Asymmetric synthesis of taxol and taxotère side chains by enolate hydroxylation

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Abstract: We report an asymmetric synthesis of the taxol and taxotère side chains by hydroxylation of enolates derived from N-substitued methyl 3-amino-3-phenyl propionate with the oxodiperoxymolybdenum (pyridine) (hexamethyl phosphoric triamide) complex (MoOPH).

Key words: taxol and taxotère side chains, hydroxylation.

Résumé : Nous décrivons une synthèse asymétrique des chaînes latérales du taxol et du taxotère par hydroxylation des énolates dérivés d'esters de l'acide 3-amino-3-phénylpropionique L-homo-phénylglycine au moyen du complexe oxodiperoxopyridino (hexaméthylphosphoramido) molybdène (MoOPH).

Mots clés : chaines latérales du taxol et du taxotère, hydroxylation.

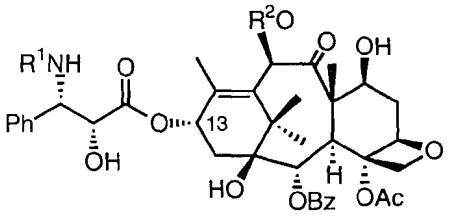
Introduction

Taxol **1**, a complex diterpene isolated from the bark of *Taxus brefivolia* (1), and taxotère **2** a semi-synthetic analog (2), are currently considered to be among the most promising anticancer agents (3) (Fig. 1). Their clinically demonstrated effectiveness has stimulated considerable effort in total and analog synthesis (3), as well as in the development of efficient syntheses of the (2*S*,3*R*)-3-phenyl isoserine ester moiety at C-13 that is crucial for bioactivity. The synthetic approaches to this amino acid are centered around the use of chiral glycidate esters (4), opening of β-lactam rings derived from cycloaddition reactions (5), aldol condensations (6), and homologation of *(S)*-phenylglycine (7), intermediates derived from asymmetric dihydroxylation (8), or enzymes (9). With a few exceptions (4*a*, 4*d*), the methods involving glycidic esters and dihydroxycinnamic esters have relied principally on azide ion as a source of nitrogen. To the best of our knowledge only two methods are based on the introduction of the 2-hydroxyl group by hydroxylation of an enolate (10*a*,*b*). Our recent studies on stereocontrolled oxidation of enolates (11) derived from L-aspartic and glutamic acid derivatives (12) prompted us to extend our methodology to the synthesis of the taxol and taxotère side chains. In this paper we describe a stereocontrolled synthesis of methyl esters **6***a* and **6***b* by direct oxidation of β-aminoesters **5***a* and **5***b* using MoOPH as an electrophilic source of oxygen (Scheme 1).

Results

Methyl 3-amino-3-phenyl propionate **4** of high enantiomeric purity (>95%) was obtained from the corresponding acid **3** by resolution with D-tartaric acid following a literature procedure (13*a*). Benzoylation of **4** with benzoyl chloride, or treatment with di-*tert*-butyl dicarbonate in the presence of sodium bicarbonate furnished the N-protected derivatives **5***a* and **5***b* in 75% yield in each case.

Fig. 1.



R^1= PhCO, R^2= Ac Taxol **1**
R^1=*t*-BuOCO, R^2= H Taxotère **2**

Initially, we investigated the hydroxylation of the enolate dianions of **5***a* and **5***b* using racemic 2-phenylsulfonyl-3-phenyloxaziridine (14). Davis et al (10*b*) recently reported that reaction of the lithium dianion of **5***a* generated in the presence of LDA and LiCl with (+)-(camphorsulfonyl)oxaziridine at −100°C to −78°C afforded a preponderance of the desired *syn* isomer **6***a* (*syn/anti* 86:14). In an independent study, we had observed that treatment of the potassium enolate (KHMDS, −78°C to −25°C) of **5***a* with 2-phenylsulfonyl-3-phenyloxaziridine at −60°C led to a 86:14 *syn/anti* mixture in 65% yield. However, similar treatment of the potassium enolate of **5***b* proceeded with only moderate diastereoselectivity in favor of the *anti* isomer (*syn/anti* 40:60) in 62% yield. To clarify this intriguing reversal of selectivity, other metals were examined as counterions. Although the sodium enolate generated with NaHMDS gave a similar ratio (*syn/anti* 35:65), the use of LiHMDS furnished the highest *anti* selectivity (*syn/anti* 10:90). The sense of chiral induction with **5***a* can be rationalized according to Davis et al. (10*b*) where the potassium enolate, which may exist as an eight-membered ring **I** (Scheme 2), is preferentially attacked from the less hindered face of the

Received August 25, 1995.

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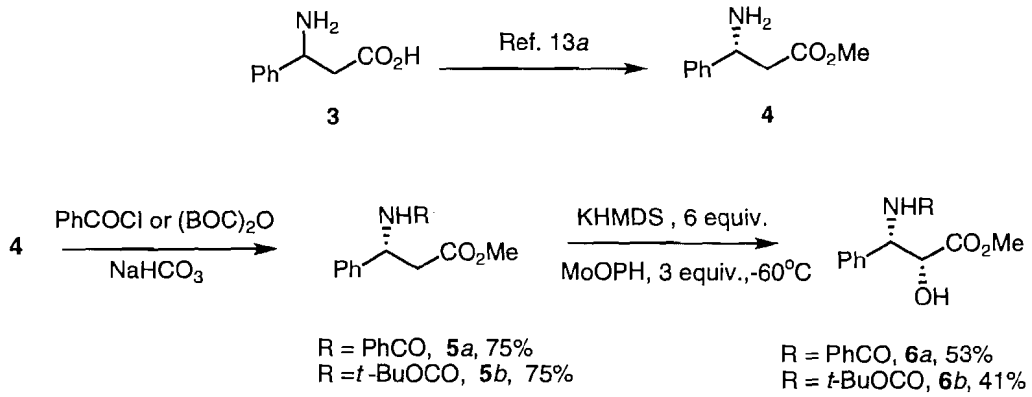
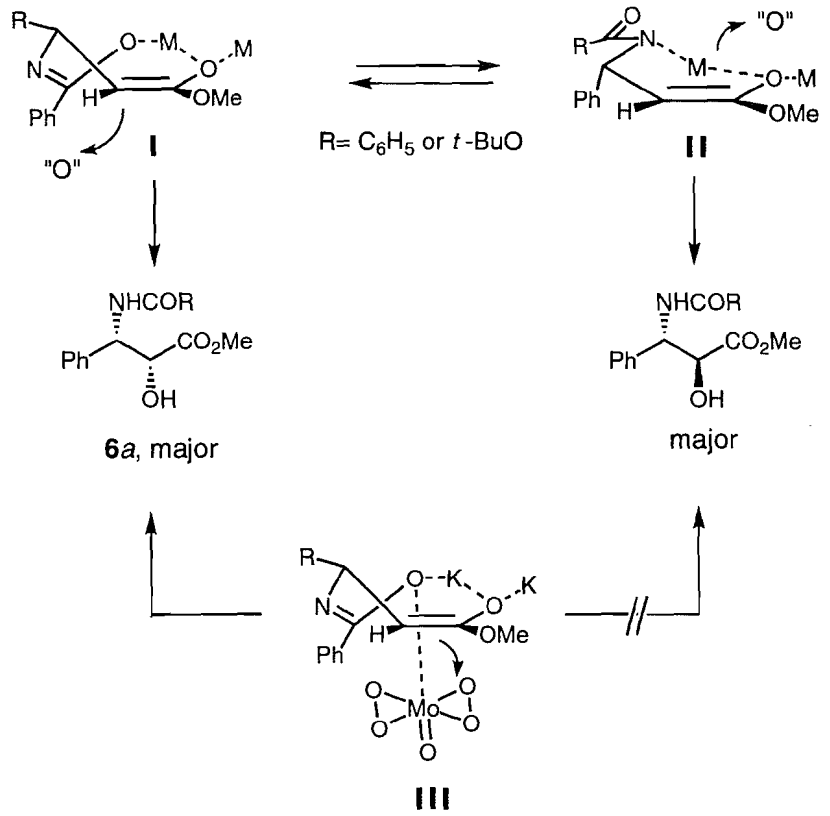
Scheme 1.



Scheme 2.



enolate, resulting in the formation of the *syn* hydroxylated product **6***a*. On the other hand, it is possible that the enolates of the carbamate derivative **5***b* preferentially adopt a six-membered ring chelate **II** resulting in a reversal of selectivity.

To improve the *syn* selectivity, we examined hydroxylations of **5***a* and **5***b* with MoOPH (15) in anticipation of an "internal" delivery of oxygen (12). Reaction of the potassium enolate derivative of **5***a* (KHMDS, −78°C to −25°C) with MoOPH (3 equiv.) was carried out at −60°C to give **6***a* as a 86:14 *syn/anti* mixture in 83% after column chromatography. The minor *anti* isomer can be removed almost quantitatively by one recrystallization from $CHCl_3$, yielding the expected amino acid **6***a* in 53% yield. The enantiomeric purity of this material was determined to be >97% by ^1H NMR and ^{19}F NMR analysis of its Mosher ester (16). Interestingly, treatment of the potassium enolate of **5***b* with MoOPH also proceeded with *syn* selectivity (*syn/anti* 86:14) in 65% yield. The taxotère side chain **6***b* could be isolated as a single diastereoisomer after two chromatographic purifications in 41% yield (ee >95% determined by analysis of ^1H NMR and ^{19}F NMR of Mosher ester derivative). The preponderance of the *syn* product in hydroxylations of **5**a and **5***b* with MoOPH can be rationalized by an initial coordination of the MoOPH reagent with the amide or carbamate groups (N or O) followed by an intramolecular delivery of oxygen as depicted in Scheme 2, expression **III** (12).

Previous examples of related enolate hydroxylations have utilized chiral non-racemic oxaziridine reagents derived from camphor (10*a*,*b*). As mentioned above, the Davis method (10*b*) generates the lithium enolate in the presence of lithium chloride (−42°C), and temperatures of −100°C to −78°C are needed for the stereoselective hydroxylation. Davies and co-

workers (10*a*), on the other hand, produce the *anti* isomer as a result of a mismatched reagent combination, which has to be inverted by a Mitsunobu protocol to give the desired *syn* product.

In summary, we have demonstrated that MoOPH can be an alternative reagent to provide the side-chain amino acids in taxol and taxotère in enantiomerically pure form. In both examples of hydroxylation, it was necessary to use more than stoechiometric amounts of base in order to achieve the yields quoted above.

Experimental

Tetrahydrofuran was distilled over benzophenone and potassium prior to use. Analytical thin-layer chromatography (TLC) was carried out on Merck Kieselgel silica gel 60 F_{254} glass plates. ^{1}H nuclear magnetic resonance spectra at 400 MHz were obtained on a Bruker WH-400 spectrometer. ^{1}H multiplicities are recorded by use of the following abbreviations: s, singlet; d, doublet; m, multiplet; br, broad; *J*, coupling constant (Hz). High-resolution FAB mass spectra were obtained by means of Kratos MS5OTCTA and AEI-MS 902 spectrometers at the Université de Montréal. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 25°C.

Melting points were measured on Büchi apparatus and are uncorrected. Column chromatography was done using the flash technique (17).

(3*R*)-Methyl-3-amino-3-phenylpropionate (4)

The procedure described by Wasserman and Berger (13*a*) for the preparation of (3*S*)-**4** was followed. A solution of (±)-**4** (3.8 g, 21.2 mmol) in MeOH was added in one portion to a refluxing solution of D-tartaric acid in MeOH (20 mL). After cooling overnight at −5°C, the white crystals were filtered off, mp 168–169°C; $[\alpha]_D$ −16.9 (*c* 3, H_2O). Recrystallization of this material from MeOH (20 mL) gave the D-tartrate salt (35–40% yield), which was recrystallized to constant physical properties; mp 169–170°C; $[\alpha]_D$ 19.3 (*c* 3, H_2O) (lit. (13*b*) mp 169–171°C; $[\alpha]_D$ −20.2 (*c* 7, H_2O)); ^{1}H NMR (D_2O) δ: 3.15 (dd, 2H), 3.67 (s, 3H), 4.49 (s, 2H), 7.47 (s, 5H). A solution of the above salt (3.72 g, 11.3 mmol) was treated with 1 N NaOH, affording **4** (1.7 g, 84%) as a colorless oil; bp 175–180°C (5 Torr (1 Torr = 133.3 Pa), Kugelrohr); $[\alpha]_D$ +11.6 (neat); (lit. (13*b*) $[\alpha]_D$ +12.1 (neat); lit. (13*c*) $[\alpha]_D$, +22.3 (*c* 1.99, $CHCl_3$)). ^{1}H NMR ($CDCl_3$) δ: 1.77 (s, 2H), 2.6 (d, 2H), 3.67 (s, 3H), 4.4 (m, 1H), 7.33–7.34 (m, 5H). The enantiomeric purity was detemined to be >95% by ^{1}H and ^{19}F NMR analysis of the corresponding Mosher ester derivative.

(3*R*)-*N*-Benzoyl-methyl-3-amino-3-phenylpropionate (5*a*)

To a stirred emulsion of **4** (204 mg, 1.14 mmol) and $NaHCO_3$ (163 mg) in CH_2Cl_2–H_2O (2:2 mL) was added freshly distilled benzoyl chloride (192 mg, 1.36 mmol). After vigorous stirring overnight, the aqueous phase was extracted three times with CH_2Cl_2 (20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. The resulting white solid was recrystallized from CH_2Cl_2–Et_2O (1:3), giving white needles of **5***a*, (244 mg, 75%); mp 120–121°C; $[\alpha]_D$ −20.2 (*c* 1.17, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 3 (dd, *J* = 5.6 Hz, *J* = 15.7 Hz, 2H), 3.65 (s, 3H), 5.64 (dd, *J* = 5.6 Hz, *J* = 8.4 Hz, 1H), 7.34–7.35 (m, 8H), 7.83–7.86 (d, 2H). MS (EI) *m/z*: 105 (100), 178 (15), 210; HRMS calcd. for $C_{17}H_{17}NO_3$: 283.3268; found: 283.2103.

(3*R*)-*N*-(*tert*-Butoxycarbonyl)-methyl-3-amino-3-phenylpropionate (5*b*)

To a stirred emulsion of **4** (767 mg, 4.3 mmol) and $NaHCO_3$ (363 mg) in CH_2Cl_2–H_2O (2:2 mL) was added di-*tert*-butyl dicarbonate (938 mg, 4.3 mmol). After vigorous stirring overnight, the aqueous phase was extracted three times with CH_2Cl_2 (20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. The resulting white solid was purified by column chromatography with 30% EtOAc – hexanes to provide **5***b* (905 mg, 75%) as white needles, mp 92–94°C; $[\alpha]_D$ +28 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.4 (s, 9H), 2.82 (m, 2H), 3.6 (s, 3H), 5.1 (br s, 1H), 5.45 (br s, 1H), 7.2–7.4 (m, 5H); MS (EI) *m/z*: 83, 106, 150, 163, 223; HRMS calcd. for $C_{11}H_{13}NO_4$ (M – isobutylene)$^+$: 223.1332; found: 223.0845.

(2*R*,3*S*)-*N*-Benzoyl-3-phenylisoserine methyl ester (6*a*)

To a solution of KHMDS (0.5 M in toluene, 40 mL, 20 mmol, 6 equiv.) in dry THF (10 mL) was added dropwise at −78°C a solution of **5***a* (1g, 3.5 mmol) in THF (30 mL). The reaction mixture was warmed up to −25°C, stirred at this temperature, and then cooled back to −78°C. Freshly prepared MoOPH (15) (2.9 g, 5.25 mmol) was added in one portion. The resulting green solution was stirred at −60°C for 3 h, then quenched with saturated Na_2SO_3 (10 mL) followed by saturated NH_4Cl. The mixture was warmed up to room temperature and stirred until dissolution of the solids. The aqueous layer was extracted with THF (25 mL). The combined organic layers were washed successively with a mixture of 10% HCl – brine (1:1, 10 mL), 2% Na_2CO_3, brine, and dried over Na_2SO_4. After removal of the solvent, flash chromatography with 5% ether in CH_2Cl_2 gave unreacted ester **5***a* (50 mg), then **6***a* (86:14 *syn/anti* mixture by ^{1}H NMR, 833 mg, 84% yield based on consumed ester **5***a*). Recrystallization of this mixture from $CHCl_3$ yielded white needles of taxol side chain methyl ester **6***a* (560 mg, 53%), mp 180–181°C; $[\alpha]_D$ −47.5 (*c* 0.99, MeOH) (lit.(1) mp 184–185°C; $[\alpha]_D$ −49.6; lit.(4*g*) mp 184–185°C; $[\alpha]_D$ −48.1). ^{1}H NMR ($CDCl_3$) δ: 3.25 (br s, 1H), 3.86 (s, 3H), 4.65 (d, *J* = 1.83 Hz,1H), 5.76 (dd, *J* = 9.15 Hz, *J* = 1.83 Hz, 1H), 6.98 (d, *J* = 9.2 Hz, 1H); 7.3–7.6 (m, 8H), 7.7–7.8 (d, 2H). ^{1}H NMR and ^{19}F NMR analysis of this material showed the presence of small amounts of the *anti* diastereoisomer (<5%) and confirmed the enantiomeric purity (>97%).

(2*R*,3*S*)-*N*-(*tert*-Butoxycarbonyl)-3-phenylisoserine methyl ester (6*b*)

To a solution of KHMDS (0.5 M in toluene, 24 mL, 12 mmol, 6 equiv.) in dry THF (10 mL) was added dropwise at −78°C a solution of **5***b* (558 mg, 2 mmol) in THF (30 mL). The reaction mixture was warmed up to −25°C, stirred at this temperature, and then cooled back to −78°C. Freshly prepared MoOPH (1.3 g, 6 mmol, 3 equiv.) was added in one portion. The resulting green solution was stirred at −60°C for 3 h, then quenched with saturated Na_2SO_3 (10 mL) followed by saturated NH_4Cl. The mixture was warmed up to room temperature and stirred until dissolution of the solids. The aqueous layer was extracted with THF (25 mL). The combined organic layers were washed successively with a mixture of 10% HCl – brine (1:1, 10 mL),

2% Na_2CO_3, and brine, and dried over Na_2SO_4. After removal of the solvent, flash chromatography with 1% ether in CH_2Cl_2 gave **6***b* (86:14 *syn/anti* mixture by ^1H NMR) (383 mg, 65% yield based on consumed ester **5***b*). Two chromatographic purifications of this mixture with 20% EtOAc – hexanes provided the taxotère side–chain methyl ester **6***b* (240 mg, 41%) as white needles, mp 128–129°C; $[\alpha]_D$ −6.6 (*c* 1.1, $CHCl_3$) (lit. (4*g*) mp 130.5–131.5°C; $[\alpha]_D$ −7 (*c* 1.2, $CHCl_3$)). ^1H NMR ($CDCl_3$) δ: 1.4 (br s, 9H), 3.12 (br s, 1H), 3.84 (s, 3H), 4.47 (br s, 1H), 5.21 (d, 1H), 5.4 (d, 1H), 7.3–7.6 (m, 8H), 7.25–7.4 (m, 5H). ^1H NMR and ^{19}F NMR analysis of this material showed the presence of only one diastereisomer and confirmed the enantiomeric purity (>95%).

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada (NSERCC) and le Fonds pour la formation de chercheurs et l'aide à la recherche (FCAR) for generous financial assistance.

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