Conversion of D-(−)-Quinic Acid into an Enantiopure C-4 Functionalized 2-Iodocyclohexenone Acetal

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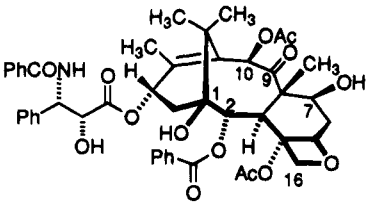
Taxol (**1**), a powerful anticancer drug originally discovered in the bark of the western yew *Taxus brevifolia*,[1] has the remarkable capacity for inhibiting cell replication by stabilizing microtubule assembly.[2] An approach to **1** that has been under exploration in this laboratory features an α-ketol rearrangement to set the bridgehead hydroxyl early in the synthesis[3] and a charge-accelerated [3,3] sigmatropic rearrangement to establish the structural framework rapidly.[4] This scheme readily accommodates stereocontrolled introduction of the C-2 and C-10



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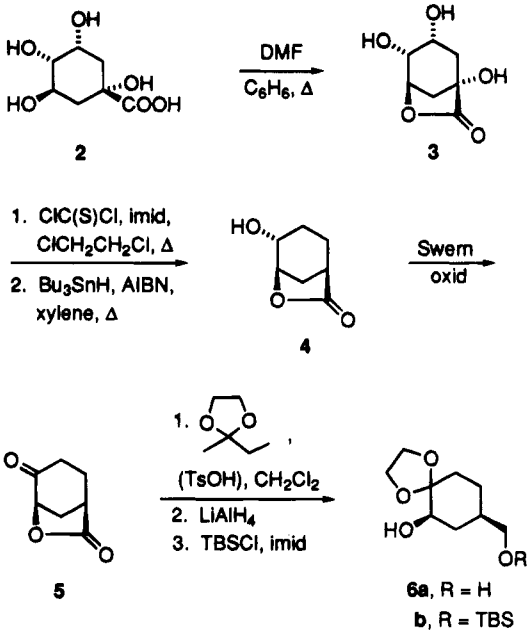
oxygenated substituents (taxol numbering) in addition to the carbonyl group at C-9.[5] Recently, the serviceability of 2-bromo-2-cyclohexenone acetals for introducing the C-7 oxygen was reported.[6] Although nucleophilic oxetane equivalents are also available,[7] no direct way of simultaneously achieving the tandem oxygenation of C-7 and incorporation of C-16 has yet been developed. For this reason, we set out to generate a precursor of the proper absolute configuration that would offer this capability. Here we detail the preparation of the functionalized cyclohexenyl iodide **10** from commercially available D-(−)-quinic acid (**2**).

The thermally induced cyclodehydration of **2** to bicyclic lactone **3**, previously described by Philippe et al.[8] proceeded with an average efficiency of 75% (Scheme 1).

A two-step reductive deoxygenation of **3** to give **4**, originally devised by a Merck group,[9] was shortened in an effort to heighten yields. Notwithstanding, the conversion of **3** to the monohydroxy derivative constitutes the least efficient segment of the overall sequence.

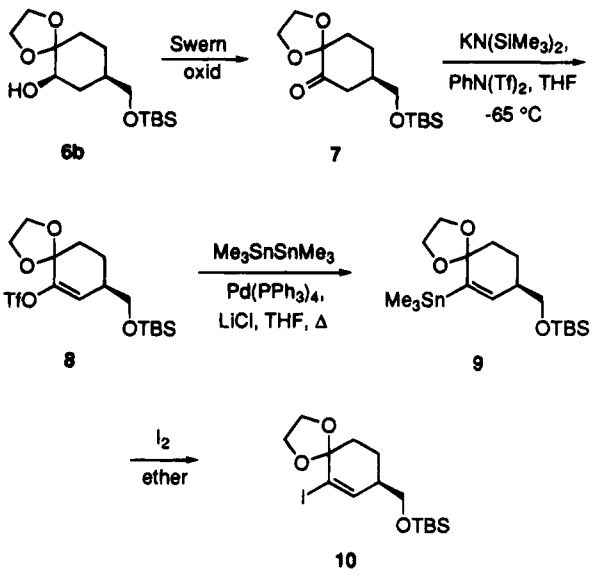
Scheme 1



Following Swern oxidation of **4** to furnish the crystalline lactone **5**, its ketone functionality was subjected to transfer ketalization with methyl ethyl 1,3-dioxolane[10] in advance of lithium aluminum hydride reduction in order to arrive at **6a**. The key stereochemical marker in **6a**, its hydroxymethyl substituent, could be selectively silylated as in **6b** (80%).

Once **6b** has been subjected to oxidation, treatment of the resultant ketone **7** with potassium hexamethyldisilazide and *N*-phenyltriflimide[11] afforded the enol triflate **8** as a colorless oil in 97% yield (Scheme 2). Upon exposure of **8** to hexamethylditin and tetrakis(triphenylphosphine)palladium in the presence of lithium chloride,[12] conversion to the vinylstannane **9** materialized

Scheme 2



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(87%). Formation of the targeted vinyl iodide was observed when **9** was stirred with elemental iodine in ether solution[13] at rt for 1.5 h (86%).

The chemistry described herein establishes that D-(−)-quinic acid can serve as a suitable precursor to a 2-halo-2-cyclohexenone acetal substituted with a protected hydroxymethyl side chain destined to become C-16 in taxol. In order to set the requisite *S* configuration in **10**, it was necessary to deoxygenate the hydroxyl group positioned α to the carboxyl group in **2** with retention of configuration. Prior conversion to the bridged bicyclic lactone **3** safeguarded this stereochemical outcome. Beyond that, regiocontrolled deoxygenation of **3** was carried out in the manner previously defined by Mills et al.[9] The ensuing acetalization of **5** made possible the necessary clear distinction between the two ring-oxygenated centers in **7**. Subsequently, tin-mediated methodology emerged as the method of choice for introduction of the vinyl halide component of **10**.

Experimental Section[14]

(1*R*,4*R*,5*R*)-4-Hydroxy-6-oxabicyclo[3.2.1]octan-7-one (4). Thiophosgene (138 g, 1.2 mol) was added dropwise under N_2 to a rapidly stirred suspension of imidazole (326.4 g, 4.8 mol) in dry 1,2-dichloroethane (1500 mL). Following completion of the addition, the mixture was agitated for 30 min prior to the introduction of **3**[8] (90 g, 0.517 mol) in one portion. The reaction mixture was refluxed for 3 h, cooled to rt, and filtered to remove the imidazole salt. The filtrate was concentrated to give a yellow solid which was washed with 300 mL of 50% of 2-butanone in acetonitrile. There was isolated 75 g (45%) of the known[9] bisthiocarbonyl lactone as a white solid: mp 184−185.5 °C dec; IR (film, cm^{-1}) 1809, 1789, 1322, 1270; ^1H NMR (300 MHz, DMSO-d_6) δ 8.53 (t, J = 0.9 Hz, 1 H), 7.83 (t, J = 1.4 Hz, 1 H), 7.12 (t, J = 0.8 Hz, 1 H), 5.67 (dt, J = 2.8, 8.0 Hz, 1 H), 5.37 (m, 2 H), 3.87−3.81 (m, 1 H), 3.04 (dd, J = 2.9, 15.3 Hz, 1 H), 2.89−2.80 (m, 1 H), 2.44 (d, J = 2.8 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) ppm 189.8, 179.6, 170.0, 137.2, 131.3, 118.8, 80.9, 78.2, 76.7, 73.3, 34.0, 29.4.

A suspension of the above bisthiocarbonyl lactone (15 g, 46 mmol) in dry xylene (1200 mL) was brought to reflux under N_2 and treated with tri-*n*-butyltin hydride in three portions: 8.78 g (30.2 mmol) at first, an additional 8.78 g after 30 min, and finally 15.4 g more together with 0.3 g of AIBN 1 h later. The reaction mixture was heated vigorously for 2.5 h, cooled to rt, and concentrated in vacuo. Chromatography of the residue on silica gel (elution with 1:1 ethyl acetate−hexanes) gave 2.00 g (31%) of **4**[9] as colorless crystals: mp 157−160 °C; IR (film, cm^{-1}) 3409, 1753; ^1H NMR (300 MHz, $CDCl_3$) δ 4.64 (t, J = 5.3 Hz, 1 H), 4.12 (d, J = 2.8 Hz, 1 H), 2.79 (d, J = 3.3 Hz, 1 H), 2.56 (t, J = 5.0 Hz, 1 H), 2.37 (d, J = 11.9 Hz, 1 H), 2.20−2.15 (m, 1 H), 1.91−1.71 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 179.3, 79.3, 64.8, 38.5, 31.1, 27.0, 22.6.

(1*R*,5*R*)-6-Oxabicyclo[3.2.1]octane-4,7-dione (5). A solution of oxalyl chloride (3.35 g, 26.4 mmol) in dry CH_2Cl_2 (170 mL) was cooled to −78 °C and treated dropwise with DMSO (4.12 g, 52.8 mmol) under N_2. After 15 min, a solution of **4** (1.5 g, 10.6 mmol) in dry CH_2Cl_2 (10 mL) was slowly introduced, the mixture was stirred for 30 min, and triethylamine (6.41 g, 63.3 mmol) was then added. After an additional 30 min at −78 °C, the reaction mixture was allowed to warm slowly to rt and washed with brine. The aqueous phases were back-extracted with ether and the combined organic solutions were dried and evaporated to leave a residue which was purified chromatographically (silica gel, elution with 40% ethyl acetate in hexanes) to give 1.25 g (85%) of **5** as a colorless crystalline solid, mp 87.5−89 °C; IR (film, cm^{-1}) 1783, 1727; ^1H NMR (300 MHz, $CDCl_3$) δ 4.64 (d, J = 6.5 Hz, 1 H), 2.89−2.72 (m, 2 H), 2.77 (dd, J = 9.1, 16.3 Hz, 1 H), 2.56 (dd, J = 6.8, 16.2 Hz, 1 H), 2.34−2.23 (m, 1 H), 2.07 (d, J = 12.6 Hz, 1 H), 1.98−1.87 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 203.9, 176.7, 82.1, 37.7, 36.8, 34.9, 25.6; MS m/z (M^+) calcd 140.0473, obsd 140.0471; $[\alpha]^{23}_D$ −238.3° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_7H_8O_3$: C, 60.00; H, 5.75. Found: C, 59.79; H, 5.80.

(6*R*,8*R*)-6-Hydroxy-1,4-dioxaspiro[4.5]decane-8-methanol (6a). A solution of **5** (1.14 g, 8.1 mmol) in dry CH_2Cl_2 (25 mL) was treated with 2-methyl-2-ethyl-1,3-dioxolane (10 mL) and *p*-toluenesulfonic acid monohydrate (10 mg), stirred at rt for 2 h, and quenched with triethylamine (1 mL). After dilution of the reaction mixture with THF (50 mL), the solvent was evaporated in vacuo and the residue was taken up in dry THF (200 mL) and ether (50 mL). This solution was cooled to 4 °C and treated portionwise with 1.0 g of lithium aluminum hydride. After 30 min, saturated NH_4Cl solution was slowly introduced until the solids turned white. The salts were filtered and washed repeatedly with a 1:1 mixture of ether and THF. The combined filtrates were dried and evaporated to leave a residue, purification of which by silica gel chromatography (elution with 3:1 ethyl acetate-hexanes) gave 0.98 g (64%) of **6a** as a colorless crystalline solid, mp 134−135.5 °C; IR (film, cm^{-1}) 3354, 3260, 1179, 1085, 1047, 698, 656; ^1H NMR (300 MHz, $CDCl_3$) δ 4.08−3.96 (m, 4 H), 3.66 (m, 1 H), 3.51 (d, J = 5.9 Hz, 2 H), 2.07−1.97 (m, 1 H), 1.96 (s, 1 H), 1.85 (dt, J = 3.4, 13.4 Hz, 1 H), 1.76−1.58 (m, 2 H), 1.53 (s, 1 H), 1.44 (dt, J = 3.9, 13.3 Hz, 1 H), 1.29 (q, J = 11.8 Hz, 1 H), 1.32−1.20 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) pm 109.5, 72.5, 67.3, 65.5, 65.4, 38.2, 34.9, 32.7, 26.0; MS m/z (M^+) calcd 188.1048, obsd 188.1053; $[\alpha]^{23}_D$ +5.9° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.10; H, 8.69.

(6*R*,8*R*)-8-[(*tert*-Butyldimethylsiloxy)methyl]-1,4-dioxaspiro[4.5]decan-6-ol (6b). A solution of **6a** (418 mg, 2.22 mmol) and imidazole (226 mg, 3.33 mmol) in dry DMF (5 mL) was treated with *tert*-butyldimethylsilyl chloride (402 mg, 2.67 mmol) under N_2, stirred overnight at rt, diluted with ether (150 mL), and washed with brine. The organic phase was dried and concentrated to leave a residue which was chromatographed on silica gel (elution with 1:4 ethyl acetate in hexanes) to afford 536 mg (80%) of **6b** as a colorless oil: IR (neat, cm^{-1}) 3440, 1087, 837; ^1H NMR (300 MHz, $CDCl_3$) δ 4.09−3.96 (m, 4 H), 3.65 (dd, J 4.9, 11.8 Hz, 1 H), 3.44 (d, J = 7.1 Hz, 2 H), 2.06−1.99 (m, 1 H), 1.86−1.79 (dm, 2 H), 1.75−1.55 (dm, 2 H), 1.42 (dt, J = 4.0, 13.5 Hz, 1 H), 1.28−1.10 (m, 2 H), 0.89 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 109.7, 72.7, 67.6, 65.5, 65.4, 38.5, 35.3, 32.9, 26.2, 25.9, 18.3, −5.4; FAB MS m/z (M^+ + 1) calcd 303.20, obsd 303.21; $[\alpha]^{23}_D$ +5.8° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.51; H, 10.03.

(*R*)-8-[(*tert*-Butyldimethylsiloxy)methyl]-1,4-dioxaspiro[4.5]decan-6-one (7). The oxidation of **6b** was performed in the manner described above. From 130 mg (0.43 mmol) of this alcohol there was obtained 125 mg (97%) of **7** as a faint yellow oil following silica gel chromatography (elution with 1:6 ether in hexanes): IR (neat, cm^{-1}) 1729, 1090, 839; ^1H NMR (300 MHz, C_6D_6) δ 3.88 (dd, J = 7.0, 14.1 Hz, 1 H), 3.57 (m, 1 H), 3.44 (d, J = 7.0 Hz, 1 H), 3.42 (dd, J = 2.0, 7.0 Hz, 1 H), 3.19 (d, J = 5.1 Hz, 2 H), 2.43−2.49 (m, 2 H), 2.00−2.08 (m, 1 H), 1.52−1.85 (m, 4 H), 0.91 (s, 9 H), −0.04 (s, 6 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 204.2, 106.7, 66.8, 65.9, 64.5, 42.5, 40.6, 35.2, 26.0, 25.8, 18.4, −5.4; MS m/z (M^+) calcd 300.1757, obsd 300.1780; $[\alpha]^{23}_D$ +31.8° (*c* 1.2, ethyl acetate).

(*R*)-8-[(*tert*-Butyldimethylsiloxy)methyl]-1,4-dioxaspiro[4.5]dec-6-en-6-yl Trifluoromethanesulfonate (8). A solution of **7** (90 mg, 0.30 mmol) in anhydrous THF (2 mL) was treated at −78 °C under N_2 with a solution of potassium hexamethyldisilazide in THF (0.40 mmol) and stirred for 1 h prior to the addition of *N*-phenyltriflimide (150 mg, 0.42 mmol) dissolved in THF (2 mL). The reaction mixture was stirred for 2 h at −78 °C and for 4 h at 0 °C prior to solvent evaporation under vacuum. The residue was purified by silica gel chromatography (elution with 4% ethyl acetate in hexane) to give 126 mg (97%) of **8** as a colorless oil: IR (neat, cm^{-1}) 1415, 1208, 1105, 839; ^1H NMR (300 MHz, C_6D_6) δ 5.95 (d, J = 2.7 Hz, 1 H), 3.80 (q, J = 6.8 Hz, 1 H), 3.67 (m, 1 H), 3.45 (m, 1 H), 3.30 (q, J = 7.0 Hz, 1 H), 3.25−3.05 (m, 2 H), 2.12 (m, 1 H), 1.81−1.62 (m, 2 H), 1.48−1.38 (m, 2 H), 0.91 (s, 9 H), −0.48 (s, 3 H), −0.53

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(14) For general information, see ref 7.

(s, 3H); ^{13}C NMR (75 MHz, C_6D_6) ppm 147.6, 125.2, 104.6, 66.2, 65.5, 65.4, 38.8, 34.2, 25.9, 23.1, 18.3, −5.5, −5.6; MS m/z (M^+) calcd 432.1249, obsd 432.1216; $[\alpha]^{23}_D$ +26.5° (c 1.35, hexane).

***tert*-Butyldimethyl[[(*R*)-6-(trimethylstannyl)-1,4-dioxaspiro[4.5]dec-6-en-8-yl]methoxy]silane (9).** A solution of **8** (18 mg, 0.042 mmol) in THF (2 mL) was treated sequentially with hexamethylditin (23 mg, 0.070 mmol) tetrakis(triphenylphosphine)palladium (5 mg), and lithium chloride (7 mg) under N_2. The resulting mixture was refluxed with stirring for 14 h, cooled, diluted with ether and hexane, and washed with saturated $NaHCO_3$ solution prior to drying and concentration. Chromatography of the residue on silica gel (elution with 1:60 ethyl acetate–hexanes) afforded 16 mg (87%) of **9** as a colorless oil; IR (neat, cm^{-1}) 1251, 1084, 839, 772; ^1H NMR (300 MHz, C_6D_6) δ 6.25 (d, J = 2.5 Hz, 1 H), 3.52–3.40 (m, 6 H), 2.31 (m, 1 H), 1.84–1.75 (m, 2 H), 1.61 (m, 2 H), 0.96 (s, 9 H), 0.30 (s, 9 H), 0.02 (s, 3H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 145.3, 143.7, 109.1, 66.9, 64.3, 63.8, 40.7, 31.1, 26.1, 23.7, 18.5, −5.3, −8.7; MS m/z (M^+) calcd 448.1455, obsd 448.1485.

***tert*-Butyl[[(*R*)-6-iodo-1,4-dioxaspiro[4.5]dec-6-en-8-yl]methoxy]dimethylsilane (10).** A magnetically stirred solution of **9** (7 mg, 0.015 mmol) in dry ether (1 mL) was treated with iodine (4.4 mg, 0.17 mmol) under N_2, diluted with ether (10 mL) after 1.5 h, and washed sequentially with 1% NH_4OH solution and brine prior to drying and solvent evaporation. Purification of the residue by chromatography on silica gel (elution with 1.5% ethyl acetate and 0.1% triethylamine in hexanes) furnished 5.5 mg (86%) of **10** as a colorless oil: IR (neat, cm^{-1}) 1255, 1161, 1085, 835, 744; ^1H NMR (300 MHz, C_6D_6) δ 6.58 (d, J = 2.8 Hz, 1 H), 3.90 (q, J = 6.6 Hz, 1 H), 3.83–3.75 (m, 1 H), 3.52–3.36 (m, 2 H), 3.18–3.07 (m, 2 H), 2.14–2.03 (m, 1 H), 1.95–1.86 (m, 1 H), 1.79–1.50 (m, 3 H), 0.91 (s, 9 H), −0.05 (s, 6 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 145.3, 106.6, 106.2, 65.9, 65.6, 65.4, 43.2, 33.4, 26.0, 23.6, 18.4, −5.4; MS m/z (M^+) calcd 410.0734, obsd 410.0775; $[\alpha]^{23}_D$ +9.7° (c 1.75, ethyl acetate).

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Supplementary Material Available: Copies of the ^1H and ^{13}C NMR spectra for **7**–**10** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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