Total synthesis of taxol

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TAXOL[1–4], a substance originally isolated from the Pacific yew tree (*Taxus brevifolia*) more than two decades ago, has recently been approved for the clinical treatment of cancer patients. Hailed as having provided one of the most significant advances in cancer therapy[5], this molecule exerts its anticancer activity by inhibiting mitosis through enhancement of the polymerization of tubulin and consequent stabilization of microtubules[6]. The scarcity of taxol and the ecological impact of harvesting it have prompted extensive searches for alternative sources including semisynthesis, cellular culture production and chemical synthesis[2,3]. The latter has been attempted for almost two decades, but these attempts have been thwarted by the magnitude of the synthetic challenge. Here we report the total synthesis of taxol by a convergent strategy, which opens a chemical pathway for the production of both the natural product itself and a variety of designed taxoids.

The strategy for the present synthesis of taxol (**1**, Fig. 1*a*) was based on a retrosynthetic analysis involving the bond disconnections[7] shown in Fig. 1*b*. Thus, in the synthetic direction the following key operations were proposed: (1) two fragments, representing precursors to rings A and C (see Fig. 1*a*), were to be coupled by a Shapiro reaction[8] and a McMurry coupling[9] to assemble the ABC ring skeleton; (2) instalment of the oxetane ring; (3) addition[10] of the various substituents around the peripheries of rings B and C; (4) oxygenation[10] at C-13; and (5) esterification to attach the side chain[11].

The previously reported intermediates **2** (ref. 12) (Fig. 2) and **8** (refs 7, 13) (Fig. 3) served as the starting points for the convergent synthesis of taxol reported here. Figure 2 presents the construction of the requisite C-ring aldehyde **7** from **2**. Protection of both hydroxyl groups in **2** with TBS groups (95%) (for abbreviations see figure legend) followed by selective reduction of the ester group with $LiAlH_4$ at 0 °C, furnished primary alcohol **3** (94% yield). Acid-catalysed deprotection of the secondary alcohol in **3** proceeded in a highly selective manner to give the corresponding diol (90% yield), which was then selectively protected with a TPS group at the primary position and a benzyl group at the secondary to afford compound **4** in 80% overall yield. The γ-lactone in **4** was then reductively opened with concomitant desilylation at the tertiary position using $LiAlH_4$ at

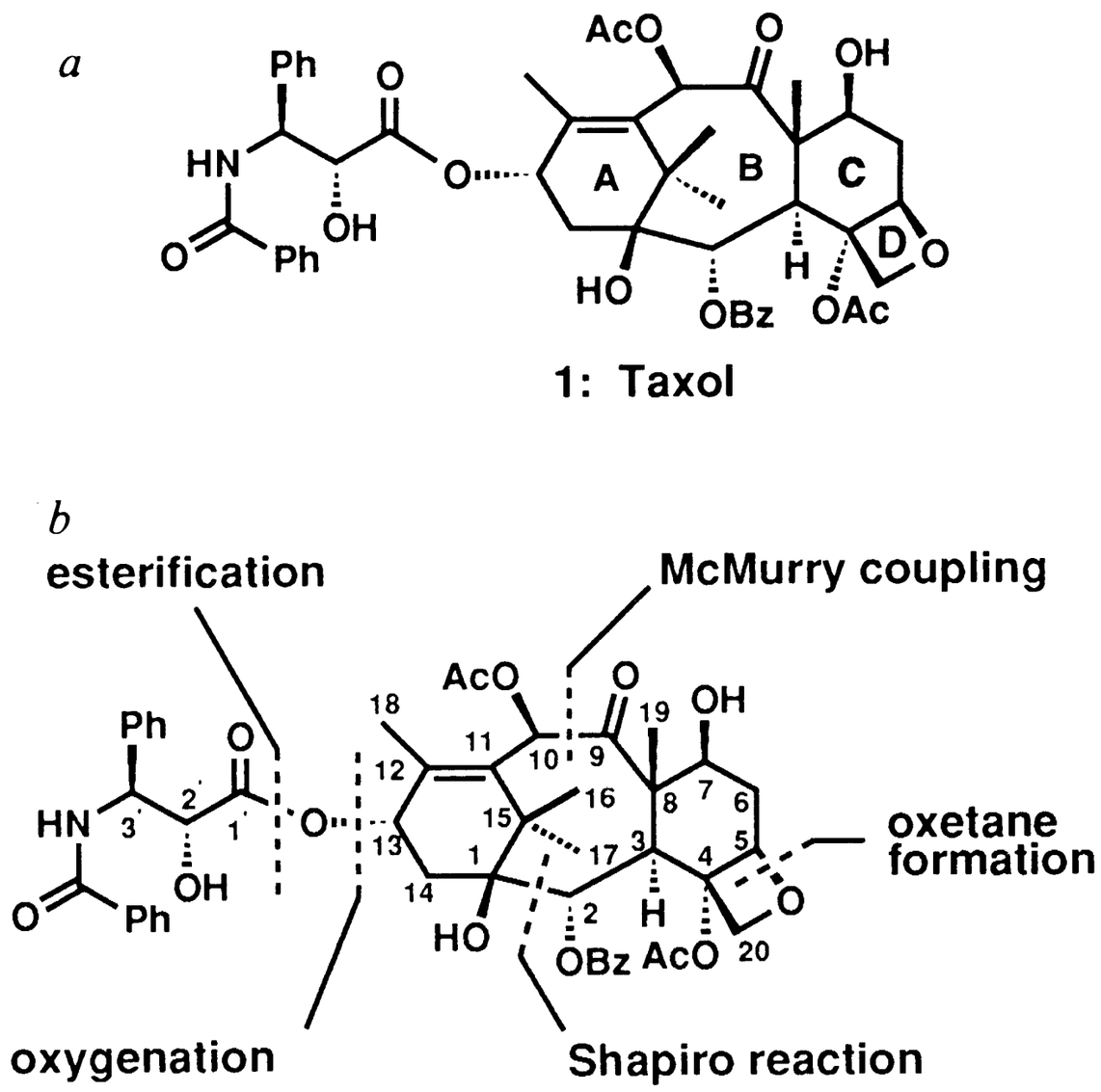


FIG. 1 Structure (*a*) and strategic bond disconnections of taxol (*b*). Abbreviations for chemical groups (see also Figs 2, 3 and 5): Ph, phenyl; OBz, benzoyl; OAc, acetyl.

25 °C to produce triol **5** in 80% yield. Finally, acetonide formation followed by TPAP[14] oxidation in the presence of NMO resulted in the formation of the targeted aldehyde **7** in 80% overall yield.

Figure 3 summarizes the coupling of intermediates **7** and **8** and elaboration of the coupling product to give the requisite tricyclic system **13**. When the vinyl lithium reagent derived from aryl hydrazone **8** and *n*-C_4H_9Li (refs 8, 13) was reacted with aldehyde **7** at −78 °C, a single diastereoisomer of hydroxy-compound **9** was obtained in 82% yield. Directed epoxidation of the C1–C14 double bond in **9** was realized, in 87% yield, using *t*-C_4H_9OOH in the presence of $VO(acac)_2$ (ref. 15), leading selectively to epoxide **10** which was regioselectively opened with $LiAlH_4$ to give the 1,2-diol **11** (76% yield). X-ray crystallographic analysis of this compound (**11**) confirmed the designated stereochemistry for intermediates **9–11** and their relatives (Fig. 4*a*). To prepare the molecule for closure of the 8-membered B ring, and in order to create subsequent opportunities for the introduction of the benzoate functionality at C-2, diol **11** was converted to its cyclic carbonate by exposure to phosgene in the presence of KH, furnishing dialdehyde **12**, after desilylation (*n*-$(C_4H_9)_4NF$) and oxidation (TPAP-NMO)[14] in 32% overall yield. The suitably preorganized dialdehyde **12** was then subjected to a McMurry-type[9,13] cyclization to afford the taxoid ABC ring system **13** in 23% yield (stereochemistry at the newly generated centres assigned by X-ray crystallographic analysis of a subsequent intermediate, **13′**; see below and Fig. 4*c*).

The next important intermediate in the synthesis was **19**, a compound that was reached from **13** as outlined in Fig. 5. Monoacetylation of **13** followed by oxidation with TPAP-NMO[14] furnished, regioselectively in 88% overall yield, ketoacetate **14**. The stereochemistry of the acetate group at C-10 was confirmed through conversion of **14** to the crystalline benzoate **14′** (PCC, $NaO(CO)CH_3$, celite, benzene, heat) and X-ray crystallographic analysis on the latter (see ORTEP drawing, Fig. 4*b*). Hydroboration of compound **14** followed by basic hydrogen peroxide treatment led to a mixure of two regioisomeric alcohols (55%, ~3:1 by ^1H NMR) which was subjected to acid-induced removal of the acetonide group and chromatographic separation to afford triol **15** (33% yield from **14**) as the major product. The primary hydroxyl group in **15** was then selectively acetylated under standard conditions, furnishing compound **16** in 95% yield. At this stage the benzyl protecting group on the C-7 oxygen was replaced by a triethyl silyl group (TES) for reasons arising from later stages of the synthesis, and the resulting compound was selectively monodeacetylated under mildly basic conditions (K_2CO_3-CH_3OH) leading to triol **17** (78% overall yield). The oxetane ring was finally constructed by sequential monosilylation with TMSCl (primary OH), triflate formation (secondary OH) and mild acid treatment to afford, after acetylation of the remaining tertiary hydroxyl group, the targeted intermediate **19** in 38% overall yield[16]. Racemic **19**, obtained from this sequence, was identical in all respects (except for optical rota-

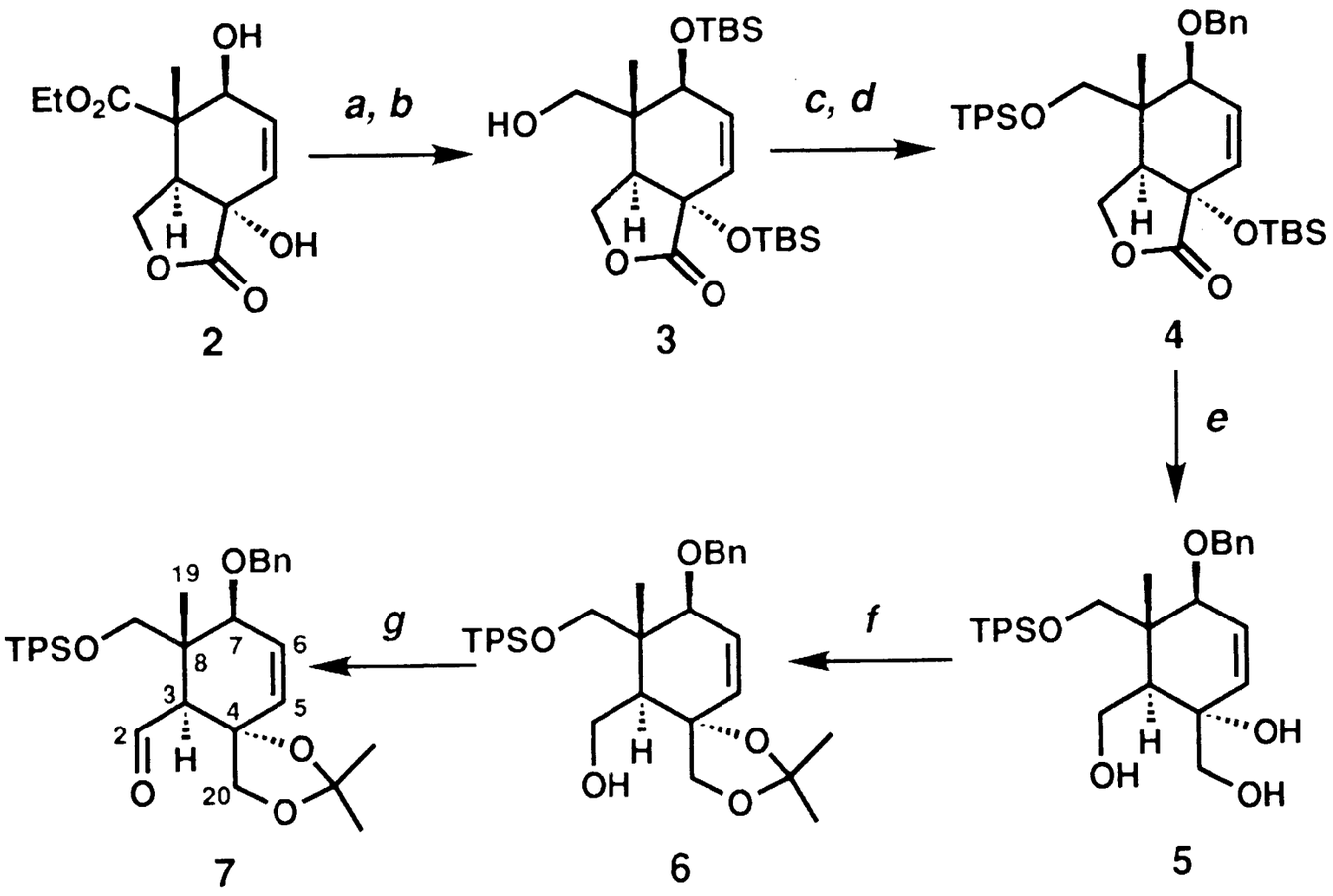


FIG. 2 Construction of C-ring system **7**. Reagents and conditions. (*a*) *t*-$BuMe_2SiOTf$ (4 equivalents (eq.)), 2,6-lutidine (4 eq.), 4-DMAP (0.01 eq.), CH_2Cl_2, 0 °C, 4 h, 95%; (*b*) $LiAlH_4$ (1.1 eq.), Et_2O, 0 °C, 1 h, 94%; (*c*) (1) CSA (0.05 eq.), MeOH, CH_2Cl_2, 25 °C, 1 h, 90%; (2) t-$BuPh_2SiCl$ (1.5 eq.), imidazole (1.6 eq.), DMF, 25 °C 6 h, 92%; (*d*) KH (1.2 eq.), Et_2O, *n*-Bu_4NI (cat.), BnBr (1.2 eq.), 25 °C, 2 h, 87%; (*e*) $LiAlH_4$ (3 eq.), Et_2O, 25 °C, 12 h, 80%; (*f*) 2,2-dimethoxypropane (5 eq.), CSA (0.1 eq.), CH_2Cl_2, 25 °C, 7 h 82%; (*g*) TPAP (0.05 eq.), NMO (1.5 eq.), CH_3CN, 25 °C, 2 h, 95%. (Bn = CH_2Ph; CSA = (±)-camphorsulphonic acid; 4-DMAP = 4-dimethylaminopyridine; DMF = N,N-dimethylformamide; NMO = N-methylmorpholine-N-oxide; TBS = *t*-$BuMe_2Si$; TPAP = tetra-*n*-propylammonium perruthenate; TPS = *t*-$BuPh_2Si$.) Selected physical data for compound **7**: ^1H NMR (500 MHz, $CDCl_3$, taxol numbering): δ 9.98 p.p.m. (d, J = 3.5 Hz, 1 H, 2-H), 7.65 − 7.12 (m, 15 H, aromatic), 5.84 (dd, J = 10.5, 1.5 Hz, 1 H, 6-H), 5.71 (dd, J = 10.5, 2.0 Hz, 1 H, 5-H), 4.50 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 4.22 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 4.20 (d, J = 9.5 Hz, 1 H, 20-H), 4.10 (dd, J = 2.0, 1.5 Hz, 1 H, 7-H), 3.84 (d, J = 9.5 Hz, 1 H, 20-H), 3.72 (d, J = 10.0 Hz, 1 H, 9-H), 3.70 (d, J = 10.0 Hz, 1 H, 9-H), 3.18 (d, J = 3.5 Hz, 1 H, 3-H), 1.42 (s, 3 H, CH_3-acetonide), 1.39 (s, 3 H, CH_3-acetonide), 1.09 (s, 9 H, $(CH_3)_3$ CSi), 1.04 (s, 3 H, 19-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.3, 138,1, 135.8, 135.6, 133.0, 132.9, 131.1, 129.7, 129.4, 129.5, 128.8, 128.2, 127.6, 127.4, 127.4, 127.2, 127.2, 127.1, 108.6, 80.6, 75.4, 71.8, 70.0, 65.7, 57.6, 44.9, 26.9, 26.8, 26.5, 19.3, 13.6; infrared (pure compound): ν_{max} 2,931.4, 2,857.0, 1,720.4, 1,111.5 cm^{-1}; high resolution mass spectrometry (fast atom bombardment) (HRMS (FAB)): calcd for $C_{36}H_{44}O_5Si$ ($M^+ + Cs$) mass-to-charge ratio m/z = 607.2856 atomic mass units (a.m.u.), found 607.2865 a.m.u.

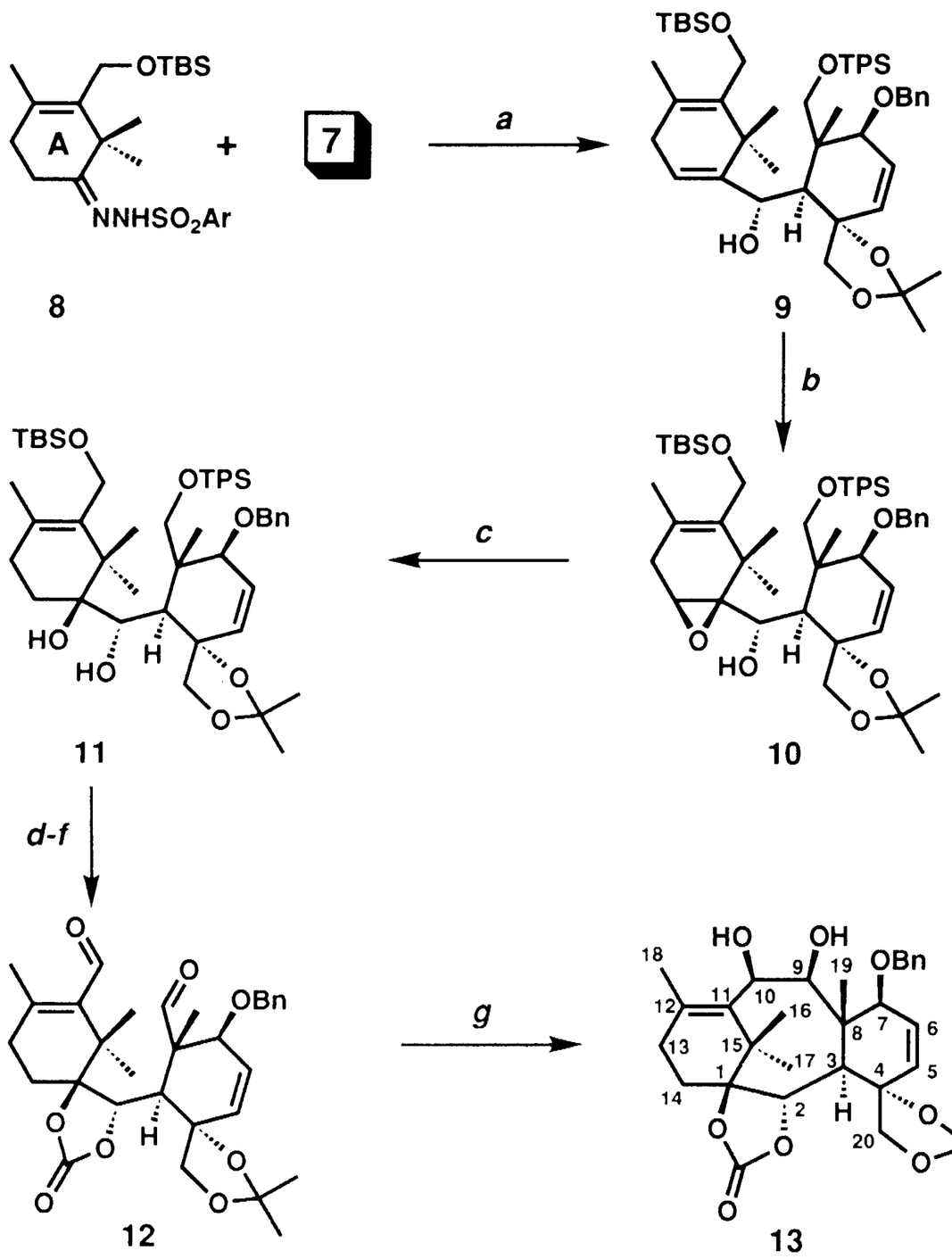


FIG. 3 Construction of ABC ring system 13. Reagents and conditions. (*a*) (1) **8**, *n*-BuLi (2.05 eq.), THF, −78 °C → 25 °C, cool to 0 °C and add **7** (1.0 eq. in THF), 0.5 h, 82%; (*b*) $VO(acac)_2$ (0.03 eq.), *t*-BuOOH (3 eq.), 4-Å molecular sieve (cat.), benzene, 25 °C, 12 h, 87%; (*c*) $LiAlH_4$ (3 eq.), Et_2O, 25 °C, 7 h, 76%; (*d*) KH (3 eq.), HMPA/Et_2O (30/70), $COCl_2$ (20% in benzene, 2 eq.), 25 °C, 2 h, 48%; (*e*) TBAF (10 eq.), THF, 25 °C, 7 h, 80%; (*f*) TPAP (0.05 eq.), NMO (3 eq.), CH_3CN/CH_2Cl_2 (2:1), 25 °C, 2 h, 82%; (*g*) $(TiCl_3)_2$–$(DME)_3$ (10 eq.), Zn–Cu (20 eq.), DME, 70 °C, 1 h, 23%. Ar = 2,4,6-triisopropylbenzene sulphonyl; HMPA = hexamethyl-phosphoric triamide; NMO = 4-methylmorpholine-N-oxide; TBAF = tetra-*n*-butylammonium fluoride; TBS = *t*-$BuMe_2Si$; TPAP = tetra-*n*-propylammonium perruthenate. Selected physical data for compound **13**: ^1H NMR (500 MHz, $CDCl_3$, taxol numbering): δ 7.42–7.31 (m, 5 H, aromatic), 5.97 (dd, J = 10.0, 1.5 Hz, 1 H, 5-H), 5.63 (dd, J = 10.0, 1.5 Hz, 1 H, 6-H), 5.46 (d, J = 5.0 Hz, 1 H, 2-H), 4.77 (d, J = 12.0 Hz, 1 H, OCH_2Ph), 4.49 (d, J = 8.5 Hz, 1 H, 20-H), 4.39 (d, J = 12.0 Hz, 1 H, OCH_2Ph), 4.29 (d, J = 5.5 Hz, 1 H, 10-H), 4.24 (d, J = 5.5 Hz, 1 H, 9-H), 3.80 (d, J = 8.5 Hz, 1 H, 20-H), 3.58 (b, 1 H, 7-H), 2.75–2.71 (m, 1 H, 13-H), 2.61–2.50 (m, 1 H, 13-H), 2.34 (d, J = 5.0 Hz, 1 H, 3-H), 1.98–1.92 (m, 1 H, 14-H), 1.83–1.74 (m, 1 H, 14-H), 1.58 (s, 3 H, 18-CH_3), 1.45 (s, 3 H, 19-CH_3), 1.42 (s, 3 H, CH_3-acetonide), 1.41 (s, 3 H, CH_3-acetonide), 1.19 (s, 3 H, 16-CH_3), 1.08 (s, 3 H, 17-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.9, 139.4, 137.3, 136.1, 135.6, 128.7, 128.5, 128.3, 122.0, 108.2, 93.4, 82.4, 77.9, 75.7, 74.2, 71.2, 70.4, 69.3, 46.3, 44.3, 40.0, 31.2, 29.6, 28.9, 27.9, 26.8, 23.6, 21.7, 21.3, 16.0; infrafred (pure compound): ν_{max} 2,970.3, 1,789.1, 1,455.6, 1,100.3 cm^{-1}; HRMS (FAB) calcd for $C_{31}H_{40}O_8$ ($M^+ + Cs$), m/z = 673.1778 a.m.u., found 673.1782 a.m.u.

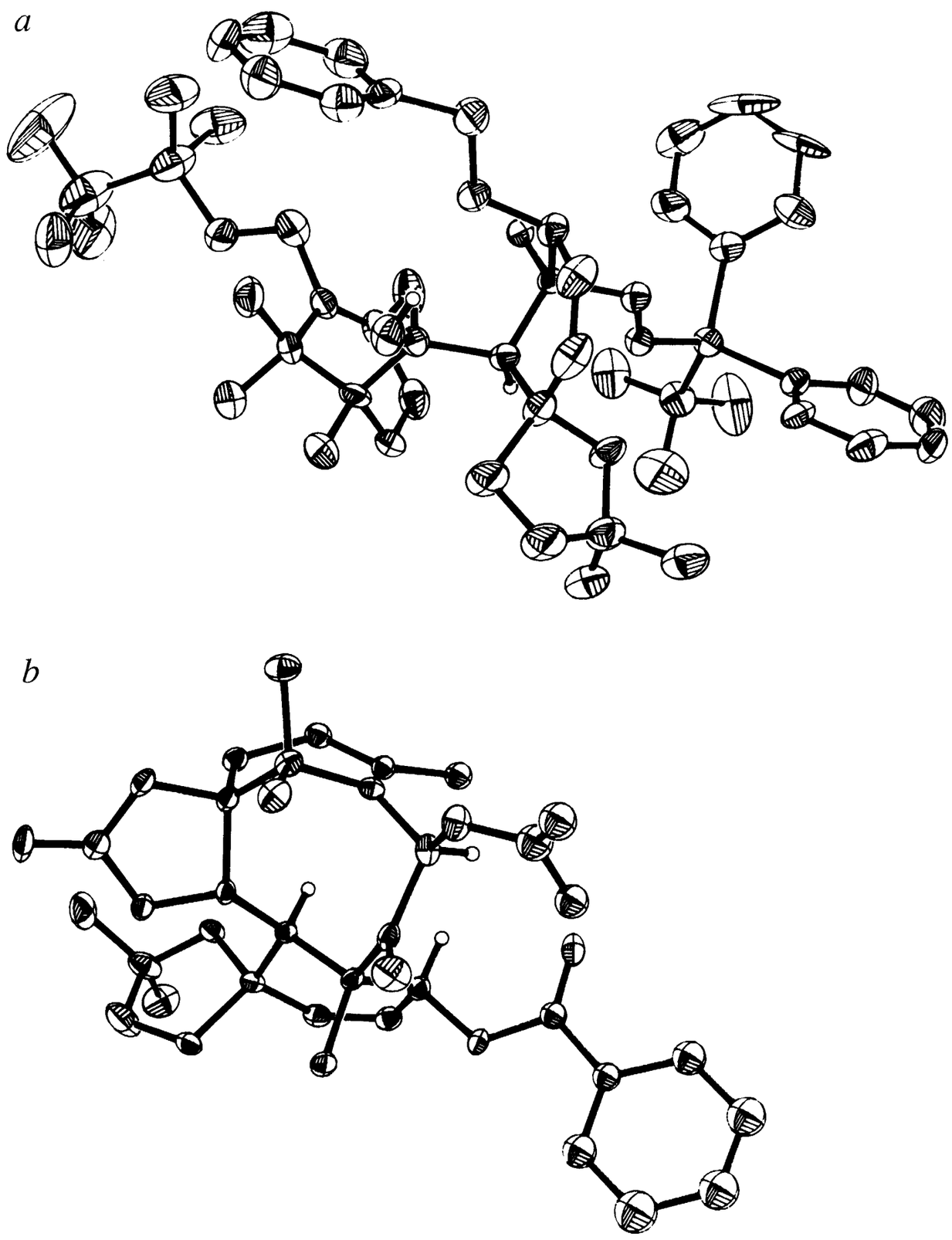
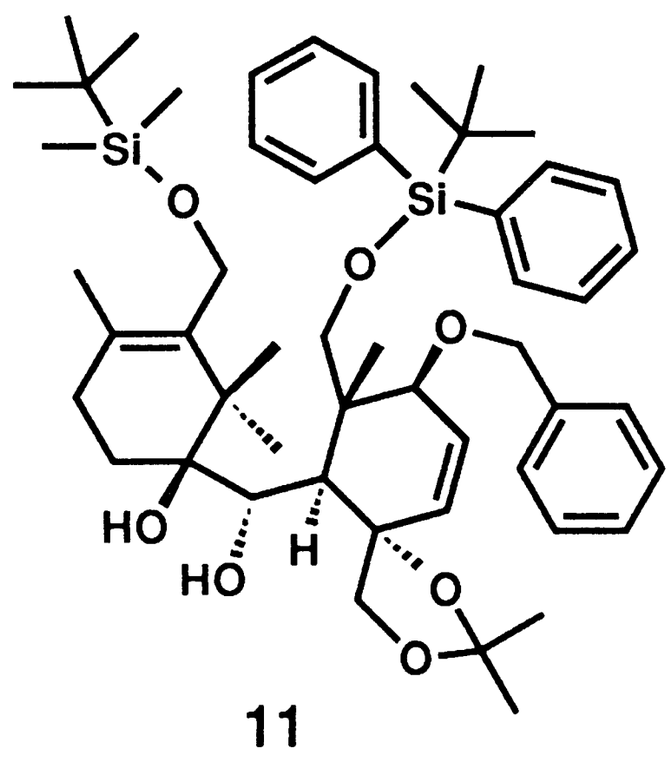


FIG. 4 ORTEP drawings of compounds **11** (*a*), **14′** (*b*) and **13′** (*c*). (ORTEP, Oregon national thermal ellipsoid program.)



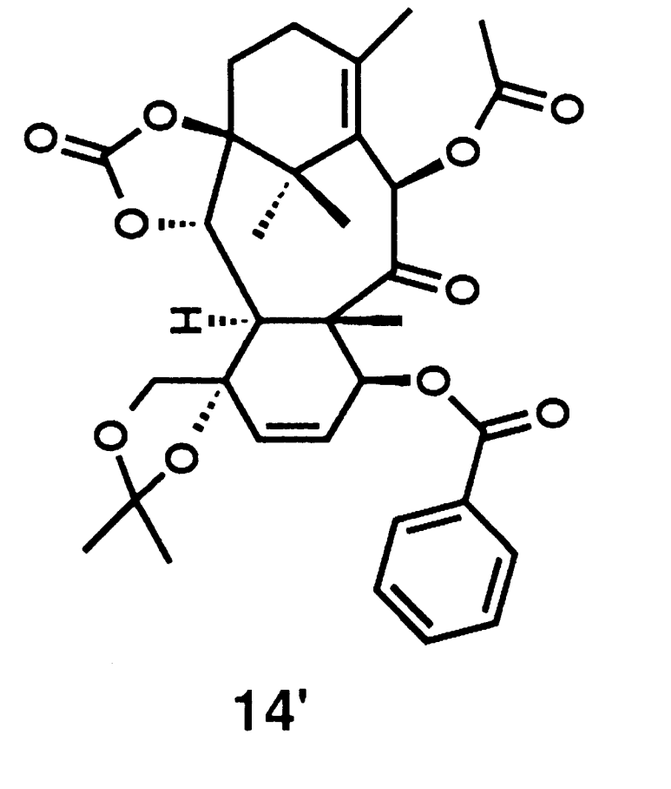
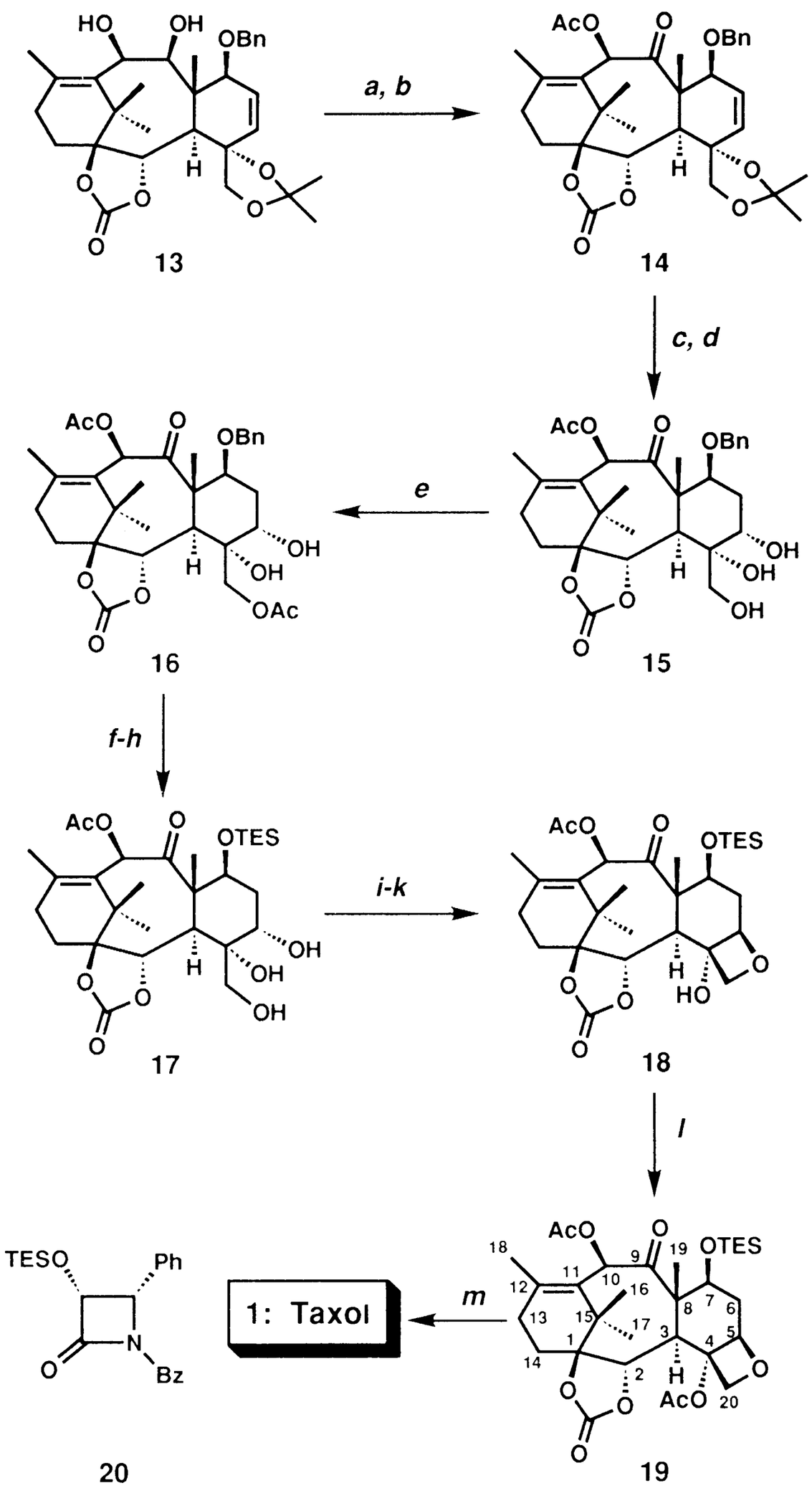


FIG. 5 Total synthesis of ABCD ring system **19** and taxol (**1**). Reagents and conditions. (*a*) Ac_2O (1.5 eq.), 4-DMAP (1.5 eq.), CH_2Cl_2, 25 °C, 2 h, 95%; (*b*) TPAP (0.1 eq.), NMO (3 eq.), CH_3CN, 25 °C, 2 h, 93%; (*c*) BH_3–THF (5.0 eq.), THF, 0 °C, 2 h then H_2O_2, aqueous $NaHCO_3$, 0.5 h, 55% (~3:1 mixture of C5–C6 regioisomers by ^1H NMR); (*d*) conc. HCl, MeOH, H_2O, 25 °C, 5 h 80%; (*e*) Ac_2O (1.5 eq.), 4-DMAP (1.5 eq.), CH_2Cl_2, 25 °C, 0.5 h, 95%; (*f*) H_2, 10% $Pd(OH)_2$(C), EtOAc, 25 °C, 0.5 h, 97%; (*g*) Et_3SiCl (25 eq.), pyridine, 25 °C, 12 h, 85%; (*h*) K_2CO_3 (10 eq.), MeOH, 0 °C, 15 min., 95%; (*i*) Me_3SiCl (10 eq.), pyridine (30 eq.), CH_2Cl_2, 0 °C, 15 min., 96%; (*j*) Tf_2O (15 eq.), *i*-Pr_2NEt (30 eq.), CH_2Cl_2, 25 °C, 0.5 h 70%; (*k*) CSA (cat.), MeOH, 25 °C, 10 min., then silica gel, CH_2Cl_2, 25 °C, 4 h, 60%; (*l*) Ac_2O (10 eq.), 4-DMAP (20 eq.), CH_2Cl_2, 25 °C, 4 h, 94%; (*m*) (1) PhLi (5 eq.), THF, −78 °C, 10 min., 80%; (2) PCC (30 eq.), NaOAc, celite, benzene, reflux, 1 h, 75%; (3) $NaBH_4$ (10 eq.), MeOH, 25 °C, 5 h, 83%; (4) $NaN(SiMe_3)_2$ (3.5 eq.), *β*-lactam **20**, THF, 0 °C, 87%, based on 90% conversion; (5) HF-pyridine, THF, 25 °C, 1.5 h, 80%. (CSA = (±)-camphorsulphonic acid; 4-DMAP = N-dimethylaminopyridine; NMO = 4-methylmorpholine-N-oxide; TPAP = tetra-*n*-propylammonium perruthenate. Selected physical data for compound **19**: ^1H NMR (500 MHz, $CDCl_3$, taxol numbering): δ 6.40 (s, 1 H, 10-H), 4.95 (d, J = 9.0 Hz, 1 H, 5-H), 4.60 (d, J = 9.0 Hz, 1 H, 20-H), 4.47 (d, J = 9.0 Hz, 1 H, 20-H), 4.43 (dd, J = 10.0, 7.5 Hz, 1 H, 7-H), 4.39 (d, J = 5.5 Hz, 1 H, 2-H), 3.36 (d, J = 5.5 Hz, 1 H, 3-H), 2.71 (m, 1 H, 13α-H), 2.56 (m, 1 H, 6-H), 2.17 (s, 3 H, OAc), 2.15 (s, 3 H, OAc), 2.12 (m, 1 H, CH_2), 2.07 (s, 3 H, 18-CH_3), 1.97 (m, 1 H, CH_2), 1.88 (m, 2 H, CH_2), 1.78 (s, 3 H, 19-CH_3), 1.23 (s, 3 H, 16-CH_3), 1.17 (s, 3 H, 17-CH_3), 0.88 (t, J = 7.5 Hz, 9 H, $Si(CH_2CH_3)_3$, 0.55 (dq, J = 8.0, 3.0 Hz, 6 H, $SI(CH_2CH_3)_3$; ^{13}C NMR (125 MHz, $CDCl_3$); δ 202.6, 170.3, 169.2, 153.1, 144.0, 130.7, 92.8, 84.0, 80.3, 80.0, 76.4, 76.1, 60.3, 43.5, 38.0, 29.7, 29.4, 25.5, 23.1, 21.9, 21.1, 19.1, 9.8, 6.7, 5.2; infrared (pure compound) ν_{max} 2,924, 1,814, 1,728, 1,461, 1,372, 1,238 cm^{-1}; HRMS (FAB) calcd for $C_{31}H_{46}O_{10}Si$ ($M^+ + Cs$) m/z = 739.1915 a.m.u., found 739.1929 a.m.u.



tion) with an authentic sample generated from taxol (**1**) or 10-deacetyl baccatin III (ref. 17) as described elsewhere[10]. Optically active **19** was obtained by the same route using enantiomerically pure diol **13** secured by resolution with 1(S)-(−)-camphanic chloride. Thus, reaction of racemic **13** with 1(S)-(−)-camphanic chloride gave, in 86% total yield, two diastereoisomers (**13′** and **13″**) which were chromatographically separated and characterized by X-ray crystallographic analysis on one of them (more polar isomer, silica gel, 15% $C_2H_5O(CO)CH_3$ in benzene, R_F = 0.21) (see ORTEP drawing for **13′**, antipode to desired enantiomer; Fig. 4*c*). Optically pure **13** ($[\alpha]_D^{22}$ + 187°($CHCl_3$, *c* 0.5)) was then generated from the correct diastereoisomer (**13″**, less polar, silica gel, 15% $C_2H_5O(CO)CH_3$ in benzene, R_F = 0.26) by exposure to methanolic K_2CO_3 (90% yield).

The conversion of enantiomerically pure **19** to taxol (**1**) followed the sequence[10]: (1) excess C_6H_5Li, −78 °C to regioselectively open the carbonate ring and afford the desired hydroxybenzoate functionality (80%); (2) PCC-$NaO(CO)CH_3$, benzene, reflux to introduce a carbonyl group at C-13 (75%); (3) excess $NaBH_4$-CH_3OH to stereospecifically generate the C-13 hydroxyl group (83%); (4) $NaN(Si(CH_3)_3)_2$ then Ojima's *β*-

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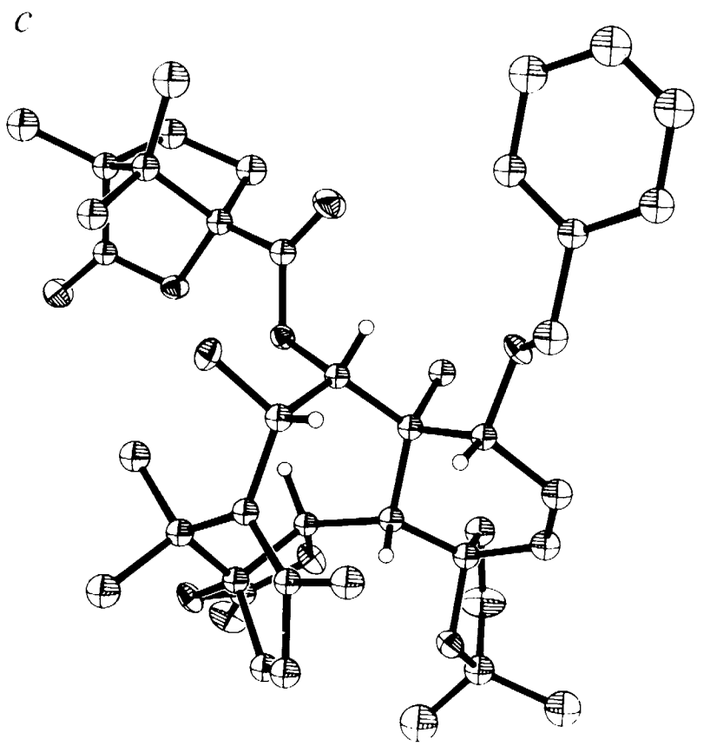

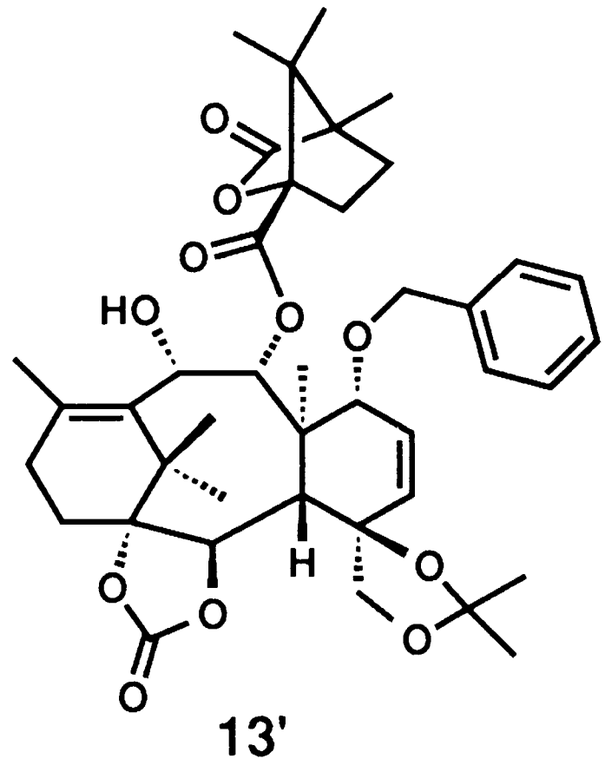

lactam (**20**)[11], 0 °C, to attach the side chain (87% yield based on 90% conversion); and (5) HF–pyridine, to remove the silyl groups (80%). Synthetic taxol was found to be identical in all respects with naturally occurring taxol, including spectroscopic characteristics (^{1}H and ^{13}C NMR, infrared spectroscopy, mass spectra, $[\alpha]_D^{22}$) and biological activity (microtubule stabilization and cytotoxicity against Molt-4 leukaemia cells).

The chemistry described here not only offers a solution to a formidable synthetic challenge but also opens a completely chemical avenue to taxol, other naturally occurring taxoids and synthetic, designed taxoid derivatives. □

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