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TETRAHEDRON LETTERS

A stereocontrolled approach towards highly oxygenated taxane C and CD-ring precursors

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Abstract—Based upon a remarkable β-face diastereoselection, a stereocontrolled construction of bicyclic systems with the appropriate stereochemical disposition of the substituents belonging either to a Baccatin-I C-ring precursor or a Taxol® CD-ring precursor is reported. © 2002 Elsevier Science Ltd. All rights reserved.

Paclitaxel[1] (Taxol®, Fig. 1) and its synthetic analogs[2] are well-known to exhibit promising antitumor activity and several other natural taxanes were recently revealed to be inhibitors against the P-glycoprotein.[3] These properties have stimulated considerable effort towards a wide variety of strategies for construction of the core structure.

To date, six total syntheses of paclitaxel[4] have been reported and two of them, the Nicolaou[4a,4b] and Danishefsky[4c,4d] routes, utilized an A+C connection to form the central B-ring. In spite of these successes, convenient accesses to the fully functionalized A-ring, C-ring and the construction of the sterically congested eight-membered B-ring remain a challenge and excellent works are still in progress.[5] In the course of our interest in the synthesis of natural products, we reported recently the enantioselective synthesis of karahana lactone and elegansidiol using a domino ring-closure sequence (Fig. 2).[6] Based upon a related methodology, we therefore started studies to investigate syntheses for the taxoid diterpene framework.

In this communication, we would like to disclose portions of our endeavor directed towards a stereocontrolled approach of highly oxygenated taxane C and CD-ring precursors **1** and **2**, that could be used in the synthesis of several members of this family of natural products (Fig. 1). Our methodology is outlined in Scheme 1.

The starting material for the synthesis is 4-hydroxy-3-methyl-cyclohex-2-en-1-one **3** which is readily available in 75% yield following the literature procedure.[7] Using the standard method,[8] TBS (*tert*-butyldimethylsilane) derivative **4** was obtained in 96% yield. The protected ketol **4** was converted into 2-carbomethoxycyclohexanone **5** (mixture of keto and enol forms, 81% yield) by

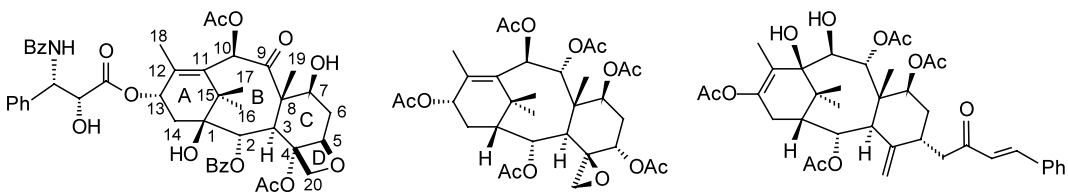

Figure 1. Taxoid representatives.

Keywords: taxoids; domino reaction; stereoselective reaction; stereoselective epoxidation; synthesis.
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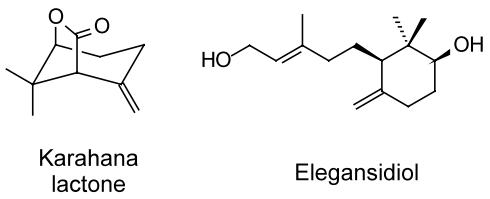

Figure 2.

the copper-catalyzed 1,4-addition of vinylmagnesium bromide at −78°C followed by the quenching with methylcyanoformate in hexamethylphosphoric triamide at the same temperature.[9] Treatment of **5** with *p*-TsOH·H_2O (1.2 equiv.) in refluxing toluene for 1 hour, afforded the keto-lactone **6** in 92% yield (mp 60°C). Reaction of **6** with the salt-free Wittig reagent prepared from methyl triphenylphosphonium iodide and *tert*-BuOK gave the colorless lactone **7** in 83% yield (mp 51 °C). Allylic hydroxylation of **7** using selenium dioxide and *tert*-BuOOH (70 wt.% in water) in dichloromethane provided, after stirring for 3 days at reflux, the alcohol **8** as a single stereomer in 85% isolated yield (mp 85°C). At this stage, the stereostructure of **8** could be supported with reasonable certitude by spectroscopic data,[10] and next epoxidation of **8** would be directed by the appropriately disposed hydroxyl group. In fact, subjection of **8** to hydroxyl directed epoxidation[11] ($VO(acac)_2$, *tert*-BuOOH, 10 min reflux in benzene) gave an 88% isolated yield of the single solid epoxy-alcohol **9** (mp 105°C) whose structure was secured by an X-ray crystallographic analysis. As expected, ORTEP representation showed a C-5β hydroxyl group, a C-4(20)-β epoxide and confirmed the whole structure constructed so far. The stereochemistry of C-5 was inverted at this stage by a two-step procedure which gave better results than the one-step Mitsunobu reaction.[12] Thus, Dess–Martin periodinane oxidation of **9** and subsequent $NaBH_4$-$CeCl_3$ Luche reduction of the intermediate ketone afforded the C-5β hydroxylated Baccatin-I C-ring precursor **1** as a single stereomer in 89% isolated yield over two steps (mp 143°C). Next, for the synthesis of Taxol® CD-ring precursor **2**, the C-4(20)-α epoxide was required. For this purpose, starting from **8**, the same oxidation/reduction sequences clearly provided the reverse C-5α hydroxy derivative **10**, again as a single stereomer, in 85% yield. Hydroxyl directed epoxidation of the latter, using $VO(acac)_2$ and *tert*-BuOOH (30 min reflux in benzene) led exclusively to **2** (74% yield) with the α-epoxide stereochemistry.

In summary, based upon a remarkable β-face diastereoselection of the bicyclic framework **7**, in the allylic hydroxylation as well as in the Luche reduction, we have developed a stereoselective construction of bicyclic systems with the appropriate stereochemical disposition of the substituents belonging either to a Baccatin-I C-ring precursor or a Taxol® CD-ring precursor. Our current efforts are concerned with the further reductive opening of the lactone moiety of these precursors with Dibal-H, and they are presently in progress with encouraging results.

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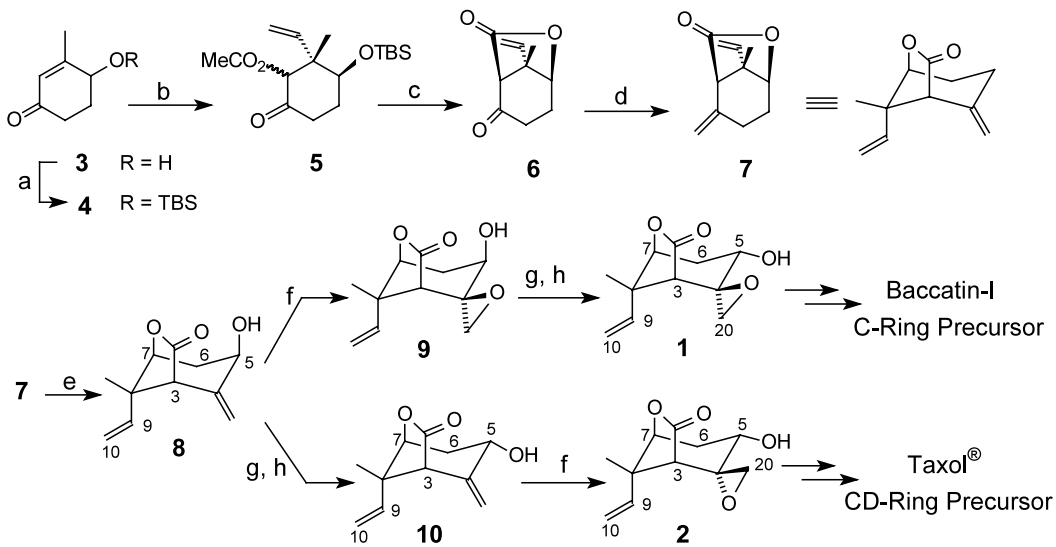

Scheme 1. *Reagents and conditions*: (a) TBSCl, imidazole, DMF, rt, 96%; (b) CH_2=$CHMgBr$, $CuBr{\cdot}SMe_2$, THF, −78°C, then HMPA and $CNCO_2Me$, −78°C to rt, 81%; (c) 1.2 equiv. *p*-TsOH·H_2O, toluene, reflux, 92%; (d) 2.5 equiv. $Ph_3(CH_3)P^+I^-$, *tert*-BuOK, toluene, rt, 83%; (e) cat. SeO_2, cat. salicylic acid, *tert*-BuOOH 70% in water, CH_2Cl_2, reflux, 85%; (f) $VO(acac)_2$, *tert*-BuOOH, benzene, reflux, **9** 88%, **2** 74%; (g) Dess–Martin reagent, CH_2Cl_2 and (h) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −18°C, **1** 89%, **10** 85%.

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10. All new compounds were fully characterized by IR, ^{1}H NMR (NOE effect) and ^{13}C NMR. Selected analytical data: **8**. IR (film): 3439, 3093, 1759, 1646, 1035 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.78 (dd, 1H, $J=17.6$, 11.1 Hz, C_9–H), 5.23 (dd, 1H, $J=11.1$, 0.9 Hz, C_{10}–H_{cis}), 5.23 (s, 1H, C–$H_{methylene}$), 5.15 (dd, 1H, $J=17.6$, 0.9 Hz, C_{10}–H_{trans}), 5.10 (s, 1H, C–$H_{methylene}$), 4.43–4.36 (m, 2H, C_5–H and C_7–H), 2.91 (s, 1H, C_3–H), 2.18 (t, 2H, $J=3.2$ Hz, C_6–H), 1.30 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 176.1 (CO), 143.3 (C), 137.2 (CH), 118.0 (CH_2), 117.9 (CH_2), 84.1 (CH), 67.9 (CH), 56.3 (CH), 47.9 (C), 32.6 (CH_2), 22.6 (CH_3). Anal. calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.21; H, 7.25. **10**. IR (film): 3428, 3081, 1754, 1637, 1048 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.92 (dd, 1H, $J=17.5$, 10.9 Hz, C_9–H), 5.36 (d, 1H, $J=2.6$ Hz, C–$H_{methylene}$), 5.28 (d, 1H, $J=11.1$ Hz, C_{10}–H_{cis}), 5.18 (d, 1H, $J=17.6$ Hz, C_{10}–H_{trans}), 5.05 (d, 1H, $J=2.6$ Hz, C–$H_{methylene}$), 4.44–4.37 (m, 2H, C_5–H and C_7–H), 3.02 (s, 1H, C_3–H), 2.49 (ddd, 1H, $J=13.6$, 7.8, 4.4 Hz, C_6–H_e), 1.84 (dd, 1H, $J=13.6$, 9.8 Hz, C_6–H_a), 1.28 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.1 (CO), 141.9 (C), 137.3 (CH), 117.8 (CH_2), 112.4 (CH_2), 85.4 (CH), 65.7 (CH), 58.3 (CH), 47.7 (C), 34.6 (CH_2), 21.6 (CH_3). Anal. calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.32; H, 7.24. **1** IR (film): 3458, 3100, 1766, 1105 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.11 (dd, 1H, $J=17.5$, 11.1 Hz, C_9–H), 5.36 (dd, 1H, $J=11.1$, 0.6 Hz, C_{10}–H_{cis}), 5.26 (dd, 1H, $J=17.5$, 0.6 Hz, C_{10}–H_{trans}), 4.43 ($d_{élargi}$, 1H, $J=4.4$ Hz, C_7–H), 4.24 (dd, 1H, $J=10.1$, 7.8 Hz, C_5–H), 3.35 and 2.67 (AB, 2H, $J=4.8$ Hz, C_{20}–H), 2.60 (ddd, 1H, $J=14.2$, 7.8, 4.4 Hz, C_6–H_e), 2.07 (d, 1H, $J=1.4$ Hz, C_3–H), 1.99 (ddd, 1H, $J=14.2$, 10.3, 1.0 Hz, C_6–H_a), 1.31 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.8 (CO), 136.0 (CH), 118.7 (CH_2), 84.5 (CH), 64.0 (CH), 59.8 (C), 55.5

(CH), 50.0 (CH_2), 48.4 (C), 32.9 (CH_2), 21.7 (CH_3). Anal. calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.08; H, 6.73.

2. IR (film): 3449, 3097, 1759, 1095 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.33 (dd, 1H, $J=17.6$, 11.1 Hz, C_9–H), 5.34 (d, 1H, $J=11.1$ Hz, C_{10}–H_{cis}), 5.24 (d, 1H, $J=17.6$ Hz, C_{10}–H_{trans}), 4.48 (d, 1H, $J=4.6$ Hz, C_7–H), 4.18 (dd, 1H, $J=9.6$, 7.6 Hz, C_5–H), 2.94 and 2.76 (AB, 2H, $J=4.7$ Hz, C_{20}–H), 2.61 (ddd, 1H, $J=14.3$, 7.4, 4.6 Hz, C_6–H_e), 2.19 (d, 1H, $J=1.4$ Hz, C_3–H), 1.95 (dd, 1H, $J=14.3$, 9.6 Hz, C_6–H_a), 1.28 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.2 (CO), 136.9 (CH), 117.9 (CH_2), 85.2 (CH), 62.2 (CH), 57.5 (C), 55.4 (CH), 48.2 (CH_2), 47.7 (C), 33.7 (CH_2), 22.2 (CH_3). Anal. calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.17; H, 6.69.

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