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TETRAHEDRON: *ASYMMETRY*

Synthesis of (2*R*,3*S*)-isobutyl phenylisoserinate, the Taxol® side chain, from ethyl benzoylacetate

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Abstract

Reduction of ethyl 2-chloro-3-phenyl-3-oxopropionate with borohydride affords predominately the *syn*-chlorohydrin. Resolution of this ester with the lipase MAP-10 gives (2*S*,3*R*)-2-chloro-3-hydroxypropionic acid which after esterification with MeOH/HCl is converted to the *cis*-epoxide with potassium carbonate and DMF. Aminolysis of the epoxide with aqueous ammonia results in ring opening and amide formation. The amide is converted to an ester upon treatment with isobutyl alcohol and HCl(g) at 100°C. Neutralization then affords the Taxol® side chain as the free amine. © 2000 Published by Elsevier Science Ltd.

1. Introduction

The importance of Taxol®,[1] a complex diterpene, in the armamentarium against the scourge of cancer is now well established.[2] Initially, its only source was from the bark of the pacific yew tree, *Taxus brevifolia*, which cannot be considered a renewable resource because of its slow growth and, therefore, the supply of Taxol® was quite limited during the early clinical trials. On the other hand, the supply of the key terpenoid fragment 10-desacetylbaccatin III (10-DAB) is readily obtained from a rapidly renewed resource, the yew bush: *Taxus baccata*. Since the initial work by the French group of Potier,[3] a number of methods have been developed to convert 10-DAB to Taxol®, all of which rely on coupling of a protected phenylisoserinate to a 7-protected baccatin derivative.[4,5] Because the side chain is not readily available from natural sources, its sole supply must rely on chemical synthesis. As a result, several synthetic approaches have been developed with varying degrees of efficiency and simplicity.[6] We wish to describe here an enzyme based synthesis which we feel is straight forward, uses readily available materials and could easily be scaled up to make multikilo quantities of material.

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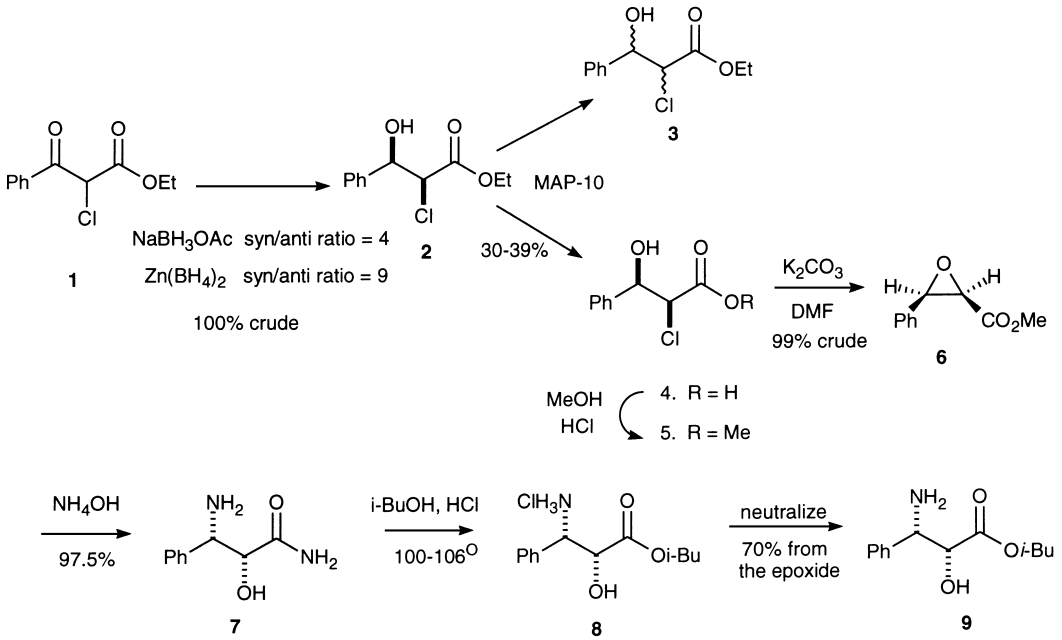
2. Results and discussion

Lipase mediated syntheses are now well known and offer rapid access to non-racemic chiral substrates. We felt that the readily available racemic chlorohydrin **2** would serve as a suitable substrate for a lipase and thus give us rapid access to the diastereomerically and enantiomerically pure epoxide **6** (Scheme 1). Thus chloride **1**,[7] obtained by simple chlorination of ethyl benzoylacetate, is reduced with $NaBH_4$ to afford a 4:1 mixture of the *syn*- and *anti*-chlorohydrins whereas reduction with $Zn(BH_4)_2$ affords a 9:1 mixture of the *syn*- and *anti*-chlorohydrins. The use of $NaBH_4$ also resulted in considerable over-reduction, but using $NaBH_3OAc$ minimized this while still giving a 4:1 ratio of products. The two isomers were not readily separable and thus no attempt was made to separate them. Enzymatic hydrolysis of this mixture using a number of lipases (Table 1) showed that the best selectivity was obtained using the Amano MAP-10 lipase which unexpectedly gave excellent *syn*/*anti*-selectivity as well as excellent enantioselectivity. The acid was produced with 90% ee. The diastereoselectivity of MAP-10 was unique among the enzymes tested. Generally, with the MAP-10 enzyme a 35% chemical yield of pure *syn*-chlorohydrin **4** could be obtained after isolation by a simple acid/base extraction protocol. The (2*S*,3*R*)-acid is then converted to the methyl ester **5** with methanol and HCl(g). Ring closure to the *cis*-epoxide is cleanly accomplished with K_2CO_3 in DMF.



Scheme 1.

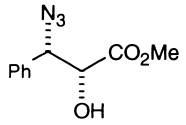
The most common procedure for opening such an epoxide is with azide ion. Although this reaction works well[6o] it is not suited to scale-up because the intermediate azido derivative has 1/3 the explosive potential of an equivalent weight of TNT. This was determined using differential scanning calorimetry on the methyl ester **10**.[8] The other method often used to open epoxides is to

Table 1
Lipase screening results

No.	Enzyme	Ratio Enz/Sub	Conversion	Temp.	Acid **4** Syn/Anti	$[\alpha]_D^{25}$
1.	PS30	1:1	66%	25	84/16	-2.2
2.	PPL	1:1	50%	25	89/11	-2.3
3.	CCL	1:1	66%	25	85/15	-2.1
4.	OF 360	1:1	100%	25	*	*
5.	AK	1:1	60%	25	*	0.0
6.	MAP 10	1:1	60%	25	99/ <1	-3.9
7.	MAP 10	5:1	40%	25	99/ <1	*

* Not determined

form amines directly with anhydrous ammonia in EtOH at elevated temperatures and pressures as done by Jacobson in his synthesis of the Taxol® side chain.[6n]



10

We have found an experimentally much simpler method utilizing aqueous ammonia. Thus, simply stirring the epoxide with concentrated aqueous ammonia results in clean opening of the epoxide and converts the ester to the amide to afford amide **7** without the need to use pressure rated equipment. It is at this point that the enantiopurity of the resulting amide is upgraded. The racemic amide **7** is insoluble in MeOH and can thus be removed by simple filtration. This was determined during an attempt to crystallize the amide from methanol. The racemic nature of the solids was confirmed by formation of the Mosher ester of the derived benzamide.

Finally, conversion of the amide to an acid or ester must be addressed. Normal methods for hydrolysis of such amides tend to be problematic and in the case of amino acids the isolation is not always straightforward. We found that conversion of the amide to the isobutyl ester was conveniently achieved by heating an isobutyl alcohol slurry of the amide to 100°C after saturating with HCl gas.[9] After neutralization and isolation a 70% overall yield of amine **9** from epoxide **6** is obtained. At this point the material can be benzoylated to give the paclitaxel side chain, derivatized with $(BOC)_2O$ to give the Taxotere® side chain or alternately derivatized as part of an analog program.

In conclusion, we have described a simple and safe synthesis of the phenylisoserine subunit of paclitaxel that should be amenable to scale-up and uses only readily available low cost reagents. We have shown that a lipase may be used for a very efficient resolution of a 2-chloro-3-hydroxy-3-phenyl propionate, a process that has the potential to be extended to a number of other related

substrates. In our synthesis, the free amine is isolated which gives this approach considerable flexibility with regard to analog development.

3. Experimental

3.1. Ethyl 2-chloro-3-hydroxy-3-phenylpropionate **2** from $NaBH_3OAc$

A solution of **1** (100 g, 0.44 mol) and glacial acetic acid (25 mL, 0.44 mol) in ethanol (1 L) was cooled to –5°C and stirred for 10 min. Sodium borohydride pellets (12.54 g, 0.33 mol, diam. 11 mm) were added in portions (4.2 g×3) with vigorous stirring. The reaction temperature was maintained at –5 to 0°C. After the addition, the reaction mixture was stirred continuously at 0°C for 5 h and was then poured slowly into ice-water with stirring. The mixture was extracted with ethyl acetate (1 L). The organic phase was washed three times with water (100 mL) and brine (100 mL), dried over magnesium sulfate, and the solvent was removed under reduced pressure to give crude **2** as an oil (105 g, 100%). The chlorohydrin **2** is a 1:4 mixture of the *anti*- and *syn*-isomers as determined by NMR. MS m/z (CI+NH_3) 246 (M^++17), 228 (M^+), 210, 194. *anti*-**2**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.60–7.50 (m, 5H), 5.33 (d, J=6.5 Hz, 1H), 4.64 (d, J=6.5 Hz, 1H), 4.33 (q, J=7.1 Hz, 2H), 1.33 (t, J=7.1 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) 167.9, 138.2, 128.7, 128.5, 126.7, 74.6, 62.9, 62.2, 13.7. *syn*-**2**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.60–7.50 (m, 5H), 5.24 (d, J=7.7 Hz, 1H), 4.58 (d, J=7.7 Hz, 1H), 4.44 (q, J=7.2 Hz, 2H), 1.46 (t, J=7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) 168.9, 138.8, 126.7, 126.5, 126.9, 75.2, 62.3, 59.2, 13.8.

3.2. Ethyl 2-chloro-3-hydroxy-3-phenylpropionate **2** from $Zn(BH_4)_2$

A solution of **1** (6.8 g, 30 mmol) in dichloromethane (68 mL) was cooled to –5°C and a 0.4 M solution of zinc borohydride (38 mL, 15 mmol) in ethyl ether was added dropwise over 30 min. After the addition, the reaction mixture was stirred at 0°C for 30 min and then poured into a cold solution (0°C) of acetic acid (5 mL) in water (15 mL). The resulting mixture was extracted with dichloromethane (30 mL×2). The combined organic phases were washed with water (30 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate in hexane (5–25%) to give **2** (4.9 g, 72%) as a 91:9 mixture of *syn*- and *anti*-isomers as determined by NMR.

3.3. (2S,3R)-2-Chloro-3-hydroxy-3-phenylpropionic acid **4**

(±)-Ethyl-2-chloro-3-hydroxy-3-phenyl propionate (5.5 g, 24 mmol, *syn*/*anti*=14:3) was incubated with lipase MAP-10 (1 g) in 0.2 M pH 7.0 phosphate buffer (100 mL). The reaction mixture was stirred vigorously at 25°C for 6 days. The conversion was checked by HPLC (nucleosil C-18 column, CH_3CN:H_2O, 30:70, flow 2 mL/min, 207 nm) which showed **2** (60–65%, retention time 10.9 min) and **3** (40–35%, retention time 1.0 min). The resulting reaction mixture was acidified with 5% HCl (15 mL) to pH<2 and extracted with ethyl acetate (50 mL×3). The combined organic solution was extracted with 10% aqueous potassium carbonate (25 mL) and then washed with water (25 mL×2). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give **3** (3.3 g, 60%). The combined aqueous solution was washed with ethyl ether (30 mL) and acidified with 10% HCl (50 mL) to pH<2. The acidic solution was extracted with ethyl

acetate (50 mL×2). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give **4** (1.9 g, 39.5%). The overall reaction time can be reduced by using a higher loading of the enzyme. Compound **3**: the ratio of *syn*:*anti* was 2:1 from ^{1}H NMR; $[\alpha]_D^{25}$ +6.35 (*c* 3.23, $CHCl_3$). Compound **4**: an analytical sample was prepared by recrystallization by dissolving the acid in 5 mL/g hot chloroform, adding 1.5 mL/g heptane then cooling to 0°C for 1 h. Filtration and drying gives colorless crystals: mp 98–100°C; $[\alpha]_D^{25}$ = +1.95 (*c* 1.48, MeOH) and –3.9 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 7.42–7.39 (m, 5H), 5.28 (d, *J* = 8.4 Hz, 1H), 4.58 (d, *J* = 8.4 Hz, 1H). Anal. calcd for $C_9H_9O_3Cl$: C 53.87, H 4.52, Cl 17.71. Found: C 53.50, H 4.68, Cl 17.45. MS m/z 200 (M+), 165, 147, 129, 119, 107, 91, 79, 65, 51; HRMS calcd for $C_9H_9O_3Cl$ 200.0240, obsd 200.0240.

3.4. *Methyl (2*S*,3*R*)-2-chloro-3-hydroxy-3-phenylpropionate* **5**

A solution of (2*S*,3*R*)-2-chloro-3-hydroxy-3-phenyl propionic acid **4** (2 g, 10 mmol) in methanol (20 mL, saturated with HCl) was stirred at 25°C for 1 h. The reaction mixture was poured into saturated aqueous sodium bicarbonate (20 mL) and extracted with ethyl acetate (20 mL×3). The combined organic phases were washed with water (20 mL) and dried over magnesium sulfate. Filtration and solvent removal under reduced pressure gave the methyl ester **5** (2.05 g, 95%): $[\alpha]_D^{25}$ = –5.0 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 7.41–7.35 (m, 5H), 5.19 (d, *J* = 6.2 Hz, 1H), 4.51 (d, *J* = 6.2 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) 168.4, 138.1, 128.7, 128.5, 126.5, 74.4, 62.8, 53.0.

3.5. *Methyl (2*R*,3*R*)-2,3-epoxy-3-phenylpropionate* **6**

To a solution of (2*S*,3*R*)-methyl-2-chloro-3-hydroxy phenylpropionate **5** (31.6 g, 0.15 mol) in DMF (730 mL) was added water (13.5 mL) followed by potassium carbonate (62 g, 0.45 mol) at 25°C with stirring. The mixture was allowed to stir at 25°C for 72 h and then poured into a mixture of ethyl acetate (3 l) and water (500 mL). The organic layer was separated and the aqueous layer was back washed with ethyl acetate (400 mL×2). The combined organic layers were washed with water (400 mL×3). The water layers were extracted with ethyl acetate (100 mL). The combined organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to about 800 mL. The organic solution was again washed with water (250 mL×4), dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give the epoxide **6** as a colorless oil (26 g, 99%): $[\alpha]_D^{25}$ = +15.0 (*c* 1.52, chloroform); ^{1}H NMR (300 MHz, $CDCl_3$): 7.45–7.33 (m, 5H), 4.30 (d, *J* = 4.6 Hz, 1H), 3.88 (d, *J* = 4.6 Hz, 1H), 3.58 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): 167.0, 132.7, 128.5, 128.0, 126.5, 57.5, 55.8, 52.0. MS m/z 178 (M+), 161, 131, 107, 105, 91, 79, 77, 51.

3.6. *(2*R*,3*S*)-3-Amino-2-hydroxy-3-phenylpropionamide 7*

Epoxy ester (+)-**6** (21.2 g, 0.12 mol) was added to a cold (0°C) solution of ammonium hydroxide (220 mL, 30%) with stirring (the addition took about 30 min). The reaction mixture was then stirred at 25°C for 4 days. The resulting mixture was evaporated to dryness under vacuum (~27 in) in a 30–35°C water bath to give amide (+)-**7** (20.9 g, 97.5%). An analytical sample was prepared by recrystallization: The crude product (2 g) was dissolved in refluxing methanol (30 mL). After 15 min of refluxing, the suspension was filtered at the boiling temperature

and a white powder (300 mg)[10] collected which did not dissolve in methanol. This material proved to be the racemic amide based on derivatization as Mosher's ester. The filtrate was kept in the freezer at –20°C overnight to give the first crop of crystals (730 mg). The mother liquor was evaporated under reduced pressure to a volume of about 10 mL. After standing at –20°C, a second crop of crystals (500 mg) was obtained: mp 175–178°C (lit.[9] mp 172–173°C); $[\alpha]_D^{25} = +60$ (*c* 0.66, MeOH); IR (mineral oil) 3425, 3416, 3139, 1640, 1451, 1316, 996, 971, 647 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6: D_2O, 3:1): 7.13–7.36 (m, 5H), 4.10 (d, $J = 3.2$ Hz, 1H), 3.88 (d, $J = 3.2$ Hz, 1H). ^{13}C NMR (300 MHz, DMSO-d_6: D_2O, 3:1): 174.8, 144.1, 127.7, 127.0, 126.3, 75.5, 57.2. MS m/z 181 (M^++1), 164, 106, 105; HRMS m/z calcd for $C_9H_{12}N_2O_2$+H_1 181.0977, obsd 181.0975.

3.7. *Isobutyl (2R,3S)-3-amino-2-hydroxy-3-phenylpropionate* **9**

To a suspension of (2*R*,3*S*)-2-hydroxy-3-amine-3-phenylpropionamide (180 mg, 1 mmol) in isobutyl alcohol (2.5 mL) was bubbled anhydrous hydrogen chloride gas until saturated allowing the temperature to rise. The reaction mixture was then heated to 100°C overnight. The resulting solution was evaporated to dryness under reduced pressure at 50°C. The residue was dissolved in water (5 mL), and neutralized with saturated potassium carbonate solution to pH > 9. The aqueous phase was extracted with ethyl acetate (15 mL×3). The combined organic solution was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (1–5% methanol in dichloromethane) to give the isobutyl ester **9** (165 mg, 70% overall from epoxide **6**) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) 7.44–7.28 (m, 5H), 4.34 (d, $J = 3.3$ Hz, 1H), 4.30 (d, $J = 3.3$ Hz, 1H), 4.00 (d, $J = 6.7$ Hz, 2H), 1.95 (m, 1H), 0.95 (d, $J = 6.7$ Hz, 6H). ^{13}C NMR (300 MHz, $CDCl_3$) 173.5, 142.3, 128.5, 127.5, 126.7, 75.0, 71.8, 58.0, 27.6, 18.9. MS m/z 238 (M^++1), 165, 136, 118, 107, 106, 104, 91, 79, 77, 57. HRMS m/z calcd for $C_{13}H_{19}N_1O_3$+H_1 238.1443, obsd 238.1441.

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10. This white powder (mp 215–220°C dec.) was examined by IR, NMR, and HRMS. The ^{1}H and ^{13}C NMR are the same as the methanol crystallized sample. A sample was benzoylated and derivatized as the Mosher ester, which by NMR proved to be a 1:1 diastereomeric mixture. Thus, the methanol insoluble material is racemic.