Enantioselective Taxanes Approach Using Both Enantiomers of the Same Building-Block. Part 1: Taxol® A-Ring Subunit

Gérard Audran, Jean-Pierre Uttaro, Honoré Monti*

Laboratoire de Réactivité Organique Sélective UMR 6516 Faculté des Sciences de St-Jérôme (case 551), Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France
Fax +33(4)91288862; E-mail: honore.monti@univ.u-3mrs.fr

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Abstract: An efficient enantioselective synthesis of fully-oxygenated Taxol® A-ring subunit has been achieved using (–)-karahana lactone, (–)-**2**, as an enantiopure starting building-block and a diastereoselective allylic hydroxylation as the key step.

Key words: stereoselectivity, enantioselective synthesis, Taxol®, antitumor agents

Paclitaxel[1] (Taxol®, Figure 1), a substance originally isolated[2] from Pacific yew tree *Taxus brevifolia*, and its synthetic analogs,[3] have attracted considerable interest from synthetic organic chemists owing to their remarkable anticancer activities and their low natural availability. At this time, six total syntheses of Taxol® have been reported[4] and two of them, the Nicolaou[4a,b] and Danishefsky[4c,d] convergent strategies, utilized an A + C connection to form the central B-ring.

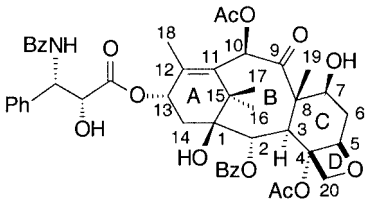
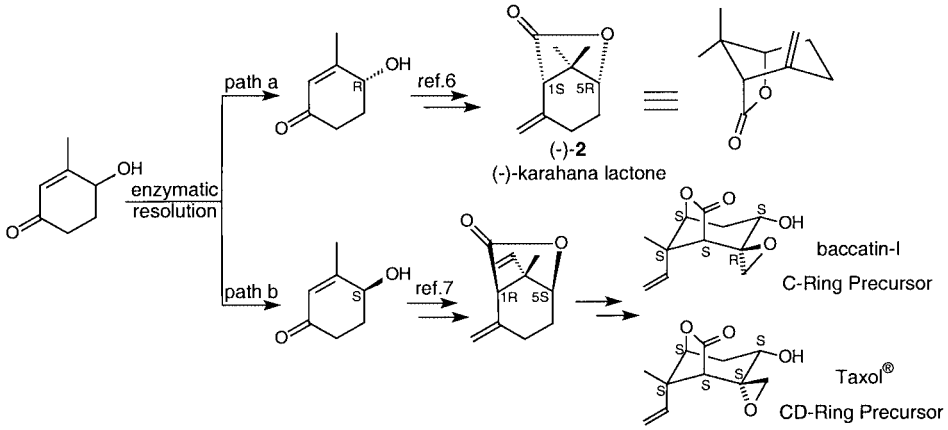


Figure 1 Paclitaxel (Taxol®)

In spite of these successes, convenient accesses to the fully-functionalized A-ring, C-ring and the construction of the sterically congested eight-membered ring remain a challenge and excellent work is still in progress.[5] Recently, we have published[6] the efficient enantioselective synthesis of (–)-karahana lactone, (–)-**2**, using a domino ring closure sequence starting from enantiopure (*R*)-4-hydroxy-3-methyl-cyclohex-2-en-1-one (Scheme 1, path a).

Based upon a related methodology, we investigated syntheses for the taxoid diterpene framework and we reported recently a stereocontrolled construction of bicyclic systems with the appropriate stereochemical disposition of the substituents belonging either to baccatin-I C-ring or Taxol® CD-ring precursors.[7] Formally, starting from enantiopure (*S*)-4-hydroxy-3-methyl-cyclohex-2-en-1-one, this strategy allowed the construction of these bicyclic systems with the required absolute configuration (Scheme 1, path b). In the continuation of our endeavor directed towards a stereocontrolled access to highly oxygenated taxane precursors, we were keen to incorporate enantioselectively the required (*S*)-C-13 oxygenation (taxane numbering) of the A-ring synthon directly rather than introducing it later by oxidation of C-13. Herein we report an enantioselective synthesis of fully-oxygenated Taxol® A-ring **1** using (1*S*,5*R*)-karahana lactone, (–)-**2**, as an enantiopure starting building block and a diastereo-



Scheme 1

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selective allylic hydroxylation as the key step (Scheme 2).[5h,j,8,9]

Allylic hydroxylation of (–)-**2** using selenium dioxide and *tert*-BuOOH (70 wt% in water) in dichloromethane afforded, after stirring for 3 days at reflux, the alcohol (–)-**3**[10] as a single stereomer in 85% isolated yield. ^{1}H and ^{13}C NMR data for (–)-**3** were fully determined by HMBC and COSY experiments.[11] The stereochemistry at the 3-position was unambiguously assigned based on NOESY analysis (Figure 2). A NOE effect between Me_β-8, H_β-4, H-9 (δ = 5.18 ppm) and H-3 established a H-3 β position and thus the α configuration of the hydroxy group.

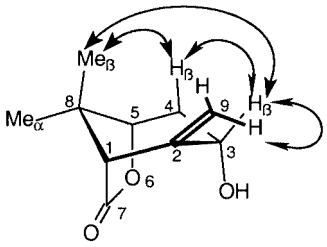

Figure 2

Treatment of (–)-**3** with TBSCl using the standard method (TBSCl, imidazole, DMF, r.t., overnight) gave protected derivative (–)-**4** in 72% yield. Reduction of (–)-**4** with DIBAL in toluene at –80 °C provided a mixture of lactols **5** and aldehyde **6**. The crude products mixture, which contained 80% of the lactols form and 20% of the opened aldehyde form (ratios based on ^{1}H NMR analysis), was subjected to isomerization to α,β-unsaturated aldehyde in the presence of catalytic MeONa/MeOH to afford (–)-**7** in 90% yield. Reaction of (–)-**7** with ethane-1,2-diol and a catalytic amount of PPTS under azeotropic elimination of water using benzene and a Dean–Stark apparatus, afforded dioxolane (–)-**8** in 71% yield without migration of the double bond to the exocyclic β,γ-position. Finally, Dess–Martin periodinane oxidation of (–)-**8** gave the desired target (–)-**1** in 86% yield.

In summary, as part of a program aimed at the enantioselective synthesis of taxanes using both enantiomers of the same building block, we have developed a new approach to a fully-oxygenated paclitaxel A-ring subunit. Starting from the opposite enantiomer, the synthetic studies on baccatin-I C-ring and Taxol® CD-ring are currently underway in our laboratory. The results of these studies will be reported shortly.

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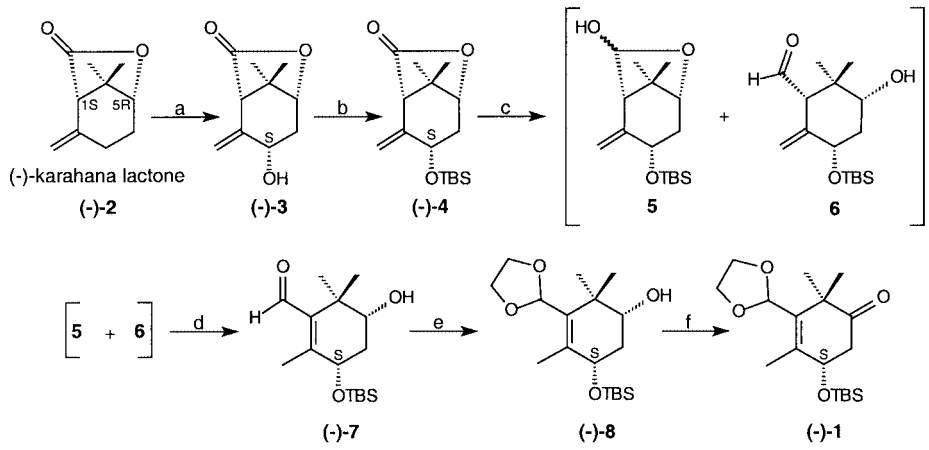

Scheme 2 (a) Cat. SeO_2, cat. salicylic acid, *tert*-BuOOH 70% in water, CH_2Cl_2, reflux, 85%. (b) TBSCl, imidazole, DMF, r.t., 72%. (c) DIBAL, toluene, –80 °C. (d) Cat. MeONa, MeOH, r.t., 90%. (e) Ethane-1,2-diol, PPTS, benzene, reflux, 71%. (f) Dess–Martin reagent, CH_2Cl_2, r.t., 86%.

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(10) **Preparation of (–)-3.** To a stirred solution of karahana lactone (–)-**2**[6] (400 mg, 2.41 mmol) in dry CH_2Cl_2 (40 mL) was added selenium dioxide (107 mg, 0.96 mmol), *tert*-butyl hydroperoxide (70 wt% in water, 868 mg, 9.64 mmol) and a catalytic amount of salicylic acid under an argon atmosphere. The reaction mixture was heated to reflux for 3 d, cooled to r.t. and Na_2SO_3 (2.5 g, 20 mmol) and 1 mL of water were added. The mixture was stirred for a further 30 min, filtered through a pad of $MgSO_4$ and concentrated. After purification by crystallization from Et_2O–hexane, 354 mg of pure alcohol (–)-**3** were obtained as white crystals (rdt 85%).

(11) Spectroscopic data of compounds (–)-**3** and (–)-**1**: (–)-**3**: mp 155 °C, $[\alpha]_D^{25}$ –142.9 (*c* 1.0, $CHCl_3$). IR (KBr): 3440, 3091, 1759, 1036, 905 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.18 (s, 1 H, H-9), 5.08 (s, 1 H, H-9), 4.42 (d, *J* = 6.1 Hz, 1 H, H-3), 4.36 (br. d, *J* = 3.7 Hz, 1 H, H-5), 2.77 (s, 1 H, H-1), 2.22 (dd, *J* = 15.7, 3.8 Hz, 1 H, H_α-4), 2.08 (ddd, *J* = 15.7, 6.1, 1.5 Hz, 1 H, H_β-4), 1.21 (s, 3 H, $CH_{3\beta}$), 0.95 (s, 3 H, $CH_{3\alpha}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.6 (C-7), 143.9 (C-2), 117.0 (CH_2-9), 84.3 (CH-5), 68.0 (CH-3), 56.6 (CH-1), 42.8 (C-8), 32.6 (CH_2-4), 25.3 (CH_3), 20.1 (CH_3). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.64; H 7.72. (–)-**1**: Mp 59 °C, $[\alpha]_D^{25}$ –39.0 (*c* 1.0, $CHCl_3$). IR (KBr): 1661, 1630, 1254, 1104 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.37 (s, 1 H, H-7), 4.26 (t, *J* = 4.8 Hz, 1 H, H-5), 4.12–4.05 (m, 2 H, $H_{dioxolane}$), 3.94–3.87 (m, 2 H, $H_{dioxolane}$), 2.76 and 2.60 (ABX, *J* = 13.7, 5.8, 4.4 Hz, 2 H, H-6), 1.92 (s, 3 H, H-8), 1.30 (s, 3 H, CH_3) 1.22 (s, 3 H, CH_3), 0.85 (s, 9 H, $(CH_3)_3C$-), 0.06 (s, 3 H, CH_3-Si), 0.05 (s, 3 H, CH_3-Si). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 212.2 (C-1), 139.1 (C=), 133.0 (C=), 102.0 (CH-7), 72.2 (CH-5), 64.7 ($CH_{2dioxolane}$), 64.4 ($CH_{2dioxolane}$), 47.1 (C-2), 45.6 (CH_2-6), 25.6 ($(CH_3)_3C$-), 24.6 (CH_3), 23.8 (CH_3), 17.9 ($(CH_3)_3C$-), 17.2 (CH_3-8), –4.6 (CH_3-Si), –4.8 (CH_3-Si). Anal. Calcd for $C_{18}H_{32}O_4Si$: C, 63.49; H, 9.47. Found: C, 63.67; H 9.45.