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Probing the formation and chemistry of enoxyoxirane derivatives in the C-ring en route to guanacastepene

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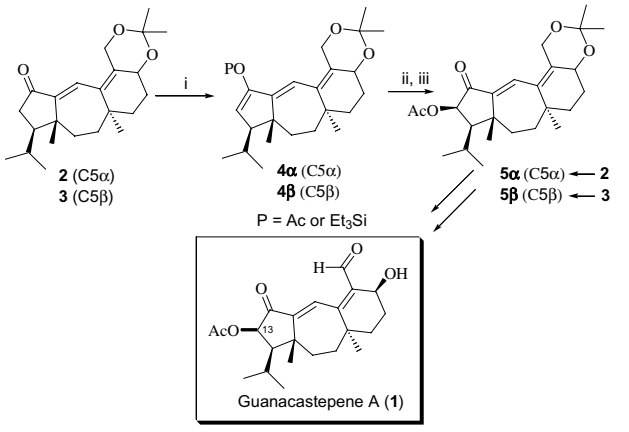
Abstract—Enol acetate and silyl enol ether, derivatives of **2** and **3** undergo stereoselective epoxidation from the β-face of the C13–C14 olefin. The progression of these compounds to the C13 acetoxy C14 ketones is described.

Recently, we described the total synthesis of guanacastepene (**1**).[1] We perceived that attempts to integrate the C13-acetoxyl function into an early stage intermediate would likely add further uncertainties to an already multilayered problem. Accordingly, introduction of the acetoxy group would be postponed till the other structural elements had been secured.

As the synthesis developed, acetoxylation en route to guanacastepene was undertaken at the stage of intermediate **3**. The sequence followed, was **3** → **5**β and thence **5**β → **1** as previously described. At an earlier stage of the progression, we reached intermediate, **2**, which is epimeric with **3** at C5. This series was also used as a model system to address the issue of C13-acetoxylation. The information garnered from our studies in the model series, wherein **2** is converted to **5**α, proved to be transmittable for the overall transformation from **3** → **5**β, and thence to target **1**. With the C4–C5 region soundly protected, we could operate at C13 via enolization of the C14 ketone. Oxidation of the appropriate enol derivatives (see systems **4**α or **4**β derived from remote C5 epimers **2** and **3**, respectively, P = protecting group) would give rise to generalized structures **5**α or **5**β. In these studies, we focused on silyl enol ethers (P in **4** = $SiEt_3$) or enol acetates (P in **4** = Ac) as the enol derivatives. In this disclosure, we describe the results of an assessment of the epoxidation of these derivatives, and the progression of these epoxides to reach C13 hydroxy or acetoxy systems (Scheme 1).



Scheme 1. Reagents and conditions: (i) Et_3SiOTf, Et_3N, CH_2Cl_2, 79% (when P = $SiEt_3$); (ii) DMDO/acetone, CH_2Cl_2, −78 °C, then Me_2S, 80%; (iii) Ac_2O, DMAP, py, CH_2Cl_2, rt, 80%.

In the enol acetate series (**4**α or β, P = Ac) there were precedents, which suggested that either of the stereoisomeric epoxides at C13–C14 could be converted to the desired **13**β compound. Thus, pathways for the conversion of such epoxides to acetoxy ketones, which involve overall retention or overall inversion are known (cf. **6** → **7** or **8**, respectively)[2] (Scheme 2).

As was previously described, epoxidation of the enol acetate **9** in the **5**α series, with 2,2-dimethyldioxirane (DMDO) results in the formation of major and minor epoxides in a variable ratio ~7–15:1. Because we were expecting α-face epoxidation, we were surprised to find that the major product, when subjected to solvolytic

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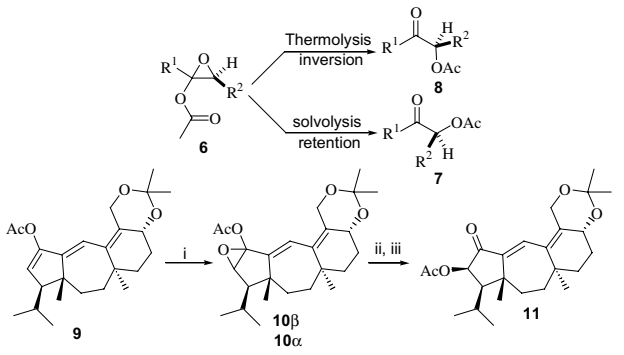


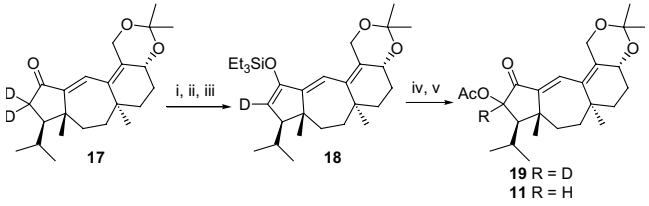
Scheme 2. Reagents and conditions: (i) DMDO/acetone, CH_2Cl_2, −50 °C, then Me_2S; (ii) 10 mol% *p*-TsOH, $MeNO_2$, rt; (iii) Ac_2O, DMAP, py, CH_2Cl_2, rt, 80%.

conditions, followed by acetylation led to the 13β-acetoxyl product. The results, via a thermolytic pathway were more complex. Upon thermolysis both 13-acetoxy and 13-hydroxy products were generated. Following acetylation an ca. 1:1 mixture of 13α and 13β acetoxy stereoisomers was obtained and separated in to homogeneous components. We shall return to this reaction (vide infra). On the basis of the solvolysis result with the epoxyacetate, it was surmised that the major product from epoxidation of **9** is the 13β, 14β-oxirane (cf. **10**β), which was then converted to **11**.

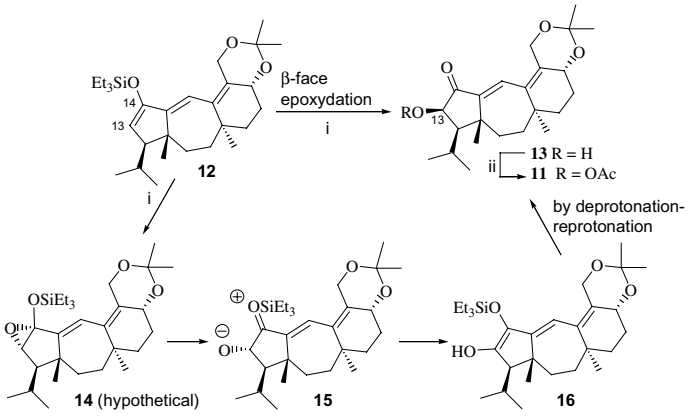
We then turned to epoxidation of silyl enol ether **12**. If the stereochemistry of the major epoxidation course of **12** is as supposed above, a Rubottom type rearrangement[3b] could constitute a more straightforward way to generate the required β stereochemistry at C13 than the technology, using the C13–C14 enol acetate discussed above. In the event, epoxidation of **12** with dimethyldioxirane under Rubottom conditions[3] did produce a vicinal hydroxyketone **13**. Following acetylation, the previously encountered **11** was indeed obtained as the major product.

The stereochemistry of the intermediate epoxidation product derived from **12** had been inferred to be β from its conversion, via **13**, to the acetoxyketone **11** of defined stereochemistry. It is well to underscore that the confidence in the correctness of the assignment of this course for the epoxidation rests squarely on the confidence level that the mechanism by which the oxirane progresses to the defined **11** is properly understood. In this connection, we noted a recent proposal of Magnus and Ollivier,[4] which elegantly pointed out the possibility that a hypothetical α-epoxide (cf. **14**) could also plausibly rearrange to the C13β-hydroxyketone **13** (by inversion at C13). Applied to the case at hand, the Magnus proposal suggests that an α-epoxide **14** could produce **13** and ultimately **11**, invoking a deprotonation–reprotonation at C13 to accomplish the inversion (Scheme 3).

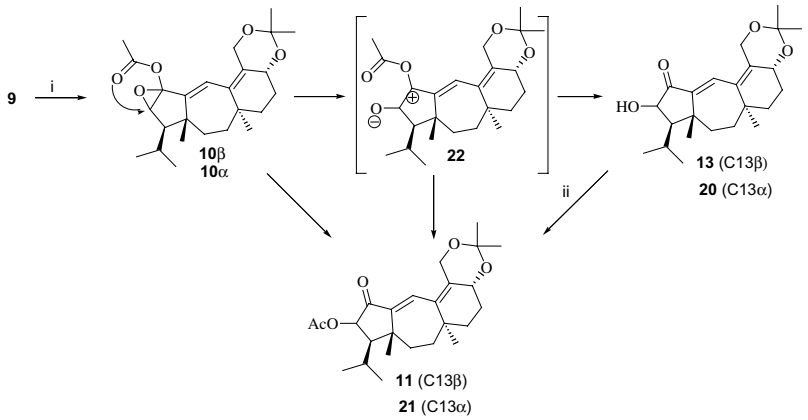
To evaluate the applicability of the Magnus mechanism to the case at hand, we prepared the substantially C13-dideuterated ketone **17** and thence the deuterated silyl enol ether **18** (C13D:C13H = 85:15). When compound **18** was subjected to the epoxidation (DMDO), Rubottom rearrangement, acetylation sequence, the deuterated acetoxyketone **19** and nondeuterated **11** were again obtained in an 85:15 ratio.[5] This result demonstrates that there is no significant deprotonation at C13 in the rearrangement of the intermediate Rubottom epoxide derived from **18**. Accordingly, the findings render the inversion pathway highly improbable, and support the proposal that epoxidation of **12** (or **18**) has instead taken place from the β-face, as independently demonstrated in the corresponding enol acetate series (cf. **9**). Moreover, the lack of deuterium exchange at C13 serves to build confidence that the desilylation–acetylation sequence following Rubottom rearrangement, does not alter the stereochemistry at C13 (Scheme 4).



Scheme 4. Reagents and conditions: (i) Et_3N, CD_3OD, rt, 20 h, 90%; (ii) DBU, CD_3OD, rt, 4 h, 95%; (iii) Et_3SiOTf, Et_3N, CH_2Cl_2, 79%; (iv) DMDO/acetone, CH_2Cl_2, −78 °C, then Me_2S; (v) Ac_2O, pyridine, DMAP, CH_2Cl_2, ca. 60%.



Scheme 3. Reagents and conditions: (i) DMDO/acetone, CH_2Cl_2, −78 °C, then Me_2S 80%; (ii) Ac_2O, DMAP, py, CH_2Cl_2, rt, 80%.



Scheme 5. Reagents and conditions: (i) DMDO/acetone, CH_2Cl_2, −50 °C, then Me_2S 80%; (ii) Ac_2O, DMAP, py, CH_2Cl_2, rt, 80%.

Confidant of our assignments, we returned to the thermolysis reaction of **10** arising from epoxidation of the enol acetate **9**. As noted above, although there were small amounts of α-epoxide present (10%), the complexity of the product mixture could not be explained by the nonhomogeneity of the starting material. Following thermolysis (150 °C for 18 min) we could identify acetoxyketone **11**, its C13 epimer **21** and a C13 hydroxyketone component. Acetylation of the C13 hydroxy compound and combination of this product with the acetoxyketones afforded overall a 1:1 mixture of **11** and **21**. As the matter was studied in finer detail, it was found that the original mixture of acetoxyketones was ca. 2:1 in favor of a product **21**. By contrast, the hydroxyketone component massively favored the C13 product **13** over the C13 product **20** by a ratio of (ca. 40:1) (Scheme 5).

These results tend to explain the course of the thermolysis reaction. Ordinarily there should have been produced by inversion from the predominant β epoxide **10**β, the α-acetoxyketone **21**. This expectation presupposes heterolysis of the C13-epoxide bond with concurrent acetoxy migration, resulting in net inversion. We propose that in the case of major epoxide **10** in the α-series there could well be a competing heterolysis of the C14-oxido bond by virtue of its allylic relationship to the 1,2-double bond. This heterolysis (cf. **22**) can be accompanied by acetyl transfer leading to **11** or de-acylation, occasioned by an adventitious nucleophile to produce **13** which, on acetylation, leads to **11**.

In summary, the unique characteristics of **10**β bring about competitive heterolysis at C13 (leading to **21**) and C14. Further bifurcation of the C14 heterolyzed intermediate as discussed, leads to **11** and **13**. These complexities are avoided in both the Rubottom reaction and in the solvolytic transformation of **10** which, following acetylation, led to the expected C13 retention (β) product. With all of the structures now well established, it is particularly timely to study the origin of the β-selectivity in the epoxidation reactions of **9** and **12**.

Acknowledgements

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5. This confidence arises from the assumption that deprotonation would inevitably result in exchange with bulk H_2O (accompanying the dioxirane), which is the only available base. Furthermore, the fact that the 85:15 ratio of **18**:**12** is not perturbed, suggests an absence of competitive deprotonation, since the deuterium isotope effect would have dictated differences in relative rates of competing mechanism.