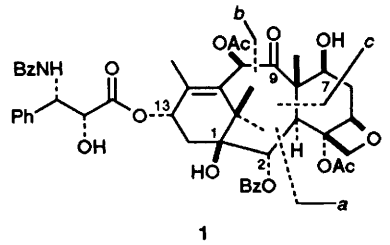
Enantioselective Synthesis of a 9,10-*seco*-Taxane Derivative *via* Electrophilic Epoxy-allylsilane Ring Closure

Lars Pettersson and Torbjörn Frejd*†

Department of Organic Chemistry 2, Chemical Center, Lund University, PO Box 124, S-221 00 Lund, Sweden

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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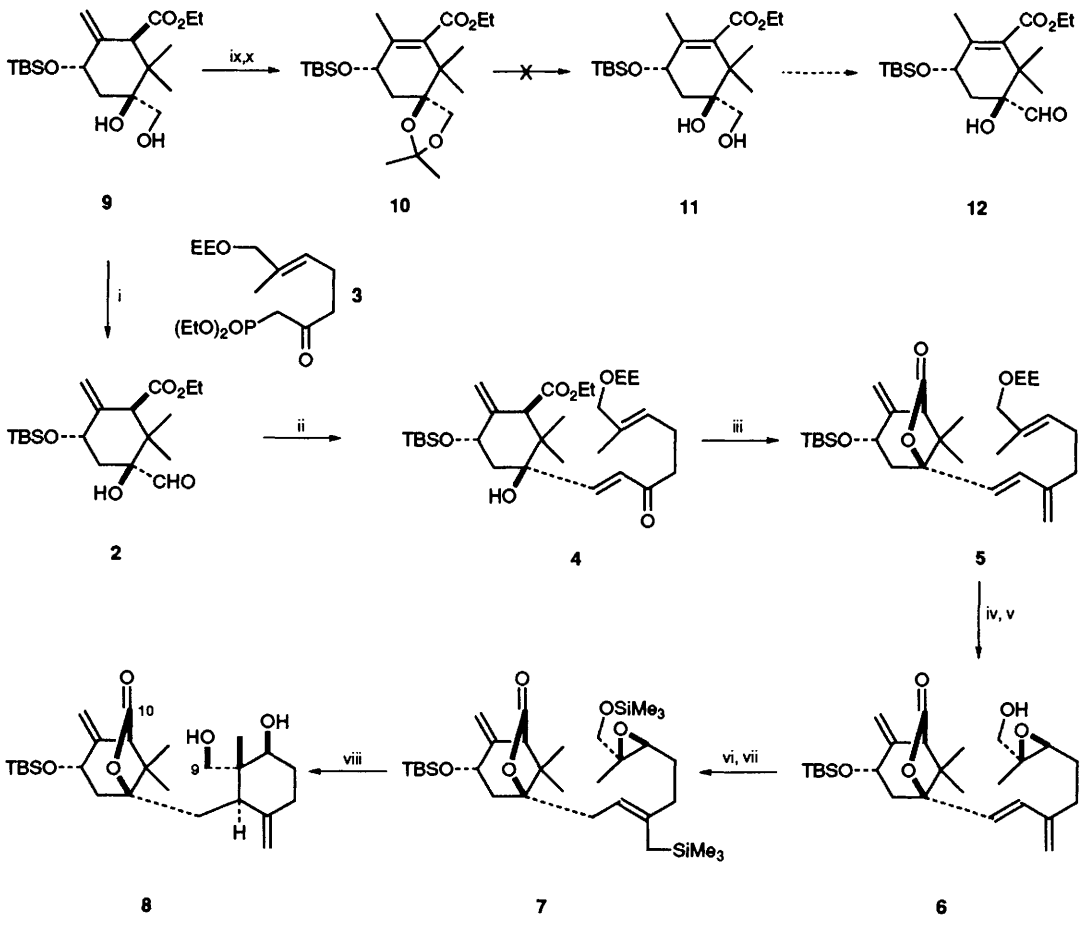
† *Present address:* Department of Organic Chemistry, Umeå University, S-901 87 Umeå, Sweden.



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.

This work was financially supported by the Swedish Natural Research Council and the Lund Institute of Technology, Lund University.

Received, 12th July 1993; Com. 3/04013E

§ 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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