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Taxol Chemistry. 7-O-Triflates as Precursors to Olefins and Cyclopropanes

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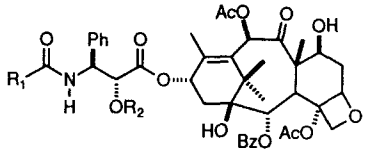
Abstract: 7-O-Triflates of baccatin III or of taxol analogs are convenient precursors in alternate syntheses of $\Delta^{6,7}$-taxols and 7β,8β-methano (cyclopropyl) taxols, two of the products initially obtained from reaction of taxols with methylDAST; hydrazine is an effective reagent for conversion of the 10-acetate group to the hydroxyl group.

Taxol, in addition to its exciting potential as an antitumor agent, presents a fascinating array of challenges to the organic chemist.[1] The highly functionalized diterpenoid nucleus of taxol not only provides a synthetic challenge but is subject to unusual and often unexpected chemical transformations. Contraction of rings A and B,[2] oxetane opening,[2,3] epimerization at C-7,[4] dienone formation,[5] and cyclopropane formation[6] are some of the fascinating modifications of taxol which have been reported to date.

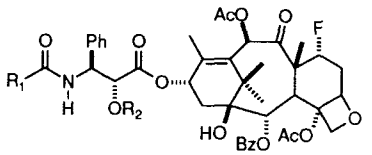
Independently of the work reported recently by Chen and coworkers,[6a,6b] we have studied the reaction of a 2'-protected taxol with the fluorinating reagent, dimethylaminosulfur trifluoride (methylDAST). Our reaction of 2'-troc-taxol[7] (**1**) with methylDAST[8] gave 2'-troc-7-deoxy-7α-fluoro-taxol (**2**, 33%) and 2'-troc-7-deoxy-7β,8β-methano-taxol (**3**, 23%),[9] results very similar to those reported by Chen and coworkers. However, we have isolated a third product from this reaction which is the olefin, 2'-troc-7-deoxy-$\Delta^{6,7}$-taxol (**4**, 4%). Removal of the 2'-troc group gives 7-deoxy-$\Delta^{6,7}$-taxol (**5**). The assignment of olefinic structures to **4** and **5** is based on three coupled, downfield signals for the C-5, C-6, and C-7 protons in the ^{1}H NMR spectra[10] and was confirmed as described below. Elimination with formation of olefins is a well documented side reaction in the reaction of alcohols with DAST.[11]

Olefins are also produced in reactions of other taxol analogs with methylDAST. For example, the reaction with the 2'-troc derivative **7** of analog **6**, in which the N-benzoyl group is replaced by benzyloxycarbonyl (Cbz), gave fluoride **8** (45%), cyclopropane **9** (18%), and olefin **10** (5%). Likewise, the reaction with the 2'-troc derivative **12** of analog **11**, in which the N-benzoyl group is replaced by *t*-butyloxycarbonyl (BOC), gave fluoride **13** (47%), cyclopropane **14** (21%), and olefin **15** (5%). The isolation of olefins from these reactions is noteworthy because in every case the olefinic product is more potent than the alcohol precursor in assays which measure potential antitumor activity.[12]

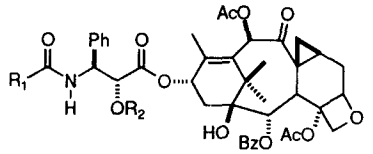
The low yields of olefins produced by the methylDAST reactions called for development of an alternate source. For this, we found it possible to prepare and purify 7-O-triflates of either baccatin III (**16**) or of the taxol analog. The reaction of **16** with triflic anhydride in CH_2Cl_2/pyridine gives baccatin III-7-OTf (**17**) in 80% yield.[13] When **17** is warmed in solution in the presence of DBU, elimination of the 7-O-triflate proceeds smoothly to generate the 6,7-olefin **18** in 70% yield.[14] The 6,7-olefins exhibit slightly enhanced sensitivity to acid catalyzed opening of the oxetane ring. Whereas the 2'-troc group of **4** can be



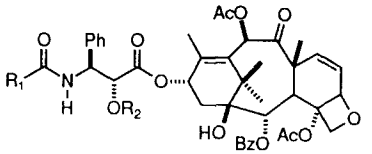
1, R_1 = Ph; R_2 = troc
6, R_1 = $PhCH_2O$; R_2 = H
7, R_1 = $PhCH_2O$; R_2 = troc
11, R_1 = Me_3CO; R_2 = H
12, R_1 = Me_3CO; R_2 = troc
31, R_1 = Me_3CNH; R_2 = H



2, R_1 = Ph; R_2 = troc
8, R_1 = $PhCH_2O$; R_2 = troc
13, R_1 = Me_3CO; R_2 = troc

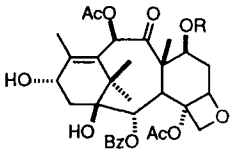


3, R_1 = Ph; R_2 = troc
9, R_1 = $PhCH_2O$; R_2 = troc
14, R_1 = Me_3CO; R_2 = troc

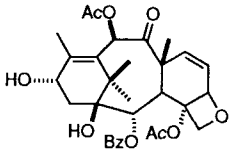


4, R_1 = Ph; R_2 = troc
5, R_1 = Ph; R_2 = H
10, R_1 = $PhCH_2O$; R_2 = troc
15, R_1 = Me_3CO; R_2 = troc
20, R_1 = Me_3CO; R_2 = H

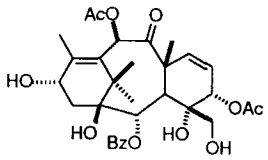
removed with zinc in HOAc-MeOH without rearrangement of the oxetane, **18** upon warming with acetic acid in $ClCH_2CH_2Cl$ rearranges to **19** (70%). The structures of both **18** and **19** have been confirmed by x-ray crystallographic studies.[15]



16, R = H
17, R = SO_2CF_3



18

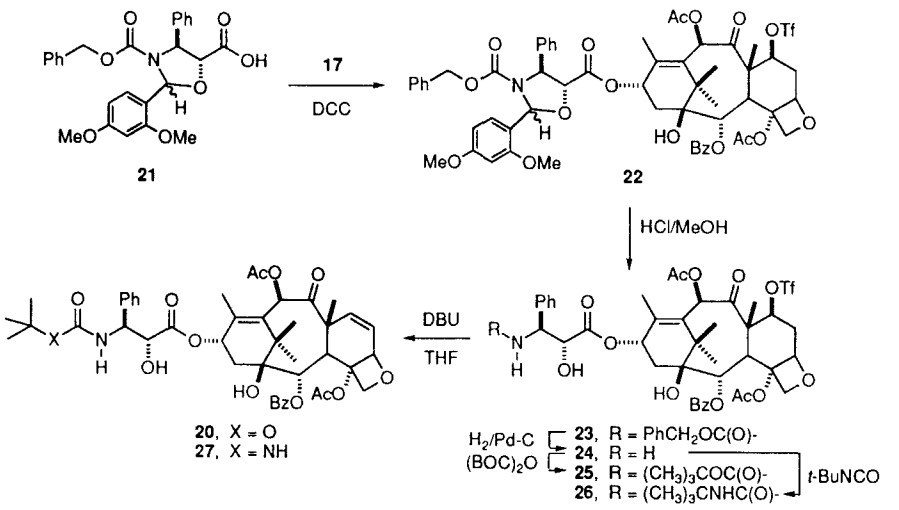


19

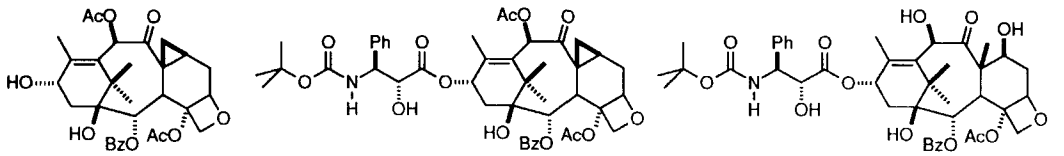
The $\Delta^{6,7}$-analog **20**, obtained by removal of the 2'-troc group from **15**, now can be prepared by the alternate route shown in Scheme 1 which we have developed independently of that by Didier and coworkers.[16] First, baccatin III-7-O-Tf (**17**) is coupled with (4*S*,5*R*)-N-Cbz-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid (**21**)[9,16] to give **22** (87%, two epimers) from which the aminal groups are removed by exchange with acidic methanol to give **23** (93%). The Cbz group is removed from **23** by hydrogenolysis, giving the versatile intermediate **24** which is useful for attachment of a variety of N-substituents. Reaction of **24** with di-*t*-butylcarbonate provides the N-BOC compound **25** (77% from **23**). Warming of **25** with DBU in THF generates the analog **20**[12,17] in 82% yield. Reaction of **24** with *t*-butylisocyanate provides the N-*t*-butylurea (TBU) compound **26** (74%). Warming of **26** with DBU in THF generates the analog **27**[12,18] in 75% yield.

The 7-O-triflates such as **17** also serve as excellent precursors for the 7β,8β-methano (cyclopropyl) taxol analogs. Simply stirring a solution of **17** with silica gel (40-63 μm, 1:60 w/w) in 1,2-dichloroethane at 60°C produces 7-deoxy-7β,8β-methanobaccatin III (**28**)[19] in 75% yield. When **28** is carried through a

Scheme 1



sequence of reactions analogous to those described in the preceding paragraph, we obtain **29** (the analog derived from **14** upon removal of the 2'-troc group). The influence of the C-9 substituent upon the reactivity of a 7-O-triflate is clearly seen by comparison of our results with those of Klein and coworkers.[6c] Their report describes migration of the C-8 methyl to C-7 when a baccatin having both 7β- and 9α-hydroxyl groups is treated with triflic anhydride. The formation of an intermediate carbocation at C-8 is postulated, which undergoes further rearrangement by contraction of ring B from eight to seven carbons in size. Our results show that when there is a carbonyl group at C-9, the 7-O-triflates are relatively stable compounds which are converted to 6,7-olefins or 7,8-cyclopropanes under the conditions described above. Clearly, the electron withdrawing effect of the C-9 carbonyl group stabilizes the 7-O-triflates and completely inhibits carbocation formation at C-8.



28 **29** **30**

As a final point of interest, we report that hydrazine (98%) in 95% ethanol is an excellent reagent for cleavage of the 10-acetate group when there is a free hydroxyl group at C-7. For example, 10-acetyltaxotere (**11**) is converted to taxotere[20] (**30**) in 86% yield at room temperature under these conditions. When the C-7 hydroxyl group is absent or masked by a protecting group, the removal of the 10-acetate by these conditions is much less effective.

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9. Upjohn PCT application, WO 9413655, June 23, 1994.
10. Spectral data for **5**: ^{1}H NMR ($CDCl_3$, TMS) δ 8.17 (d, 2H), 7.75 (d, 2H), 7.64 (t, 1H), 7.36-7.55 (m, 10H, aromatic protons), 7.02 (d, 1H, -NH-), 6.21 (t, 1H, H_{13}), 6.20 (s, 1H, H_{10}), 6.06 (dd, 1H, $H_{6\text{ or }7}$), 5.87 (d, 1H, $H_{3'}$), 5.83 (m, 2H, H_2 and $H_{6\text{ or }7}$), 5.10 (d, 1H, H_5), 4.79 (d, 1H, $H_{2'}$), 4.44 (d, 1H, H_{20a}), 4.32 (d, 1H, H_{20b}), 4.00 (d, 1H, H_3), 2.39 (s, 3H, $-CH_3$), 2.23 (s, 3H, $-CH_3$), 1.87 (s, 3H, $-CH_3$), 1.70 (s, 3H, CH_3), 1.24 (s, 3H, $-CH_3$), 1.16 (s, 3H, $-CH_3$); mass spectrum: 836.3288, $C_{47}H_{49}NO_{13}$ + H requires 836.3282.
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12. The mouse L1210 leukemic cell assay [*Cf.*, Li, L.H.; *et.al.*, *Cancer Res.* **1992**, *52*, 4904] gives IC_{50} values (μM) of 0.017 for taxol, 0.0042 for **5**, >0.1 for **7**, 0.062 for **10**, 0.0035 for **11**, 0.0016 for **20**, 0.013 for **31**, and 0.0032 for **27**. These results are from single assays. We thank Joan Culp for these assay results.
13. Reaction conditions: Baccatin III (1.0 g) in CH_2Cl_2 (4.0 mL) and pyridine (3.4 mL) was cooled (-30 °C); Tf_2O (1.2 g) was added and the solution allowed to warm to RT. After 4 hrs, workup and chromatography (flash SiO_2, 5% CH_3CN/CH_2Cl_2) gave **17** (0.978 g).
14. Reaction conditions: **17** (0.97 g) and DBU (1.03 g) in THF (6 mL) were heated (reflux) for 4 hours.
15. Fusen Han and Constance G. Chidester, unpublished results.
16. Didier, E.; Fouque, E.; Taillepied, I.; Commerçon, A. *Tetrahedron Lett.* **1994**, *35*, 2349.
17. Spectral data for **20**: ^{1}H NMR ($CDCl_3$, TMS) δ 8.15 (d, 2H, J = 7.2 Hz), 7.61 (t, 1H), 7.51 (t, 2H, J = 7.5 Hz), 7.30-7.43 (m, 5H), 6.22 (s, 1H, H_{10}), 6.21 (t, 1H, H_{13}), 6.06 (dd, 1H, J = 5.6, 9.9 Hz, H_6), 5.87 (d, 1H, J = 9.6 Hz, H_7), 5.84 (d, 1H, H_2), 5.39 (d, 1H, J = 9.6 Hz, -NH- or $H_{3'}$), 5.26 (d, 1H, $H_{3'}$ or -NH-), 5.10 (d, 1H, J = 5.6 Hz, H_5), 4.61 (m, 1H, $H_{2'}$), 4.43 (d, 1H, J = 8.1 Hz, H_{20a}), 4.30 (d, 1H, J = 8.2 Hz, H_{20b}), 4.01 (d, 1H, J = 6.5 Hz, H_3), 2.39 (s, 3H, $-CH_3$), 2.33 (m, 1H), 2.24 (s, 3H, $-CH_3$), 1.86 (s, 3H, $-CH_3$), 1.76 (s, 3H, $-CH_3$), 1.34 (s, 9H, Me_3C-), 1.27 (s, 3H, $-CH_3$), 1.16 (s, 3H, $-CH_3$); mass spectrum, found: 832.3554, $C_{45}H_{53}NO_{14}$ + H requires 832.3544, 776, 551, 491, 369, 327, 105, 57 m/z.
18. Spectral data for **27**: ^{1}H NMR ($CDCl_3$, TMS) δ 8.14 (d, 2H), 7.63 (m, 1H), 7.51 (m, 2H), 7.33 (m, 5H), 6.22 (s, 1H), 6.17 (m, 1H), 6.04 (m, 1H), 5.85 (m, 2H), 5.33 (m, 1H), 5.15 (m, 1H), 5.10 (d, 1H), 4.60 (m, 2H), 4.42 (d, 1H), 4.30 (d, 1H), 3.99 (d, 1H), 2.42 (s, 3H), 2.32 (m, 2H), 2.23 (s, 3H), 1.86 (s, 3H), 1.75 (s, 3H), 1.23 (m); mass spectrum: 831.3742; $C_{45}H_{54}N_2O_{13}$ + H requires 831.3704.
19. Spectral data for **28**: ^{1}H NMR ($CDCl_3$, TMS) δ 8.13 (dd, 2H, Ar), 7.61 (tt, 1H, Ar), 7.49 (t, 2H, Ar), 6.34 (s, 1H, H_{10}), 5.63 (d, 1H, J = 7.6 Hz, H_2), 4.83 (m, 1H, H_{13}), 4.75 (d, 1H, J = 0.9 Hz, H_5), 4.30 (d, 1H, J = 8.5 Hz, H_{20a}), 4.18 (d, 1H, J = 7.6 Hz, H_3), 4.04 (d, 1H, J = 8.5 Hz, H_{20b}), 2.48 (dt, 1H, J = 16.0 Hz, H_{6a}), 2.39-2.20, (m, 2H, $H_{14a,14b}$), 2.26 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.64 (m, 1H, H_{19b}), 1.35 (m, 1H, H_7), 1.23 (s, 3H, CH_3), 1.10 (s, 3H, CH_3); FAB mass spectrum: 569.2389, $C_{31}H_{36}O_{10}$ + H requires 569.2387.
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