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Studies in the Synthesis of a Baccatin III-Steroid Hybrid: A Remarkably Rapid Intramolecular Diels Alder Reaction

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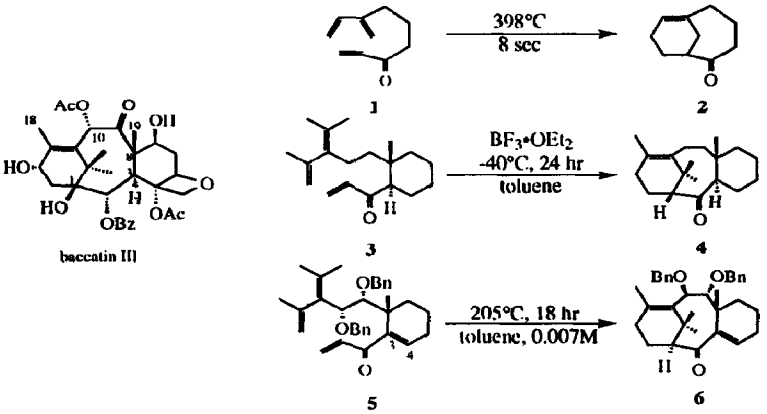
Abstract: A face selective intramolecular Diels-Alder reaction generates a 1-*epi*-baccatin III-steroid hybrid.

We have been investigating the possibility of exploiting an Intramolecular Diels Alder (IMDA)[1] reaction to generate constructs corresponding to the AB ring system of baccatin III[2,3,4] which might probe structure-activity relationships. In the research described here, we attempted to fashion a steroid-baccatin III hybrid.

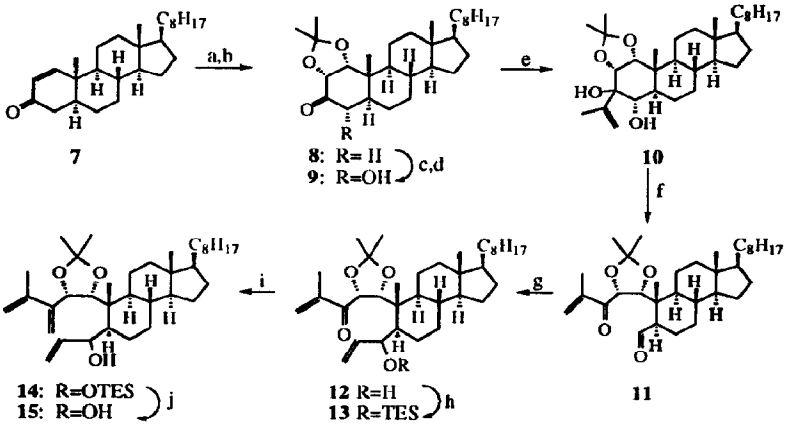
The possibility of an IMDA paradigm to address this problem had occurred to others. Shea and colleagues established the gross feasibility of generating the bridgehead olefin by such a cycloaddition (see **1**—>**2**).[5,6] Subsequently, Jenkins and collaborators dealt with the crucial issue of face orientation governing the eventual relationship between the emerging C_1 with that of C_8, and where appropriate, C_3 (baccatin III numbering).[7] Following NMR analysis, it was concluded that the IMDA reaction of **3** afforded **4** bearing the *cis* backbone relationship between C_1 and C_8.

A recent disclosure by Shea involving substrate **5** with potential functionality which begins to approach that required for a baccatin III synthesis afforded **6** bearing the 1-*epi*-baccatin III stereochemistry.[8] In attempting to reconcile Shea's finding in the context of Jenkins' report, one notes the presence of the 3,4 double bond in **5**, in contrast to the *trans*-disposed C_8-C_3 tethering arrangement in **3**. While the presence or absence of the 3,4 double bond may indeed be a factor, our work, described below, suggests that it is not the sole determinant and that subtle structural variations profoundly influence the result.



Scheme 1

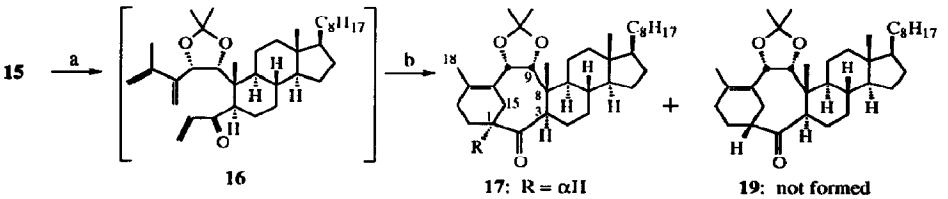
To build our steroidal construct, we started with Δ^2-cholestenone (**7**).[9] This was converted to the acetonide **8** and thence, to the hydroxylated ketone **9** as shown. Addition of isopropenylmagnesium bromide produced **10** which suffered cleavage with lead tetraacetate to afford enone aldehyde **11**. The latter was converted to **13**.[10] A variety of attempts to effect isopropylidenation of the keto group for purposes of reaching a fully alkylated diene (bearing three methyl groups) were unsuccessful.[11] As a temporary expedient to probe the general feasibility issue, we settled for methylenation (*via* Peterson olefination).[12] Cleavage of the silyl group in **14**, afforded **15**.



Scheme 2

a) *cat.* OsO_4, 3 *eq.* NMO, 1-3eq DABCO THF/H_2O, rt, 72%. b) *p*TsOH, acetone, molecular sieves, 82%. c) TBSOTf, Et_3N, Et_2O, rt, 99%. d) *i.* dimethyldioxirane, acetone -78°C-->rt. *ii.* amberlyst-15®, rt, 81%. e) isopropenyl grignard, THF, 0°C. f) $Pb(OAc)_4$, benzene, 65%. g) CH_2=CHMgBr, -78°C, 96 hrs. h) TESOTf, 2,6-lutidine, CH_2Cl_2, 72%. i) *i.* $TMSCH_2Li$, THF, 0°C-->rt. *ii.* KH, THF, 0°C, 66%. j) TBAF, THF, rt, 100%.

Compound **15** was subjected to the action of chromic acid in pyridine[13] with a view toward reaching our IMDA substrate **16** (Scheme 3). In the event, this reaction did indeed generate **16**. However, even under the conditions of formation, isolation and purification, **16** was undergoing IMDA reaction at *room temperature* to give adduct **17**. Cycloaddition is complete after 24 hours at room temperature, or more conveniently, in toluene at 90°C after 2 hours.



Scheme 3

a) CrO_3-pyr, CH_2Cl_2, rt, 84%. b) rt, 12-24 hrs or 90°C, 2 hrs, toluene, 90%.

The infrared, mass and NMR spectral properties of this product readily confirmed its gross structure. The occurrence of this reaction under the unprecedented mild conditions may be attributed to the entropy-constraining acetonide group and the absence of the geminal methyl group on the diene.

The issue of the backbone stereochemical relationship between C_1 and the *trans*-disposed C_8-C_3 junction was addressed with a series of NMR experiments, specifically, ^1H, ^{13}C, HMBC, HETCOR, COSY, DEPT 90, DEPT 135 and NOESY. All relevant signals in the AB region were assignable. Particularly crucial in this regard were H_1 and H_3. A NOESY spectrum showed an enhancement between H_1 and H_3 (as well as the reverse) of 4 percent. This clearly defines the configuration of C_1 relative to C_3 as *cis* and consequently the C_1-C_8 (angular methyl) substituents are *anti* as shown in **17**. Further corroboration was achieved first by distinguishing the facial identity of the two acetonide methyl groups. Proton 9, shows nuclear Overhauser enhancements to one of the acetonide methyls as well as to the angular methyl indicating that all three groups lie on the same side of the molecule. The lower face acetonide methyl (relative to the angular methyl) showed a nuclear Overhauser enhancement (from cross peaks in the NOESY spectrum) to H_3 and to one of the C_{15} protons. In addition, H_3 showed a correlation to this same C_{15} proton. The enhancement between H_1 and H_3 would not be possible in any of the available conformers bearing the C_1-C_3 *anti* relationship (see **19**).

A chemical argument in favor of the assignment of **17** is the fact that the C_1 proton is exchanged when **17** is exposed to $NaOCD_3$ in CD_3OD at 90°C giving **18**.[14,15] Examination of Dreiding models shows the C_1 proton in **17** to be parallel with respect to the carbonyl π system at C_2. The realization of similar overlap between the proton at C_1 and the carbonyl π orbitals in **19** would carry with it a prohibitive abutment between the C_8 angular methyl and the bridging C_{15} methylene carbon. Based on these models it seems most unlikely that deuterium exchange at C_1 in **19** would occur.[16]

Thus, the 1-*epi*-baccatin stereochemistry (see **17**) has been produced from an IMDA reaction even in a substrate lacking the C_3-C_4 double bond of the Shea case. This suggests that subtle structural details can influence the outcome. In the case at hand, the alternative baccatin III analog, **19**, would encounter a particularly serious contact between the vinylic methyl (C_{18}) and the α disposed isopropylidene blocking group. In **17**, no such interaction is present.[17] Studies on the factors which control the outcome in such IMDA reactions are continuing.

Acknowledgments

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10. Addition of vinylmagnesium bromide must be done under very controlled conditions. Portion-wise addition of the Grignard reagent over several days while maintaining a temperature of -78°C until starting material is consumed is necessary to prevent significant formation of a byproduct (resulting from an intramolecular Meerwein-Ponndorf-Verley type reaction producing a vinyl enone dienophile bearing an isopropenylcarbinol which could not be converted to the diene component).

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15. Thus far the only reaction which has been achieved at C_1 is deuterium exchange. Several attempts at oxygenation were unsuccessful.

16. We note that at this writing no one has demonstrated enolization or exchange at C_1 in a substrate which contains the angular methyl (C_{19}).

17. This interaction was not present in the Jenkins example **3-->4**.

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