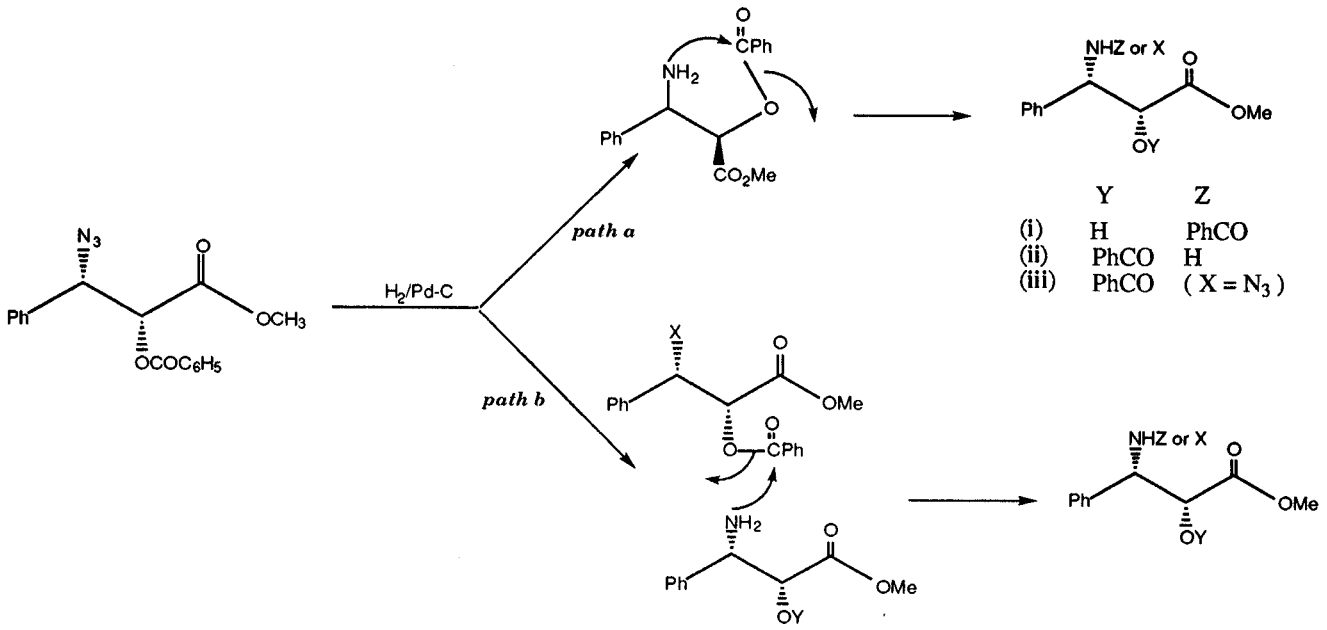
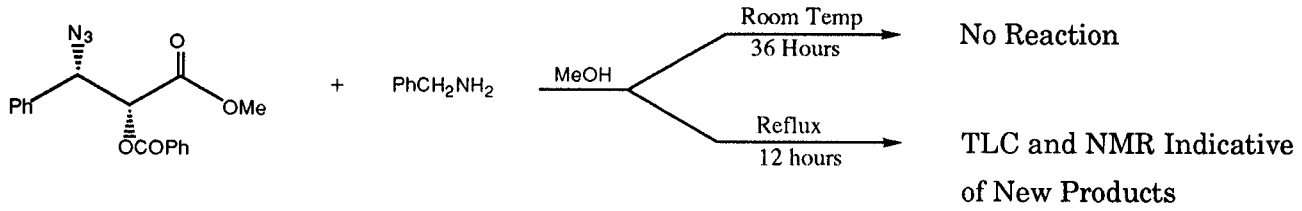
(17) Epoxide route: Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957.

Scheme 3. **Reaction pathways which can lead to relocation of the benzoyl moiety**



Scheme 4. **Evidence for an intramolecular migration of the benzoyl moiety rather than an intermolecular acyl-transfer reaction**



preliminary results suggest that the migration method is also amenable to other heteroaryl systems such as pyridyl and furoyl, both of which could become of interest clinically.[20]

Experimental Section

All reagents and solvents were of ACS grade. ^{1}H- and ^{13}C-NMR spectra were collected using a Bruker ACF 300 MHz Fourier transform spectrophotometer in deuteriochloroform using TMS as an internal standard. Chemical shifts (δ) are expressed in ppm units and coupling constants (J) in Hz; and spin multiplicities are described as s (singlet), d (doublet), t (triplet), b (broad), and m (multiplet). Optical rotations were measured with a Rudolph Research Autopol III polarimeter. All rotations were made at room temperature and observed at the sodium D line. Fourier transform infrared spectra were obtained on a Perkin-Elmer model 1600 FT-IR spectrophotometer by using 3M type 62 IR cards. Peak positions are reported in cm^{-1} units. Melting points were determined on an Electrothermal digital melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was carried out using silica on polyester with fluorescent indicator (F254) TLC plates. Catalytic hydrogenation was carried out on a Parr apparatus. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. Stirring was accomplished using magnetic stirrers. Organic phases were dried by treatment with anhydrous magnesium sulfate. Evaporations were conducted on a Buchi Rotavapor using a water aspirator to reduce pressure.

Methyl (2*R*,3*S*)-2,3-Dihydroxy-3-phenylpropionate (2). A 100 mL round-bottomed flask was charged with 25 mL of *tert*-BuOH, 25 mL of water, and 7.0 g of AD-α reagent. The mixture was stirred for 5 min, 0.81 g (5 mmol) of *trans*-methyl cinnamate was added, and then the mixture was additionally stirred at room temperature for 12 h. Sodium sulfite (6.0 g, 47.6 mmol) was added, and the mixture was stirred for 1 h. Methylene chloride (25 mL) was added, and the organic phase was separated. The aqueous phase was extracted with methylene chloride (3 × 25 mL), and the combined organic phases were dried and evaporated. A

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Scheme 5. **Representative coupling reaction sequence employing (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine methyl ester**

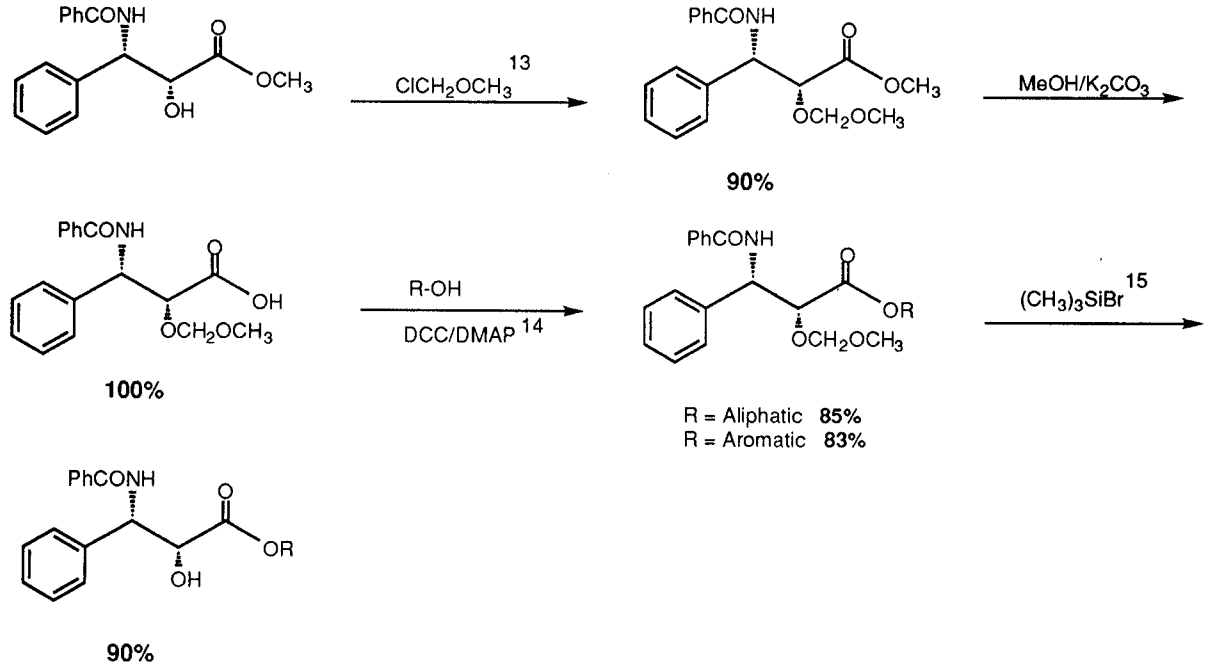

Table 1. **Scale-up of benzoyl migration method and comparison to original Sharpless method[a,b]**

method	SM amount (mmol)	yield (%) migration step	yield (%) overall	ee (%)
Sharpless[c]	400	74	23	99
Sharpless	5	55	4[d]	99
BMM[e,f]	5	50	25	99
BMM	10	46	23	nd
BMM	25	48	24	nd
BMM	50	40	20	98
BMM	100	38	19	99

[a] Reference 6. [b] BMM = benzoyl migration method; ee = enantiomeric excess; nd = not determined (all other physical and spectral properties are identical); SM = starting material = methyl cinnamate. [c] Produces the carboxylic acid as the final product. [d] Low overall yield due to low yield encountered during first step. [e] Produces the methyl ester as the final product. [f] Since the immediate chemical environment for the azide displacement and reduction sequence is very similar in both methods, the lower yields observed during the migration step in the BMM case probably reflect a somewhat less proficient migration on the part of the benzoyl moiety.

white solid was obtained and recrystallized from toluene (ca. 60 mg/mL): yield, 0.69 g (70%); mp 87−88 °C (lit.[8] 84−86 °C); [α] = +10.5° (*c* 0.5, EtOH) (lit.[21] [α] = +12.2°; for enantiomer, lit.[17] [α]= −10.7°); NMR 7.31−7.33 (m, 5H), 5.01 (d, *J* = 2.6, 1H), 4.38 (d, *J* = 2.6, 1H), 3.82 (s, 3H), 3.11 (br, 1H), 2.74 (br, 1H).

Methyl (2*S*,3*R*)-2-(Benzoyloxy)-3-bromo-3-phenylpropionate (3). Trimethyl orthobenzoate (2.62 mL, 15.28 mmol) was added to a stirred solution of diol **2** (2.30 g, 11.72 mmol) and *p*-toluenesulfonic acid monohydrate (20 mg, 0.1 mmol) in 20 mL of methylene chloride. The mixture was stirred at room temperature for 3 h. The volatiles were evaporated. The residue was taken up in 20 mL of CH_2Cl_2 and the mixture cooled to −15 to −20 °C, and acetyl bromide (1.04 mL, 13.96 mmol) was added dropwise. After 3 h, additional trimethyl orthobenzoate (0.25 mL, 1.45 mmol) and acetyl bromide (0.15 mL, 2 mmol) were added, and stirring was continued for 1 h. The mixture was evaporated to a light yellow oil. Colorless crystals were obtained from hexane−ether (6:4; ca. 30 mg/mL): yield, 2.67 g (65%); mp 91−92 °C; TLC R_f 0.51 hexane−EtOAc (7:3); [α] = −116° (*c* 0.5, MeOH); NMR 7.98−8.0 (m, 2H), 7.34−7.56 (m, 8H), 5.83 (d, 1H), 5.49 (d, 1H), 3.72 (s, 3H); ^{13}C NMR 167.3, 165.2, 136.7, 133.6, 129.9, 129.1, 128.8, 128.6, 128.5, 75.8, 52.7, 49.3; IR very strong band at 1728. Elemental anal. Theor: C, 56.20; H, 4.13. Found: C, 56.04; H, 4.08.

(2*R*,3*S*)-*N*-Benzoyl-3-phenylisoserine Methyl Ester (Paclitaxel's C-13 Side Chain). A mixture of 5.08 g (14 mmol) of benzoyloxy bromo ester **3** and 3.64 g (56 mmol) of sodium azide in 20 mL of DMF was stirred at 45−50 °C for 36 h. The mixture was diluted with 50 mL of ether, washed with water (3 × 50 mL), dried, and concentrated. The residue was dissolved in 50 mL of MeOH and hydrogenated in the presence of 1.5 g of 10% Pd−C under 45 psi of hydrogen for 36 h. The catalyst was filtered off, and the filtrate was allowed to stand for 48 h. A residue was obtained upon evaporation. Colorless crystals were obtained from 20 mL of chloroform: yield, 2.09 g (50%); mp 184−186 °C (lit.[17] mp 184−185 °C); [α] = −47.7° (*c* 1, MeOH) (lit.[17] [α] = −48°); NMR 7.75−7.78 (m, 2H), 7.30−7.51 (m, 8H), 6.99 (d, *J* = 9, 1H), 5.74 (dd, *J* = 2 and 9, 1H), 4.63 (d, *J* = 2, 1H), 3.84 (s, 3H), 3.30 (br, 1H).

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