

0040-4039(95)00021-6

The First Successful Intramolecular Diels-Alder Reaction Leading to a Baccatin III Construct Bearing Oxygen Functionality at C10

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Abstract: Application of the IMDA reaction creates a steroidal-C1-deoxybaccatin III hybrid.

In the previous Letter¹ we described a variety of unsuccessful attempts to synthesize² baccatin III constructs by type II intramolecular Diels-Alder (IMDA) reaction^{3,4} of substrate 1. The reactions which were encountered indicated considerable interactive chemistry between the trans-disposed side chains. However, adduct 2 was never obtained.

In studying structure 2 ($C_{10}R$) we note that as the interaction of the C_{17} - C_{19} methyl groups is relieved, the severity of the C_{10} benzyloxy- C_{18} methyl abutment increases. This interaction is also likely to be manifested in the transition state involved in such a cycloaddition (see structure 1). Examination of models further reveals that in the C_{10} S series the interaction is relieved and the environment of the benzyloxy group is generally less crowded. Accordingly, we undertook to evaluate compound 3 as a possible candidate for IMDA reaction.

As described in the previous Letter, compound 5 was the minor product in the addition of a 1,1,3 trimethylbutadienylcerium reagent, to the appropriate aldehyde (see dotted disconnection line). Since our purpose was to test the viability of the IMDA reaction, we continued with compound 5. It was converted to 3 through intermediates 6 and 7, as shown.



key: a) excess NaH, excess BnBr, 18-C-6, THF, reflux, overnight, 70%, b) excess TBAF, reflux, overnight, 90%, c) Dess-Martin reagent, CH₂Cl₂, rt,1h, 90%

We first surveyed the possibility of a Lewis Acid catalyzed induced IMDA³ (cf. 3) reaction with BF3 etherate as the catalyst. Compounds 9 and 10, encountered from earlier attempts with compound 1^1 , were isolated in 63% and 32% yield, respectively. Since compound 9 is obtained from both 1 and 3, a pathway involving reversible internal oxidation-reduction of a debenzylated intermediate 8, culminating in the most stable hemiketal, is strongly suggested.



We studied the possibility of thermally induced reactions. When compound 3 was heated in toluene at 197° the desired compound 4^5 was in fact obtained in 14% yield along with 12 (41%). The latter had also been encountered from thermolysis of 1. Higher temperatures tend to favor the formation of 12 (undoubtedly via the previously postulated product 11). Lower temperatures favor the formation of 4. Thus, when compound 3 was heated at 210° - 220° for 14h, the principal product was 12 (53% yield). When thermolysis was conducted at 180° for 66h, compound 12 was not detected; rather 4 was obtained in 62% yield (83% conversion).

Clearly, in the thermolysis of 3 (unlike 1) there are two competing pathways. Direct cycloaddition which leads to 4 must compete with 1,4-elimination leading to 12 via 11. The temperature-rate profile of these two competing reactions can be exploited to obtain the IMDA product 4, in reasonable yield. To our knowledge, this represents the first case where the implements for baccatin III functionality across the C9-C10 ethano bridge have been included in an IMDA route which leads to the natural (C1 β) stereochemistry.



Of course, this chemistry left unaddressed the matter of incorporation or introduction of the C₁ hydroxyl group, characteristic of baccatin III itself. Toward this end, we investigated the possibility of enolization of compound 4 at C₁. We noted at the outset, the improbability of success in such an undertaking. In a 1-desoxybaccatin III substrate, *the only way to achieve substantial overlap between the emerging carbanion and the proximal carbonyl at C₂, is to aggravate, in a most serious way, the C₁₇-C₁₉ interaction. Enolization at C₁ in a conformer where the C₁₇-C₁₉ interaction is alleviated, requires the formation of a C₁-C₂ "orthogonal enolate."*

Nonetheless, the enolization of compound 4 was attempted with several bases. The use of lithium tetramethylpiperidide in THF followed by addition of excess Davis reagent⁶ led to a complex mixture of products. We then turned to the use of potassium t-butoxide in THF-DMSO in the presence of oxygen.⁷ Surprisingly, this reaction was quite clean. However, none of the desired hydroxylation product 13 could be obtained. *Rather, the novel diene 14 was obtained in 63% yield.*⁸

The formation of diene 14 was also encountered, from a less surprising pathway. Thus, debenzylation of 4 yielded 15 whose structure was verified crystallographically. Attempted acylation of 15 with pbromobenzoyl chloride in the presence of DMAP afforded, not the expected 16, but diene 14. Of course, the formation of this compound in a base induced 1,4 elimination of *benzyloxide* was wholly unanticipated. In retrospect, we note a stereoelectronically optimal syn alignment of the C13 β proton and the C10 β benzyloxy leaving group with the C11-C12 π system. This effect is possibly critical in favoring the vinylogus elimination. Unfortunately, since we were not successful in synthesizing 2, it was not possible to test whether this syn relationship was mandatory in driving this most surprising 1,4 elimination.



In summary, a route has been charted by which the intramolecular Diels-Alder reaction can produce a baccatin III-like construct which is oxygenated at C_{10} . In principle, this capability could be used to create the substitution pattern at C_{10} and C_9 found in the natural product itself. Left unaccomplished is the issue of incorporation of hydroxyl at C_1 . From *a priori* analysis of the problem, as well as from preliminary results, we expect that such a hydroxylation from a C_1 desoxy- C_2 ketone bearing the natural stereochemistry at C_1 would be very difficult. Accordingly, additional functionality must be incorporated in the dienophile moiety to allow for eventual exposure of a C_1 hydroxyl group by this route. Another problem which would have to be solved would be that of reaching the C_{10} S oxygen functionality in suitable IMDA precursors in an efficient fashion. Approaches toward both of these goals are under careful consideration.

Acknowledgments. This work was supported by NIH Grant number: AI16943. We thank Dr. George Sukenick for his assistance in NOE experiments.

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References and Notes

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(Received in USA 28 October 1994; revised 19 December 1994; accepted 22 December 1994)