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Second-Generation, Highly Abbreviated Route for Elaboration of the Oxetane D-Ring in a Fully Functionalized Taxane

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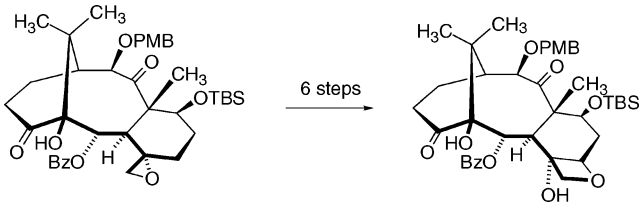
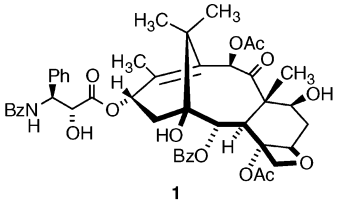
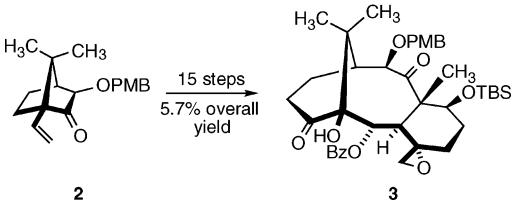


A six-step conversion of oxirane **3** to oxetane **9** is reported. The synthetic route takes particular advantage of the acid-catalyzed ring opening of **3** to allyl alcohol **4** in a polar reaction medium and of the heightened capability of the OsO_4·TMEDA complex to effect the efficient stereocontrolled dihydroxylation of this intermediate. The overall yield of the new sequence is 33%.

We have undertaken the goal of devising a notably abbreviated enantioselective route to Taxol (**1**) and biologically important analogues thereof from (+)-camphor. The chemical challenges associated with such a venture are numerous when viewed in the context of the six prior completed syntheses of this potent cytotoxic agent.[1−6] Nonetheless, it has proven possible to generate from **2** the highly functionalized intermediate **3** in 15 steps and 5.7% overall yield.[7,8] The essentially complete overlay of stereocenters resident in **3** with those found in **1** nicely sets the foundation for advancement to the target structures.





More recently, an oxetane D-ring has been fused to **3** in the manner defined by **9**.[9] The initial pathway involved a trimethylsilyl triflate-promoted oxirane ring opening (**3** → **4**), stereoreversed oxirane formation (**4** → **5**), and reduction with bis(cyclopentadienyl)titanium(III) chloride (**5** → **6**, Scheme 1). These steps were followed by the introduction of additional hydroxyl groups and their controlled protection/activation as **7** → **8** to set up the ultimate intramolecular S_N2 reaction. Despite the success of this exploratory study, the routing consisted of nine operational steps and was clearly too lengthy, especially when viewed alongside the efficiency realized in the conversion of **2** to **3**.

With heightened economy in mind, we have presently developed an alternative protocol that features the generation of **9** from **3** in only six steps (Scheme 2). The first consideration involved improvement in the generation of allylic alcohol **4** from epoxide **3**. The discovery that this ring cleavage could be effected directly with camphorsulfonic acid was initially clouded by the competitive formation of byproducts in which the C-2 benzoate functionality had been perturbed. These events occur

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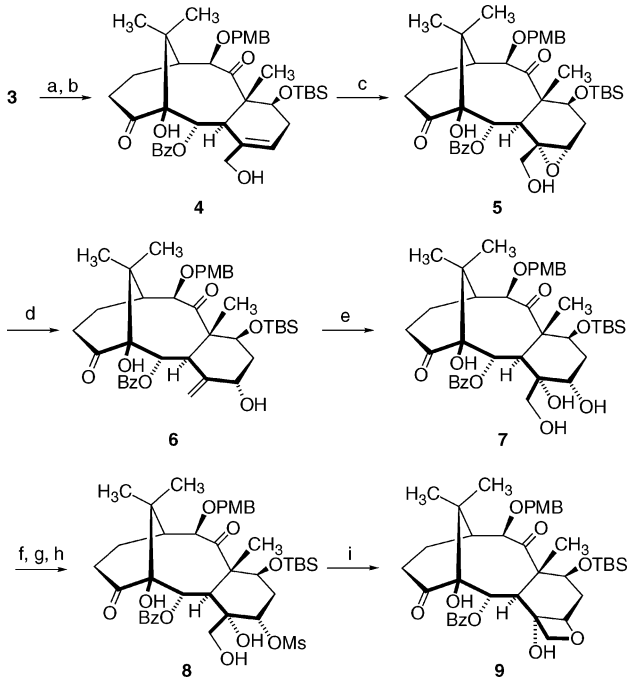
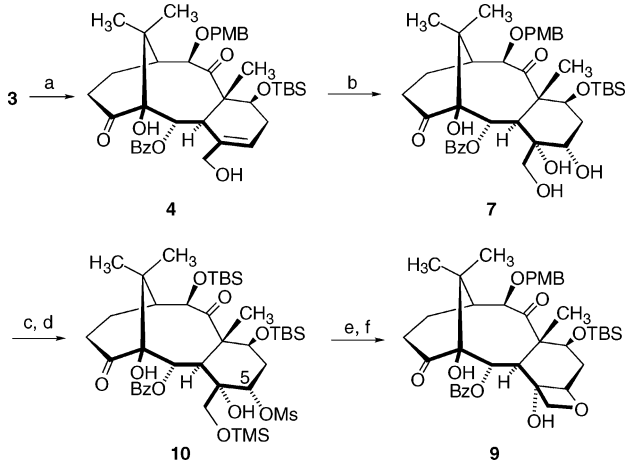
SCHEME 1[a]



[a] Key: (a) TMSOTf, 2,6-lutidine, TfOH, −78 to 0 °C; (b) CSA, CH_2Cl_2, rt (75% overall); (c) MCPBA, $NaHCO_3$, CH_2Cl_2 (90%); (d) Cp_2TiCl_2, Zn, $ZnCl_2$, THF (40%); (e) OsO_4, THF/py, rt; $Na_2S_2O_4$ (75% at 65% conversion); (f) TMSCl, 2,6-lutidine, CH_2Cl_2, −78 °C (100%); (g) MsCl, DMAP, CH_2Cl_2 (90%); (h) CSA, CH_2Cl_2, rt (95−100%); (i) Al(O *t*-Bu)$_3$, C_6H_6, rt (54%).

SCHEME 2[a]



[a] Key: (a) CSA, CH_3CN/DMSO (10:1), rt (80%); (b) OsO_4, TMEDA, CH_2Cl_2, −78 °C to rt; $NaHSO_3$ (74%); (c) TMSCl, 2,6-lutidine, CH_2Cl_2, −78 °C; (d) MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C; (e) HF·pyridine, THF, rt (87% for three steps); (f) Al(O-*i*-Pr)$_3$, *i*-PrOH, silica gel, rt (65%).

with CH_3CN as the reaction medium. A change to more polar solvents such as DMF and DMSO gave **4** cleanly with very acceptable efficiency. However, the requisite reaction times in these media were protracted (ca. 10 days) compared to only 2 h for acetonitrile. The compromise position of making recourse to a mixed solvent system (10:1 CH_3CN/DMSO) was met with excellent and reproducible conversions in a reasonable time frame.

The original three-step pathway from **4** to **7** became the next target of improvement. In the old route, direct dihydroxylation involving classical osmylating conditions was not successful. When companion studies revealed to us that the OsO_4/TMEDA chelate is a significantly more reactive species, its capability in this context was assessed. This reagent has previously been touted for its ability to engage in hydroxyl group directed dihydroxylation.[10] Although the reaction with **4** went smoothly and rapidly, an unexpected complication arose in the resistance of the resulting osmate ester to hydrolysis. The potential awkwardness of this phenomenon was conveniently skirted by making recourse to a two-step one-pot workup. After the complete consumption of **4**, an initial amount of $NaHSO_3$ was added to free up relatively pure osmate ester, which was extracted into the organic layer. At this point, the introduction of a second aliquot of $NaHSO_3$ liberated **7** in 74% yield. These optimized conditions eliminated three steps from the prior sequence.

The final ring-closure step has also been significantly improved. Previously, aluminum *tert*-butoxide in benzene served as the promoter of oxetane ring formation. These conditions suffered from low conversion and resultant difficulty in the chromatographic separation of the product from the starting material. An extensive screening of alternative protocols was rewarded with the discovery that isopropyl alcohol was a preferred solvent. Beyond that, the co-addition of silica gel improved matters to the extent that complete conversion to **9** was routinely achieved and final purification greatly facilitated.[11]

In summary, an improved means for elaborating the entire eastern sector of the Taxol structure has been accomplished in very expedient fashion. The six-step route from **3** to **9**, which proceeds in an overall yield of 33%, meshes well with our earlier achievements and now sets the stage for final elaboration of the A-ring. The possibility of arriving at **1** and derivatives thereof in less than 30 steps remains viable.

Experimental Section

Allylic Alcohol 4. A solution of **3** (740 mg, 1.05 mmol) in dry CH_3CN (112 mL) and dry DMSO (11.2 mL) was treated at rt with 1.46 g (6.30 mmol) of camphorsulfonic acid, stirred for 91 h, and quenched with saturated $NaHCO_3$ solution. After 5 min, water (40 mL) and ethyl acetate (100 mL) were introduced, and the mixture was stirred for an additional 15 min. The separated aqueous phase was extracted with ethyl acetate (2 × 50 mL), and the combined organic solutions were dried and evaporated to leave a residue that was purified by chromatography on silica gel. Elution with 35−45% ethyl acetate in hexanes afforded 590 mg (80%) of **4** as a colorless oil. The spectral properties of **4** were identical to those previously reported.[9]

Triol 7. A solution of **4** (590 mg, 0.84 mmol) in dry CH_2Cl_2 (32.4 mL) was cooled to −78 °C and treated sequentially with TMEDA (0.32 mL, 2.1 mmol) and osmium tetraoxide (531 mg, 2.09 mmol). The reaction mixture was stirred at this tempera-

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(11) The beneficial effect of silica gel was first noted during TLC analysis of the progress of this reaction. Indication of complete conversion was met upon workup with substantive levels of recovered starting material. The deduction was made that SiO_2 was likely playing a catalytic role, as subsequently established.

ture for 2 h, allowed to warm to rt during 15 min, and freed of solvent under high vacuum. The residue was taken up in THF (80 mL), acetone (40 mL), and water (40 mL), treated with 7.5 g of solid sodium bisulfite, and stirred for 3 h. Water (100 mL) and ethyl acetate (100 mL) were now introduced, the separated aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the combined organic phases were pumped free of solvent. Additional quantities of THF (80 mL), acetone (40 mL), water (40 mL), and sodium bisulfite (4.0 g) were added, and the mixture was stirred at rt for 20 h. The resultant mixture was filtered through a pad of Celite, and the residue was rinsed with ethyl acetate (3 × 150 mL). The aqueous phase was extracted with ethyl acetate (2 × 50 mL), the combined organic phases were evaporated, and the residue was subjected to flash chromatography on silica gel. Elution with 45−55% ethyl acetate in hexanes furnished 460 mg (72%) of **7** as a colorless oil. The spectral properties of **7** were identical to those previously reported.[9]

Monosilylation of 7. A 272 mg (0.367 mmol) sample of **7** in cold (−78 °C), dry CH_2Cl_2 (40 mL) was treated with 0.85 mL (7.34 mmol) of 2,6-lutidine and 0.47 mL (3.67 mmol) of trimethylsilyl chloride and allowed to stir for 45 min at this temperature. The previously described workup protocol afforded monoprotected product that was used without further purification. The spectral features were identical to those previously cited.[9]

Monomesylate 10. The above material was taken up in dry CH_2Cl_2 (37 mL) at 0 °C and treated in sequence with DMAP (247 mg, 2.02 mmol), methanesulfonyl chloride (0.14 mL, 1.81 mmol), and triethylamine (0.52 mL, 3.74 mmol). After 1 h of stirring at 0 °C followed by the predescribed workup,[9] there was isolated the monomesylate as a colorless oil that exhibited spectra identical to those of authentic **10**.

Desilylation of 10. The unpurified material from above was dissolved in dry THF (37 mL), 4.0 M HF·pyridine in the same solvent (0.5 mL, 2.0 mmol) was introduced, and stirring was maintained for 45 min. Quenching with saturated NH_4Cl solution (15 mL) was followed by dilution with water (15 mL) and ethyl acetate (15 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 30 mL), and the combined organic layers were dried, evaporated, and chromatographed on silica gel (elution with 45% ethyl acetate in hexanes) to give dihydroxy mesylate **8** (262 mg, 87% for the three steps) as a colorless oil. All spectra were superimposable upon those of the previously described material.

Oxetane 9. A 50.7 mg (0.062 mmol) sample of the predescribed monomesylate **8** was admixed with solid aluminum isopropoxide (37.9 mg, 0.186 mmol). Dilution with dry isopropyl alcohol (9.1 mL) was followed with 3.5 h of stirring at rt. At this point, 235 mg of silica gel was introduced, and agitation was continued for an additional 6 h. The solids were removed by filtration and rinsed with ethyl acetate. The filtrate was evaporated, and the residue was chromatographed on silica gel. Elution with 45% ethyl acetate in hexanes gave 29.1 mg (65%) of **9** as a colorless oil whose spectral properties were identical to those reported.[9]

Supporting Information Available: High-field ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra for all compounds described herein were recorded in $CDCl_3$ except for the mono-TMS ether of **7** and **8**−**10**, which were recorded in C_6D_6. This material is available free of charge via the Internet at http://pubs.acs.org.

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