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On the Importance of the Stereochemistry at C_{10} in Governing the Feasibility of the Intramolecular Diels-Alder Route to Baccatin III Constructs: Surprising Results in the 10R-9-Deoxy Series

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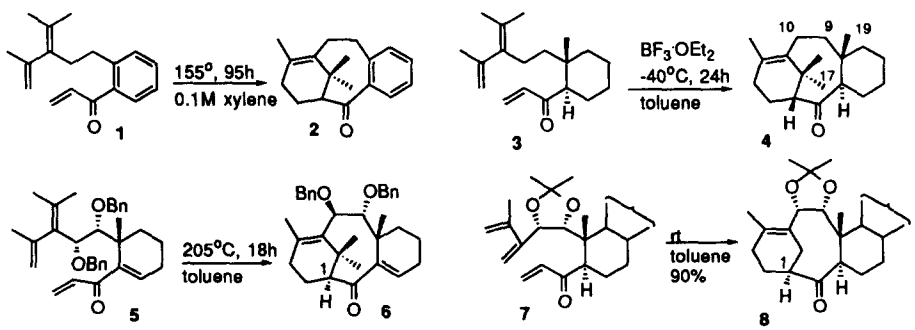
Abstract: Upon surveying many experimental conditions in the title series, no simple type II IMDA reaction (leading to **15**) was observed. A variety of alternative reactions are described.

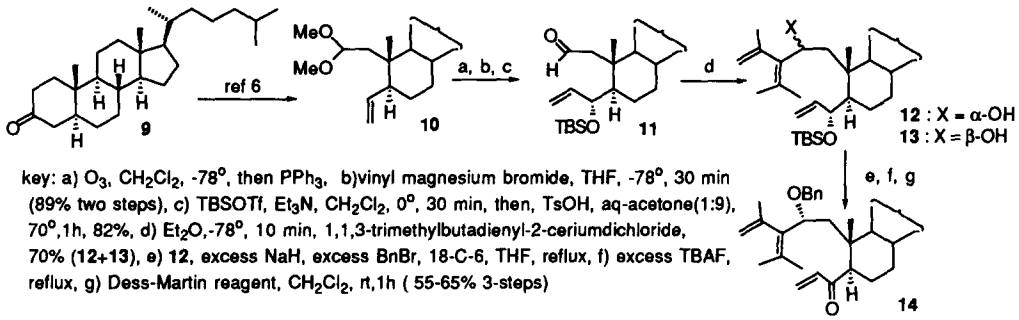
The possibility of using intramolecular Diels-Alder (IMDA) reactions as a route to establish the AB subsection of the taxanes[1] was first elegantly demonstrated by Shea (see **1** —› **2**).[2] An important advance was provided by Jenkins and colleagues who extended the method to the case where cycloaddition produces a C_{17}-C_{19} methyl methyl abutment (see **3** —›**4**).[3] The Jenkins case lacked any substituents at either C_9 or C_{10}. Two newer reports described cycloadditions in which oxygen functionality at the future C_9-C_{10} bridge was included (see, **5**—›**6**[4] and **7**—›**8** [5]). However, these cases served to raise concerns about the stereochemical outcome at the C_1 bridgehead center since, in each of these instances, the C_1-epibaccatin stereochemistry resulted from the IMDA reaction. We hoped to find the proper substitution and stereochemical pattern which would accommodate the implements needed to reach realistic and properly configured baccatin constructs.



In the research reported in this Letter, we focused on substrates which would contain oxygen substitution at the future C_{10} (baccatin III numbering).[2] Unlike our previously demonstrated case (**7** —›**8**), the gem-dimethyl arrangement at the future C_{15} would be included. In contrast to the Shea case (**5**—› **6**)[4] the future C_3 would be

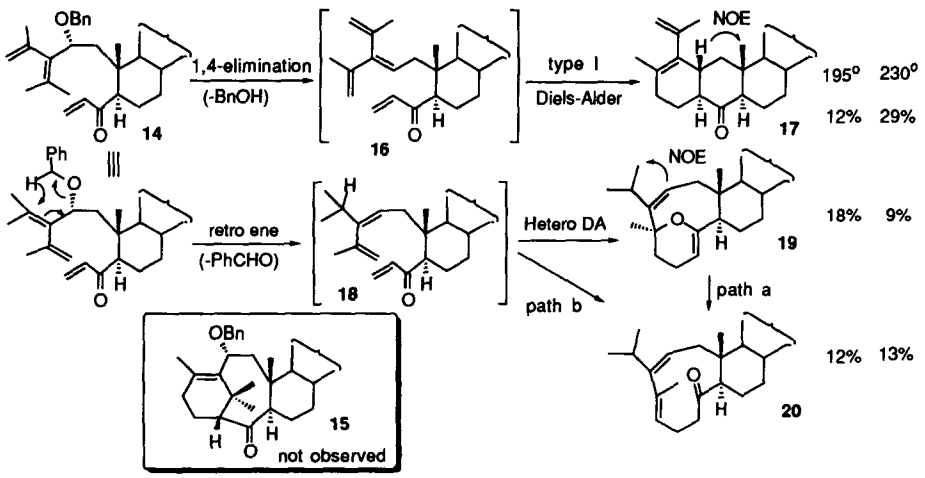
sp^3 hybridized. We chose to operate in the cholestanone setting in consideration of the availability of starting material and ease of manipulation of synthetic intermediates.

Formation of intermediate **11** by degradation of **10** was accomplished as shown.[6] Reaction of **11** with Shea's butadienyl cerium species[4] at -78° gave the diene carbinols **12** and **13** which are epimeric at C_{10} (baccatin III numbering) in a 5:2 ratio. Purified **12** was subjected to benzylation, silyl cleavage and oxidation to give high yields of the potential IMDA precursor **14**.[7]



Many conditions were explored to realize this IMDA reaction. While none of the desired product **15** (or its C_1 epimer) could be detected, the results were quite interesting and point to potential complications which can undermine the desired process if the stereochemical factors are not properly arranged.

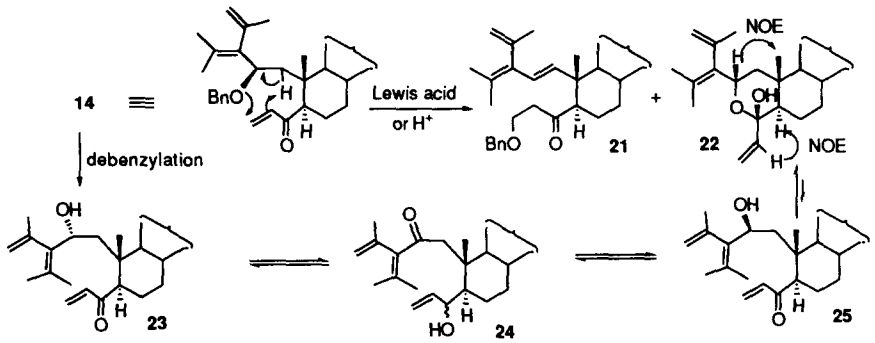
When compound **14** was heated in toluene at 195° or 230° (sealed tube), three major products, shown to be **17, 19** and **20**[7] were obtained in the indicated yields.



It seems likely that **17** is formed from **14** through a thermally induced 1,4-elimination of benzyl alcohol (see proposed intermediate **16**) followed by a type I IMDA reaction. The stereochemistry of **17** was proven by NOE

experiments as shown. The dihydropyran **19** is presumably derived from **14** by a competing retro-ene reaction leading to **18** followed by a hetero IMDA reaction.[8] The formation of a Z double bond (C_{11}-C_{12}) in **18** sets up a particularly favorable arrangement for the hetero IMDA reaction which produces **19**. The precise origin of **20** is not clear. It could arise from **19**, or by a direct cyclization with hydrogen transfer (path b).

We also examined the consequences of Lewis acid catalysis. Again fascinating alternatives to the type II IMDA reaction were encountered. Treatment of **14** in toluene with $BF_3{\cdot}OEt_2$ at -40-0° for 39h gave **21** (44%) and **22**[7](17%). It seems likely that **21** was formed through an intramolecular pathway (see **14** —›**21** arrows).[9] Hemiketal **22** is believed to arise from debenzylated intermediate **23** through reversible 1,5-hydride migration (see proposed intermediates **24** and **25**). Similarly, reaction of **14** with TFA in CH_2Cl_2 and with $Zn(OTf)_2$ in ether gave **22** in 35-40% yield. Interestingly, 5M-lithium perchlorate seems to promote 1,4-elimination in that **17** was isolated in 10% yield.[10]



In summary, it is clear that the two trans disposed side chains of **14** are quite interactive under thermal or Lewis acid catalyzed conditions. However none of the most obvious, *a priori* cycloaddition product (i.e., **15**), could be detected. In the next Letter, we discuss the dependency of this seemingly obvious IMDA reaction on the configuration at C_{10}.

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References and Notes

1) Shea, K. J.; Davis, P. D. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 419; *Angew. Chem., Suppl.* **1983**, 564.

2) Two general recent reviews about taxol, see: Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15; Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemporary Organic Synthesis*, **1994**, *1*, 47. For total syntheses of taxol, see references in the following Letter.

3) Bonnert, R. V.; Jenkins, P. R. *J. Chem. Soc. Perkin Trans 1.* **1989**, 413 and references therein.

4) Jackson, R. W.; Shea, K. J. *Tetrahedron Lett.* **1994**, *35*, 1317 and references therein.

5) Alaimo, C. A.; Coburn, C. A.; Danishefsky, S. J. *Tetrahedron Lett.* **1994**, *35*, 6603.

6) For the development of this degradative route, see: Masters, J. J.; Jung, D. K.; Danishefsky, S. J.; Snyder, L. B.; Park, T. K.; Isaacs, R. C. A.; Alaimo, C. A.; Young, Y. B. *Angew. Chem. Int. Ed. Engl.* in press.

7) Spectral data for **14**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.35-7.26 (5H, m), 6.43 (1H, dd, J = 17.4, 10.3 Hz), 5.99 (1H, dd, J = 17.4, 1.8 Hz), 5.26 (1H, dd, J = 10.3, 1.8 Hz), 4.98 (1H, s), 4.55 (1H, d, J = 11.3 Hz), 5.52 (1H, s), 4.42 (1H, br), 4.21 (1H, d, J = 11.3 Hz), 3.32 (1H, dd, J = 12.7, 3.3 Hz), 1.83 (3H, s), 1.79 (3H, s), 1.71 (3H, s), 0.96 (3H, s), 0.91-0.86 (9H, m, 3-doublet methyls), 2.17-0.70 (26H, m); IR (neat) 1688, 1466, 1453, 1449, 1398, 1383 cm^{-1}; LRMS (CI, CH_4) 601 $[M+1]^+$, 493 $[M-BnO]^+$: Other important spectral data (steroidal peaks are omitted), for **17**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.99 (1H, m), 4.56 (1H, m), 1.71 (3H, s, allylic), 1.62 (3H, s, allylic); IR(neat) 1713, 1444, 1379, 894, 757 cm^{-1}; LRMS (CI, CH_4) 493 $[M+1]^+$, for **19**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.22 (1H, dd, J = 9.0, 8.8 Hz), 4.41 (1H, dd, J = 3.3, 3.2 Hz), 1.36 (3H, s, tertiary methyl), 1.06 and 1.02 (6H, two doublets, two isopropyl methyls, J = 6.8 Hz); IR(neat) 1682 (cyclic enol ether), 1462, 1381, 1248, 1095, cm^{-1}; LRMS (CI, CH_4) , 495 $[M+1]^+$, for **20**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.36 (1H, t, J = 8.9 Hz), 4.79 (1H, m), 1.88 (3H, s, allylic methyl), for **21**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.33-7.23 (5H, m), 6.16 (1H, d, J = 16.0 Hz), 5.39 (1H, d, J = 16.0 Hz), 5.11(1H, s), 4.46-4.39 (2H, ABq, J = 12.0 Hz), 3.69-3.63 (1H, m), 3.55-3.50 (1H, m), 2.61-2.52 (3H, m), 1.77, 1.72, 1.71 (three allylic methyls); IR(neat) 1705, 1467, 1453, 1100 cm^{-1}; LRMS(CI, NH_3) 601 [M+1], for **22**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.59 (1H, dd, J = 16.8, 11.2 Hz), 5.50 (1H, dd, J = 16.8, 2.4 Hz), 5.02-4.99 (2H, m), 4.70 (1H, dd, J = 7.2, 6.8 Hz), 4.58 (1H, m), 1.88, 1.72, 1.70 (three allylic methyls); IR(neat) 3425(br), 1467, 1444, 1374, 1074 cm^{-1}; LRMS (CI, NH_3) 493$[(M-H_2O)+1]^+$

8) Benzaldehyde, a key retro-ene byproduct, was detected by mass spectral analysis from the crude reaction mixture.

9) If the process involved addition of eliminated benzyl alcohol, one would have expected crossover products (i.e., **14**+BnOH, **14**-BnOH, **22**+BnOH) to be generated. None were detected.

10) Other Lewis acids surveyed were $Zn(OAc)_2$, $Yb(OTf)_3$, $SnCl_4$, $EtAlCl_2$ and $ZnCl_2$. Compound **15** was not detected under any of these conditions.

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