Enantioselective Synthesis of a 9,10-*seco*-Taxane Derivative *via* Electrophilic Epoxy-allylsilane Ring Closure

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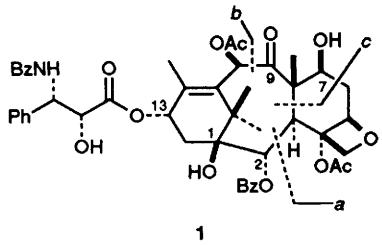
seco-Taxane **8**, a potential starting material for further development into highly substituted taxanes, is synthesized by $BF_3{\cdot}OEt_2$ treatment of epoxy-allylsilane **7**, in its turn synthesized by joining an *A*-ring derivative **2** with a *C*-ring precursor chain **3**.

We previously reported syntheses of Taxol *A*- and *C*-ring units of high optical purity potentially useful for the construction of functionalized taxoids and perhaps also Taxol.[1–5] Our attempts at the convergent strategy of directly joining the *A*- and the *C*- ring units *via* a C(2)–C(3) bond formation followed



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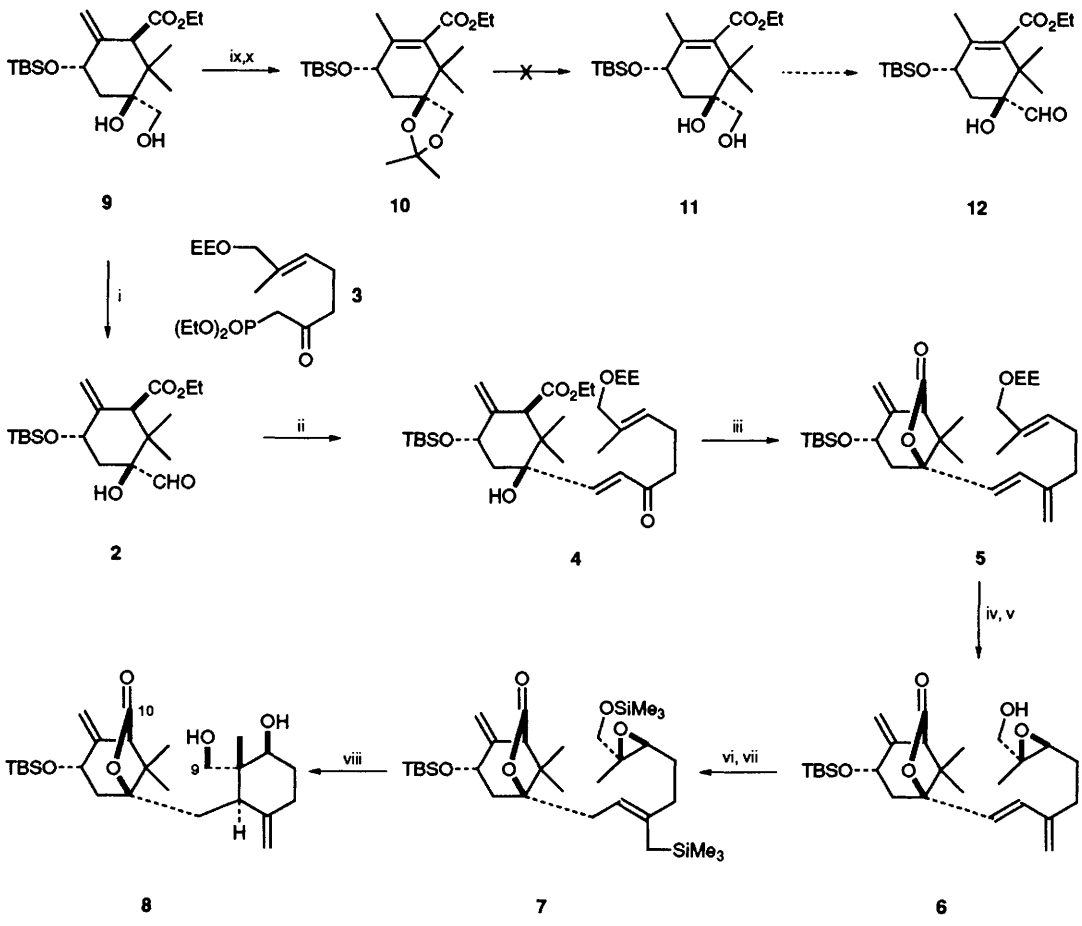

Scheme 1 *Reagents and conditions*: i, 4 equiv. of dimethyl sulfoxide, 2 equiv. of $(COCl)_2$, 8 equiv. of $EtN(Pr^i)_2$, CH_2Cl_2, −60 °C for 20 min then +20 °C 1 h, 90%; ii, 1.3 equiv. of NaH, 1.5 equiv. of **3**, 1,2-dimethoxyethane, 0 °C, 20 min then **2** at 85 °C, 10 min, 93%; iii, 2 equiv. of 1.4 mol dm^{-3} BuLi in hexane, 2 equiv. of Ph_3PCH_3Br, tetrahydrofuran, +20 °C, then add **4** rapidly at 50 °C, 15 min, 90%; iv, 0.1 equiv. of pyridinium toluene-*p*-sulfonate (PPTS), EtOH, +20 °C, 12 h, 98%; v, 0.32 equiv. of L-(+)-DET, 0.7 g of 4 Å molecular sieves, 1.53 equiv. of *tert*-butylhydroperoxide (TBHP) (anhydrous), 0.27 equiv. of $Ti(OPr^i)_4$, CH_2Cl_2, −40 °C, 1.5 h, 97%; vi, 2 equiv. of $EtN(Pr^i)_2$, 2 equiv. of Me_3SiCl, 0 °C, 5 min, 99%; vii, 0.3 ml of Me_3SiH, toluene, 230 mg of **6** (R = $SiMe_3$), 1.5 mg of $(Ph_3P)_3RhCl$, +20 °C, 16 h, occasional opening of the closed reaction vessel at 0 °C, then PPTS in EtOH, 5 min, 35%; viii, **7** in CH_2Cl_2 slowly added to 15 equiv. of $BF_3{\cdot}OEt_2$, 0 °C, then add aq. $NaHCO_3$, 30%; ix, acetone, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 3 min, 96%; x, DBU (neat, 5 times the mass of the acetonide), 185 °C, 1 h, 60%. EE = ethoxyethyl, DET = diethyltartrate, DBU = 1,8-diaza-[5.4.0]bicycloundec-7-ene. Yields are given for isolated products pure by ^1H and ^{13}C NMR spectroscopy, TLC analysis and having correct elemental analysis. All reactions were performed under N_2 in dry solvents.

by the C(9)–C(10) bond formation for the synthesis of the taxane core (formation of bond *a* followed by *b*, Fig. 1) have hitherto been unsuccessful.[3,4] Steric crowding at C-2 is probably too great, which suggested that a sterically less demanding chain-shaped *C*-ring precursor be attached to C-2 of a suitable *A*-ring structure (bond formation order *a, c, b*). As a continuation of this work we now report the synthesis of 9,10-*seco*-taxane **8** (Scheme 1), which may serve as a starting material for taxanes.[7–9] Both of the C-9 and C-10 terminals‡ could conceivably be modified to allow testing of several different C–C bond formation reactions. It was demonstrated several years ago by Kende *et al.*[8] and more recently by Nicolaou *et al.*[9] that the 9,10-*seco*-taxane route may be of great importance for the synthesis of taxanes. Syntheses of other optically active *A*-ring derivatives similar to **2** have been published.[10]

‡ Taxane numbering is used throughout.

The ideal *A*-ring unit to start with would be the C-2 aldehyde **12**. This requires that the acetonide protection is removed from **10**,[2,5] which was obtained from **9**[2,5] by acetonide formation followed by heating in neat DBU at 185 °C for 1 h. However, efforts to cleave the acetonide were all unsuccessful (*e.g.* acidic solvolysis, or treatment with Me_2BBr,[11] $PdCl_2(MeCN)_2$[12] and Ph_3CBF_4[13]); either the acetonide was too stable or the material was destroyed. Instead, the primary hydroxy group of the unconjugated *A*-ring derivative **9** was oxidized to give the α-hydroxy aldehyde **2** in 90% yield using the Swern procedure.[14] This method is well suited for 1,2-diols containing one tertiary hydroxy group, whereas other oxidizing agents may cleave the diol.[15]

The Horner–Emmons–Wadsworth (HEW) reaction[16] of **2** with the sodium salt of **3**[17] was very efficient producing the α,β-unsaturated ketone **4** in 93% yield. As indicated by the ^1H NMR spectrum ($J_{2,3}$ 15.5 Hz) the C(2)–C(3) double bond in **4** was of pure *E* configuration. The conjugated diene **5** was prepared by a Wittig reaction ($Ph_3P{=}CH_2$ in tetrahydrofuran) of **4** in 90% yield. Lactonisation took place during this

reaction. Deprotection of **5** followed by a catalytic Sharpless epoxidation[18] gave the epoxy alcohol **6** (R = H) in excellent yield (97%).§

The hydrosilylation was then performed with the trimethylsilyl-protected derivative **6** (R = $SiMe_3$) using $(Ph_3P)_3RhCl$ as a catalyst, which produced the epoxy allylsilane **7** (R = H after hydrolytic work-up) in 35% yield along with some side products (the regioisomeric allyl silane and the 1,4-hydrogenation product). The *C*-ring cyclization to give **8**¶ (30% isolated yield) was accomplished by adding **7** to 15 equiv. of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (not *vice versa*) at 0 °C, followed by column chromatography and recrystallization for heptane. Unfortunately, the crystals were not suitable for X-ray analysis.

The structure of **8** was verified by NMR techniques, including DEPT, HETCOR, HOM2DJ, COSY, and NOESY. Some important changes in the ^1H and ^{13}C NMR spectra in going from **7** to **8** are (*i*) loss of the $SiMe_3$ group, the C-3 double bond and the epoxide; (*ii*) a pronounced upfield shift of the C-19 methyl group (both in the ^1H and in the ^{13}C NMR spectrum); (*iii*) new ^1H signals for the C-20 *exo*-methylene group, the >CH(OH) moiety at C-7 and the ^{13}C signal for C-3. The relative stereochemistry at C-3, C-7 and C-8 and the assignment of H-3 were determined by 2D-techniques, including NOESY. In particular NOE effects were obtained for 2-H⟷19-H, 19-H⟷7-OH, 3-H⟷7-H indicating that the three former groupings were *cis* related on one side of the ring system and the latter two *cis* related on the other. This information together with the stereospecificity of the Sharpless epoxydation to give **6** strongly suggest that the *C*-ring precursor chain in **7** gave a six-membered ring with the correct stereochemistry at C-3, C-8 and C-7 as compared to Taxol. Thus, we now have control over five of the ten stereocentres related to Taxol (C-1, C-3, C-7, C-8, C-13) not counting those of the side chain. Obviously, the yields in the hydrosilylation and the ring closure steps need improving and further work along these lines is in progress.

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§ The diastereoisomeric excess of the epoxide **6** (R = H) was not determined. However, the set of signals corresponding to only one diastereoisomer could be detected in its ^1H NMR spectrum.

¶ Physical data for selected compounds. For **7**: R_f = 0.24 (silica, heptane : ethyl acetate 2 : 1); $[\alpha]^{20}_D$ + 101 (*c* 0.99, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$); δ 0.04 (s, 9H, -$SiMe_3$), 0.05, 0.06 [2s, 6H, -$Si(CH_3)_2$-], 0.90 (s, 9H, Bu^t), 0.99, 1.10 (2s, 6H, H-16, H-17), 1.28 (s, 3H, H-19), 1.52, 1.58 (2d, 2H, J_{AB} 13.6 Hz, H-20), 1.63–1.75 (m, 4H, H-14, H-6, -OH), 2.13 (m, 2H, H-5), 2.24 (dd, 1H, J_{AB} 15.3, *J* 8.5 Hz, H-2), 2.32 (dd, 1H, J_{AB} 14.0, *J* 7.8 Hz, H-14), 2.38 (dd, 1H, J_{AB} 15.3, *J* 5.6 Hz, H-2), 2.85 (s, 1H, H-11), 3.03 (t, 1H, *J* 6.1 Hz, H-7), 3.58 (dd, 1H, J_{AB} 12.2 *J* 8.6 Hz, H-9), 3.68 (dd, 1H, J_{AB} 12.2, *J* 4.4 Hz, H-9), 4.30 (dddd, 1H, *J* 9.3, 7.8, 2.4, 2.4 Hz, H-13), 4.95 (dd, 1H, *J* 2.4, 1.5, H-18), 5.12 (dd, 1H, *J* 8.5, 5.6 Hz, H-3), 5.24 (dd, 1H, *J* 2.4, 1.5 Hz, H-18); ^{13}C NMR ($CDCl_3$) δ −5.08, −4.84 (-$SiMe_2$-), −0.61 (-$SiMe_3$), 14.28 (C-19), 18.18 (-CMe_3), 20.13 (C-16), 21.72 (C-20), 22.46 (C-17), 25.79 (-CMe_3), 27.38, 31.68, 36.04 (C-6, C-5, C-2), 39.18 (C-14), 45.32 (C-15), 59.55, 60.81, 60.96 (C-7, C-8, C-11), 65.18 (C-9), 67.73 (C-13), 91.41 (C-1), 111.19 (C-18), 114.98 (C-3), 140.11 (C-4), 142.64 (C-12), 175.77 (C-10).

For **8**: R_f = 0.19 (silica, heptane : ethyl acetate 1 : 1); $[\alpha]^{20}_D$ + 90 (*c* 0.30, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.06, 0.06 (2s, 6H, -$SiMe_2$-), 0.71 (s, 3H, H-19), 0.91 (s, 9H, Bu^t), 0.98, 1.13 (2s, 6H, H-16, H-17), 1.50–1.62 (m, 3H, H-6, H-2, H-14), 1.81 (d, 1H, *J* 4.8 Hz, >CHOH, disappears with D_2O), 1.88 (m, 1H, H-6), 2.04 (dd, 1H, J_{AB} 12.8, *J* 4.5 Hz, broad, H-5), 2.10 (dd, 1H, *J* 4.2, 6.1 Hz, -CH_2OH, disappears with D_2O), 2.13 (dd, 1H, J_{AB} 14.9, *J* 9.6 Hz, H-2), 2.22 (d, 1H, *J* 9.6 Hz, broad, H-3), 2.39 (ddd, 1H, J_{AB} 12.8, *J* 4.2, 4.2 Hz, H-5), 2.47 (dd, 1H, J_{AB} 14.0, *J* 7.7 Hz, H-14), 2.84 (s, 1H, H-11), 3.50 (dd, 1H, J_{AB} 11.0, *J* 4.2 Hz, H-9), 3.76 (dd, 1H, J_{AB} 11.0, *J* 6.1 Hz, H-9), 3.91 (ddd, 1H, *J* 4.8, 10.5, 4.7 Hz, H-7), 4.24 (dddd, 1H, *J* 9.4, 7.7, 2.5, 2.5 Hz, H-13), 4.84 (s, 1H, H-20), 4.94 (dd, 1H, *J* 2.5, 1.5 Hz, H-18), 5.01 (s, 1H, H-20), 5.23 (dd, 1H, *J* 2.5, 1.5 Hz, H-18); ^{13}C NMR ($CDCl_3$) δ −5.09, −4.78 (-$SiMe_2$-), 10.57 (C-19), 18.20 (-CMe_3), 19.61 (C-16), 22.54 (C-17), 25.82 (-CMe_3), 26.73 (C-2), 32.29 (C-6), 33.70 (C-5), 39.34 (C-14), 40.72 (C-3), 44.84, 46.46 (C-8, C-15), 60.55 (C-11), 67.59 (C-13), 67.72 (C-9), 73.51 (C-7), 91.09 (C-1), 110.57 (C-20), 111.00 (C-18), 142.52 (C-12), 146.49 (C-4), 175.87 (C-10).

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