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SYNTHESIS OF THE TAXANE DITERPENES:

CONSTRUCTION OF A BC RING INTERMEDIATE FOR TAXANE SYNTHESIS

Charles S. Swindell* and S. Jane deSolms[1]
Department of Chemistry
Bryn Mawr College
Bryn Mawr, PA 19010
USA

Abstract: A general and practical route to a crucial BC ring intermediate for the preparation of simple taxanes is described.

The taxane diterpenes[2] have attracted the attention of synthetic chemists[3] partly because of the anti-leukemic and tumor-inhibitory properties of certain members[4] of this group and partly because of the structural and stereochemical challenges posed by these substances for preparative efforts. The latter point may be appreciated upon inspection of the structure of taxol,[4a] 1. We envision the taxane skeleton 2 to be an appropriate preliminary synthetic goal whose construction will allow us to address the formation of the carbon framework, including the incorporation of the bridgehead olefin,[5] and some of the fundamental stereochemical questions.

Our synthetic approach to the taxanes is founded on the notion that a four-carbon A ring progenitor can be annelated onto a suitably functionalized BC ring intermediate. One specific example of such a sequence which depends on the preferred conformation of BC ring enolate 3a is depicted in scheme 1. Molecular mechanics calculations (MM2)[6] on model diene 3b and enolate 3a suggest 3 to possess least energy conformation A, a circumstance which exposes the desired α face of the enolate to an external electrophile. Alternative conformation B appears to be of much higher energy while C, which exposes its β face, apparently is not a minimum on the potential surface since a trial structure approximating this conformation does not successfully refine to a realistic structure. Here we briefly describe our work toward a practical synthesis of enone 4a, a crucial intermediate for simple taxane synthesis *via* the above strategy.

In the preceding Letter[7] we described our investigation of intramolecular [2+2] photoaddition chemistry which made substances 5a,b available. Selective bond scission performed on 5a,b would clearly provide access to the carbon connectivity of 4a. Scheme 2 portrays our initial attempt to effect these transformations. Enone 6a,[8] prepared from photoproduct 5a, could be converted to a single epoxyketone 7a whose stereochemistry is determined at least in part by the obvious influence of the angular substituent. We expected this substance to suffer dissolving metal reduction in the presence of a proton source to provide first intermediate *D*. Protonation of enolate D to set up the cis 6/4 ring fusion and subsequent carbonyl reduction would lead to diol 8a possessing an equatorial secondary hydroxyl. In the event, 7a did indeed yield diol 8a but in low yield.[10] Diol 8a is perfectly constructed for 1,3-elimination. Attempted formation of the secondary mesylate (8b) of 8a led directly to enone 4b.

While the yield of the 7a to 8a transformation was clearly unacceptable, it appeared possible to enhance the efficiency of this step by concurrently carrying out the obligatory reduc-

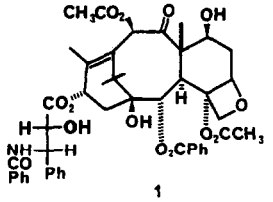
tive deamination. This reasoning led us to construct isonitrile 7c with the hope that its dissolving metal reduction would rapidly remove nitrogen[11] from the system while transforming the epoxyketone moiety as well (scheme 3). Since enone 6b was not available from 5b,[7] an efficient one flask conversion of 6a to 6b was developed. Like 6a, 6b suffered stereospecific epoxidation to deliver 7b which in turn was readily dehydrated to provide isonitrile 7c. Reduction of 7c under the specified conditions led to diol 8c but again in only moderate yield.[10] In contrast to diol 8a, diol 8c led to isolatable mesylate 8d which only slowly fragmented to enone 4a. Clearly the fragmentation is at least partially driven by the relief of steric compression involving the four substituents on the β face of the cyclobutane, a situation less severe in 8d.

The modest success of the above two sequences encouraged us to look at a third route (scheme 4) which proved more attractive for the preparation of quantities of 4a. Photoproduct 5b could be converted to epimeric alcohols 5c and 5d, or to either one alone. Mesylate 5e, available from 5c, could be transformed into unstable trans olefinic bridgehead imine 9 upon deformylation/fragmentation with one equivalent of methyl lithium. A more useful sequence originated with 5d which could be converted to 5f and then to stable cis olefinic bridgehead imine 10. Similar chemistry carried out on 5a led to acetyl mesylates 5g and 5h which proved reluctant to undergo acetyl cleavage with methyl lithium: attack occurred at the mesylate sulfur instead, returning 5i and 5j.

Imine 10 could be converted to cis enone 4c whose ring fusion stereochemistry was indicated through comparison with 4b and by its equilibration with the latter (trans/cis=2) upon exposure to hot methanolic hydroxide. The cis ring fusion stereochemistry, which must be the thermodynamic preference of the bridgehead imine, is evidently introduced prior to hydrolysis in the acidic medium and is maintained by the slow enolization of the ketone carbonyl under such conditions. Enone 4d was available through similar chemistry. Conversion of 4d to ketal 4e and then to isonitrile 4f was necessary for reductive deamination to 4g. Finally, ketal removal followed by epimerization led to 4a.

In summary, the conversion of 5b to 4a <u>via</u> scheme 4 proceeds in nine steps through which crude product mixtures can be carried to 4d and then to 4a, chromatographic purification being required at these two points only. Although the overall yield stands at 13%, this can no doubt be improved, especially with improvement of the fragmentation step. Alternative nitrogen substituents capable of triggering the fragmentation under other conditions currently receive our attention. Finally, we expect the preparation of 4a to model in part a flexible route to more complicated BC ring intermediates along the way to structurally complex taxanes.

<u>Acknowledgement</u> is made to the Research Corporation (Schering-Plough Corporation Grant) for support of this research. Purchase of a preparative liquid chromatograph was made possible by a grant from the National Science Foundation.



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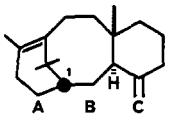

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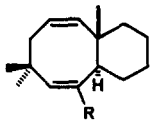
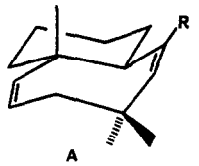


3

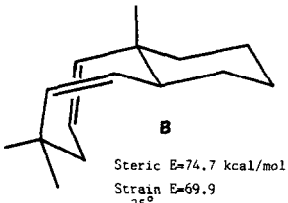
a R=O⁻
b R=H



A

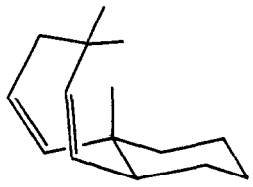
a Steric E=42.1 kcal/mol
Strain E=16.7
$H_f^{25°}$=-9.5

b Steric E=33.4 kcal/mol
Strain E=28.6
$H_f^{25°}$=-0.6



B

Steric E=74.7 kcal/mol
Strain E=69.9
$H_f^{25°}$=40.6



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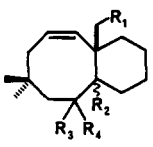
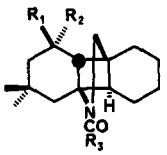
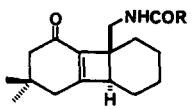


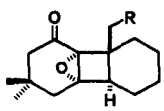
4 a R_1=H, R_2=αH, R_3,R_4=O
b R_1=NHCOCH$_3$, R_2=αH, R_3,R_4=O
c R_1=NHCOCH$_3$, R_2=βH, R_3,R_4=O
d R_1=NHCHO, R_2=βH, R_3,R_4=O
e R_1=NHCHO, R_2=βH, R_3,R_4=O(CH$_2$)$_2$O
f R_1=NC, R_2=βH, R_3,R_4=O(CH$_2$)$_2$O
g R_1=H, R_2=βH, R_3,R_4=O(CH$_2$)$_2$O



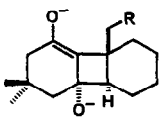
5 a R_1,R_2=O, R_3=CH$_3$
b R_1,R_2=O, R_3=H
c R_1=OH, R_2,R_3=H
d R_1=H, R_2=OH, R_3=H
e R_1=OMs, R_2,R_3=H
f R_1=H, R_2=OMs, R_3=H
g R_1=OMs, R_2=H, R_3=CH$_3$
h R_1=H, R_2=OMs, R_3=CH$_3$
i R_1=OH, R_2=H, R_3=CH$_3$
j R_1=H, R_2=OH, R_3=CH$_3$



6 a R=CH$_3$
b R=H



7 a R=NHCOCH$_3$
b R=NHCHO
c R=NC



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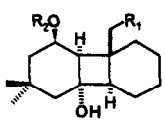
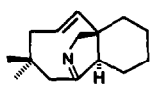


8 a R_1=NHCOCH$_3$, R_2=H
b R_1=NHCOCH$_3$, R_2=Ms
c R_1,R_2=H
d R_1=H, R_2=Ms



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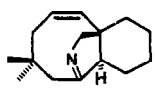
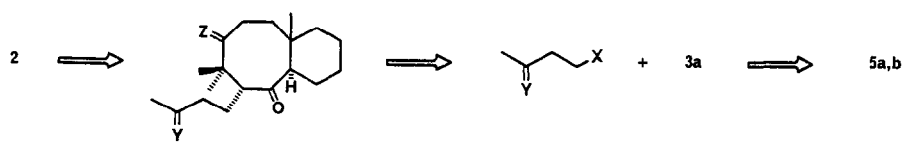
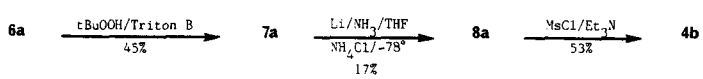


10

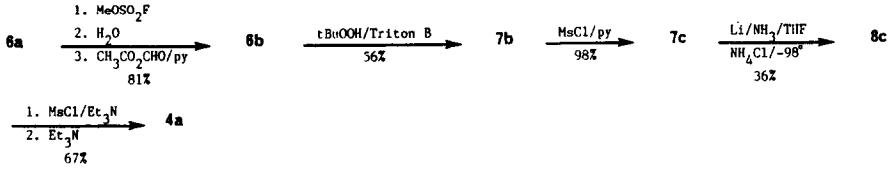
Scheme 1



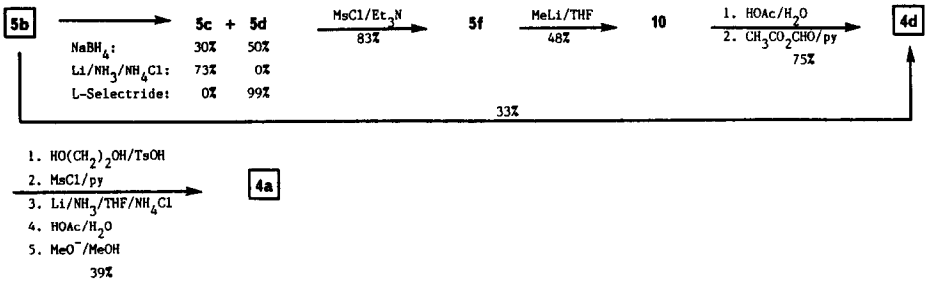
Scheme 2



Scheme 3



Scheme 4



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