Intramolecular 2 + 2 Cycloaddition in a Baccatin. From a Tetracyclic to a Hexacyclic Molecule

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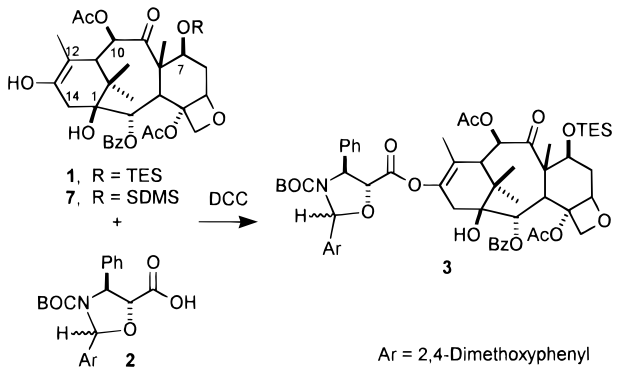
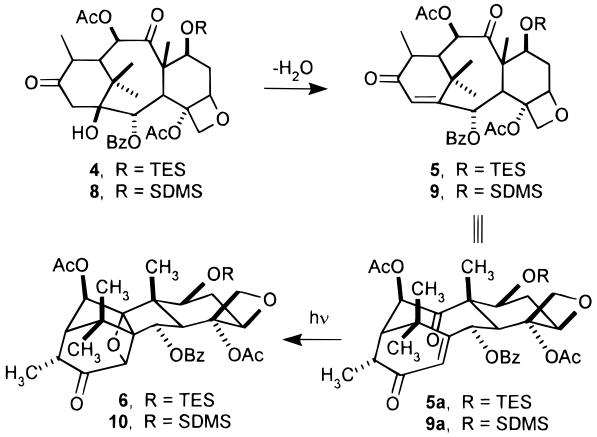
In a previous paper, we described the unexpected isolation of the baccatin enol **1**, a compound to which we gave the name 12,13-isobaccatin III-7-*O*-TES. The enol **1** was successfully coupled with the side-chain precursor **2** in the presence of dicyclohexylcarbodiimide to give the 12,13-isotaxol **3**.[1] Although stable enough to isolate and



manipulate, the enol **1** does ketonize, for example, when exposed to silica gel, giving the 11,12-dihydrobaccatin III derivative **4**. In the present paper, we describe the further chemical transformation of ketone **4** and elucidation of the structure of yet another unexpected compound derived from baccatin.



In the coupling reaction of **1** with **2**, a byproduct of the reaction is consistently isolated in 2−15% yields. On the basis of the analytical and spectral properties of this byproduct, the structure of the compound is formulated to be the 14(1)-enone **5**. Distinctive among the ^{1}H NMR signals for **5** are a doublet for the C-18 methyl group, a five-line signal for H-12, and a doublet (J = 2.8 Hz) at δ 5.94 for H-14. Signals at δ 163.9 (q) and 133.7 (t) in the DEPT ^{13}C NMR spectrum of **5** are consistent with a C-1,C-14 olefin. We speculate that the 14(1)-enone system of **5** arises as a consequence of ketonization of a small portion of **1** to **4** followed by dehydration of the C-1 hydroxyl group under the conditions of the coupling reaction.

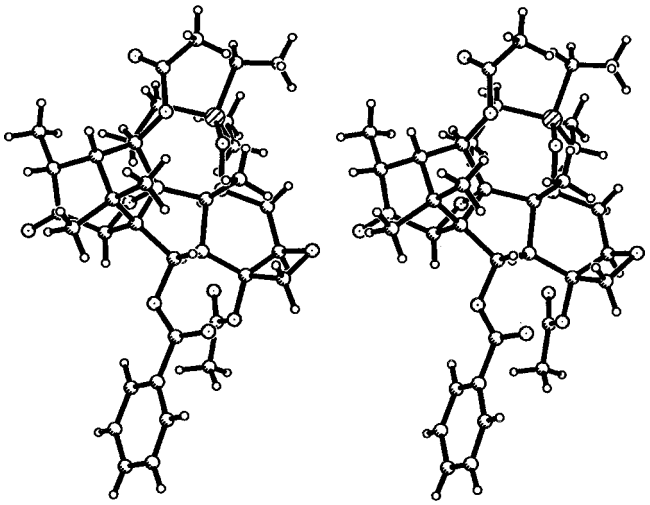


Figure 1. Stereoview of bisoxetane **6**.

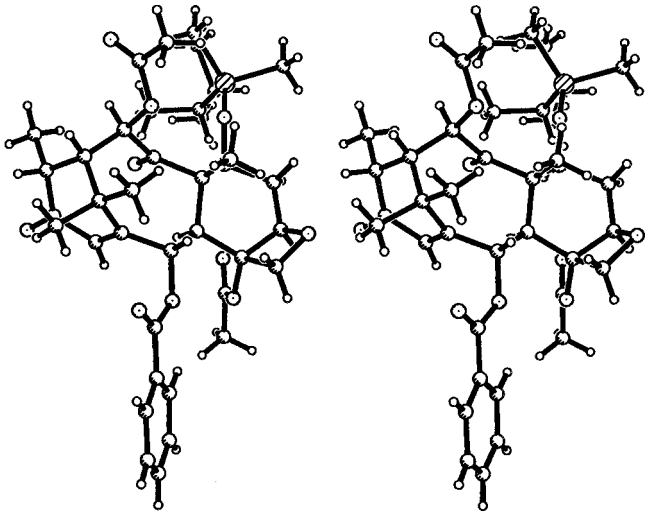


Figure 2. Stereoview of 14(1)-enone **9**.

When samples of **5** are stored neat or are kept in solution, a new compound is seen to arise. The new compound is stable under normal conditions, and analytical data indicated that the compound is isomeric with **5**. We were puzzled in our efforts to derive a plausible structure from the spectral data for this new compound until we actually built a Dreiding model of the precursor ketone **5**. Whereas a conventional drawing of **5**, such as the one used here, portrays the C-9 ketone as being far removed from the 14(1)-enone double bond, in the model these two functional groups are seen to be closely aligned and in an almost parallel orientation.[2] The drawing **5a** is an accurate representation of the conformation of the mol-

(1) Kelly, R. C.; Wicnienski, N. A.; Gebhard, I.; Qualls, S. J.; Han, F.; Dobrowolski, P, J.; Nidy, E. G.; Johnson, R. A. *J. Am. Chem. Soc.* **1996**, *118*, 919.

(2) There is a second conformation of the molecule that can be built with the Dreiding model in which the orientation of the C-9 ketone is in the opposite direction from that portrayed in the drawing of **4a**; interconversion between the two conformations appears unlikely from the Dreiding model.

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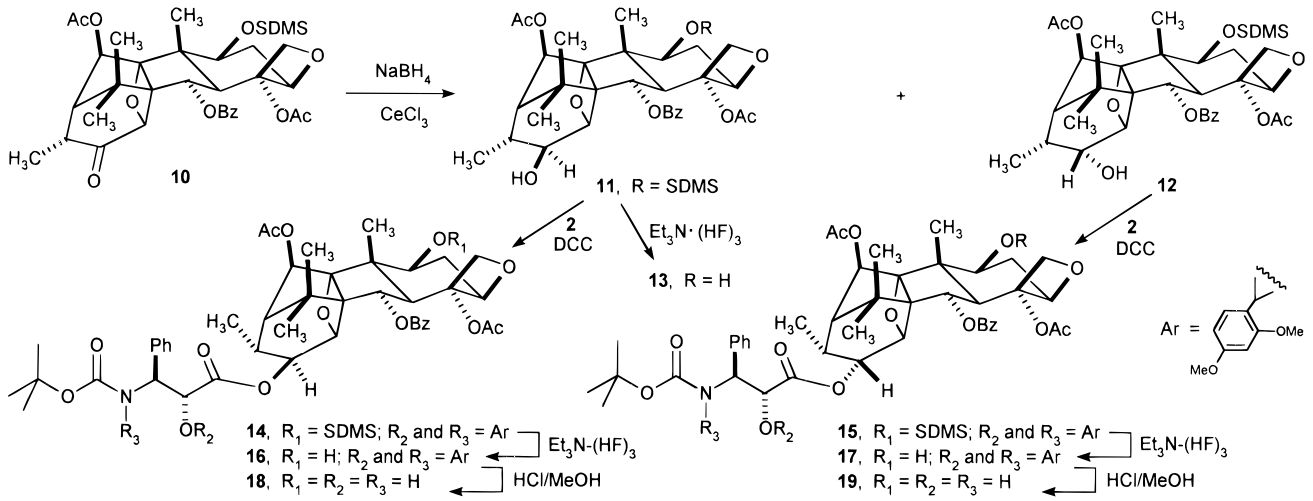
Scheme 1



ecule as seen in the Dreiding model. The orientation of the π-orbitals of these two functional groups as displayed by the model suggests that a 2 + 2 cycloaddition reaction of the groups is feasible and that the structure of the new compound may be the hexacyclic bisoxetane **6**.

The analogous baccatin enol **7**, in which the 7-*O*-TES group is replaced by the 7-*O*-SDMS (7-*O*-siamyldimethylsilyl) group, was observed to undergo the same series of transformations to ketone **8**, the 14(1)-enone **9**, and the analogous final product **10**.

The spectral data for both **6** and **10** are consistent with the bisoxetane structure. Some key elements among these data are the presence of only one ketone carbonyl signal in the ^{13}C NMR spectrum; signals at δ 102.8, 86.4, 81.7, and 80.6 are assigned to the carbon atoms adjacent to the oxetane oxygens with the δ 102.8 signal assigned to C-14. In the ^{1}H NMR spectrum, distinctive signals are seen for H-10 and H-14 at δ 5.65 and 4.58, repectively, as well as a five-line signal for H-12 at 2.92 that is coupled to a doublet for the C-18 methyl group at 1.58. Irradiation of solutions of **9** with light of only moderate intensity rapidly accelerated the conversion into **10**, consistent with formulation of the reaction as a 2 + 2 or Paterno−Buchi cyclization.[3] There is brief literature precedent for photochemical 2 + 2 cycloaddition reactions between aldehydes or ketones and electron-deficient olefins such as an enone.[4−6]

The bisoxetane **6** was crystallized and the structure determined by X-ray crystallography, confirming the structure derived from modeling and spectroscopic analysis. A stereo representation of the structure of **6** obtained by the X-ray study is shown in Figure 1.[7] We were curious about how close to each other are the two reacting π-orbitals in either **5** or **9** and we obtained crystals of **9** which gave the X-ray structure shown in Figure 2.[7] From the crystallographic data, we find that the distances, in two symmetry-independent molecules of **9**, between carbonyl oxygen (O-9) and the α-carbon of the enone (C-14), are 2.76 and 2.77 Å and between C-9 and the β-carbon (C-1) are 2.93 and 2.97 Å. In the X-ray structure of **6**, the C14−O9 bond length is 1.49 Å and the C1−C9 bond length is 1.62 Å. The distances between reacting atoms in **5** or **9** are only ~1.3 Å greater than the bond lengths in the final oxetanes. Clearly, the proximity and strict orientation of the two key functional groups in **5** and **9** are determining the regiochemical outcome of the cycloaddition reactions observed in these molecules.

The unusual structural nature of the modified baccatins **6** and **10** provided us with an opportunity to prepare new Taxol[8] analog molecules (Scheme 1). Reduction[9,10] of **10** with $NaBH_4/CeCl_3$ was essentially complete within 15 min and produced a major product (**11**, 73% yield) and a minor product (**12**, 15%). Removal of the silyl protecting group from **11** gave **13**, shown by X-ray crystallography to have the 13β-alcohol. The major reduction product **11** therefore is the 13β-alcohol and the minor product **12** is the 13α-alcohol.

Both **11** and **12** were carried on to fully developed taxotere side-chain analogs as shown in the chart. The Taxotere[11] side-chain precursor **2** was used for coupling[12] with each of the two alcohols and gave the compounds **14** and **15**, respectively. The protecting groups were removed sequentially from each intermediate. The silyl group protecting the 7-OH was removed with $Et_3N{\cdot}(HF)_3$, giving **16** and **17**, and the side-chain protecting group was removed with acidic methanol. Analogs **18** and **19**, generated by these transformations, were devoid of activity in microtubule binding experiments.

Supporting Information Available: Experimental data for compounds **5**−**7** and **9**−**19** (6 pages).

JO970645Q

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(6) Meier, R.-M.; Ganem, B. *J. Org. Chem.* **1994**, *59*, 5436.

(7) Details of the single-crystal X-ray structures obtained for **6**, **9**, and **13** will be published as part of the full account of this work. The author has deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(8) The name Taxol has been registered as a trademark by Bristol-Myers Squibb; the generic name for Taxol is paclitaxel.

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(11) Taxotere is a registered trademark of Rhône-Poulenc Rorer; the generic name for Taxotere is docetaxel.

(12) (a) Didier, E.; Fouque, E; Taillepied, I.; Commerçon, A. *Tetrahedron Lett.* **1994**, *35*, 2349. (b) Johnson, R. A; Nidy, E. G.; Dobrowolski, P. J.; Gebhart, I.; Qualls, S. J.; Wicnienski, N. A.; Kelly, R. C. *Tetrahedron Lett.* **1994**, *35*, 7893.