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Rearrangement of Epoxides in Non-aldol Aldol Process: Allylic vs. Tertiary and Secondary Carbocationic Centers

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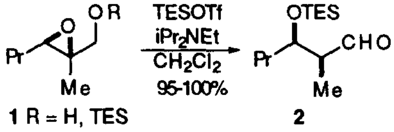
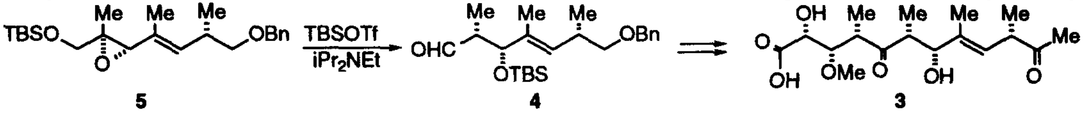
Abstract: It has been shown that allylic carbocations are formed in preference to tertiary or secondary carbocations in the rearrangement of substituted epoxides. However protection of the alkene as a bromo ether allows for the desired rearrangement and production of intermediates for the synthesis of the cytotoxic tedanolides.

Several years ago we reported a new method for the enantiospecific synthesis of simple aldol products - 3-alkoxy-2-methylalkanals - in high yield.[2,3,4] The key step involved an intramolecular transfer of hydride from the methylene group of either an epoxy alcohol (prepared with high enantiospecificity by a Sharpless asymmetric epoxidation reaction)[5] or its silyl ether **1** which opened the epoxide regiospecifically with inversion of configuration to generate the desired 2-methyl-3-silyloxyalkanals **2**. We now report herein the examination of this process with additional substrates and, in particular, ones with epoxides having both allylic and tertiary (or secondary) centers in an approach to portions of the cytotoxic tedanolides.[6]



For the synthesis of the top half of the tedanolides, e.g., the C1-C12 portion **3**, we proposed using the substituted heptenal **4** as a precursor. We envisioned preparing this piece via a non-aldol aldol process by rearrangement of the epoxide **5**. This substrate differs from all our previous substrates in that the epoxide is both tertiary and allylic



and therefore two relatively stable carbocations are possible. In order to quickly test the reaction we prepared the desmethyl analogue **7** from the aldehyde **6** (itself prepared in several steps from 2-benzyloxypropanal). Treatment of this epoxide **7** with silyl triflate and base afforded the undesired product, the ketone **8**, in excellent yield, thus demonstrating that rearrangement via migration of the silyloxymethyl group to the tertiary carbocation[7] is more favorable than the normal internal hydride transfer to the tertiary carbocation as shown in **A**.[8] Thus the route to compounds such as **4** was changed to account for the difference in carbocation stabilities, as follows. Cyclization of the

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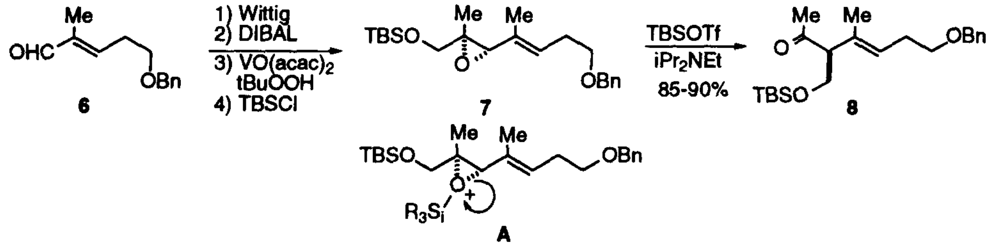
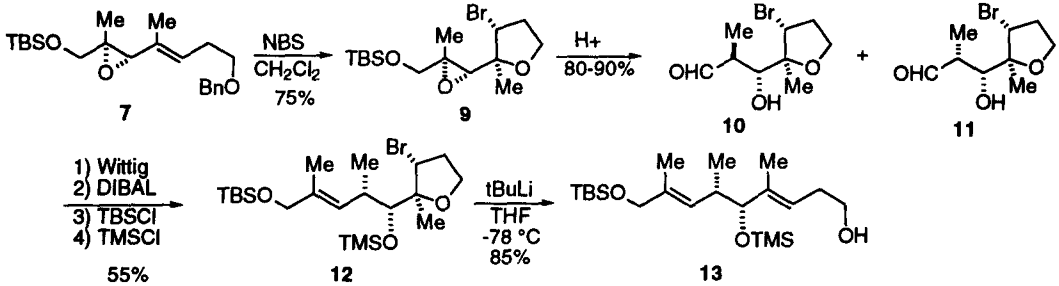
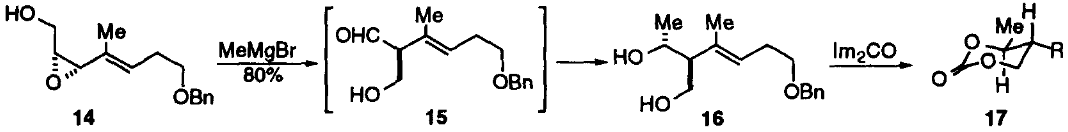


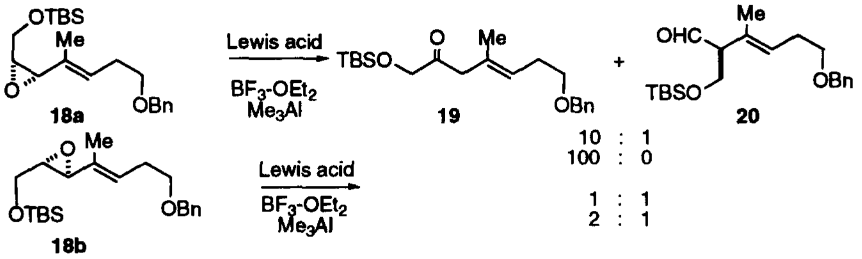
homoallylic benzyl ether **7** with NBS afforded the bromotetrahydrofuran **9** in 75% yield as a single diastereomer.[9] Treatment of **9** with silyl triflate gave little or no rearrangement presumably due to the very crowded steric environment of the epoxide. However, treatment with a stronger electrophile, e.g., strong protic acid, e.g., TfOH, HBr or even TsOH,[10] gave a rapid rearrangement to a mixture of the hydroxyaldehydes **10** and **11** in good yield.[10] The ratio of these two products varied somewhat but was usually nearly 1:1 (occasionally favoring the desired product **11**). Conversion of the desired isomer **11** to the substrate for the next rearrangement was straightforward, giving **12** in 55% yield. The 'protection' of the alkene as a bromo ether is only useful if it can be reversed easily. Thus 'deprotection' of the bromo ether was effected by treatment of **12** with *tert*-butyllithium to give the homoallylic alcohol **13** in 85% yield. Thus the desired 'non-aldol aldol' process could be made to occur in this system by a novel reversible 'protection' of the alkene as a bromo ether.



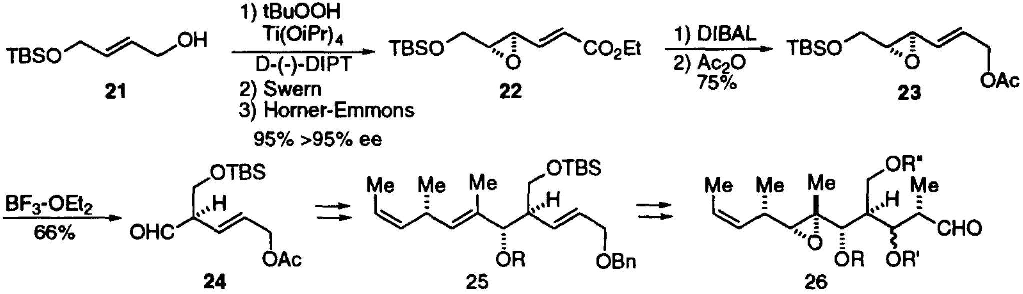
We also examined the possibility of using the undesired rearrangement above, e.g., **7** → **8**, for the preparation of the bottom half of tedanolide. Thus treatment of the allylic epoxide **14** (prepared from **6** by a similar sequence) with methyl Grignard reagent afforded the diol **16** as a single diastereomer, presumably via the intermediacy of the aldehyde **15** formed by an analogous allylic rearrangement to that seen above.[11] The structure of the diol **16** was proven by the ¹H NMR coupling constants of the cyclic carbonate **17** prepared as shown. Rearrangements of similar systems were also examined. For example, the *Z* silyl ether **18a** gave mostly the ketone **19** via hydride migration when treated with various Lewis acids while the *E* isomer **18b** gave mixtures of the ketone **19** and the



aldehyde **20**. Addition of methyl Grignard to **20** followed by desilylation gave the same diol **16** as above. Addition of methyl Grignard to the *Z* silyl ether **18a** gave the tertiary alcohol from addition of methyl anion to the ketone **19**.



Finally we have studied a somewhat different route to compounds that might serve as precursors to the bottom half of the tedanolides. Asymmetric epoxidation of the selectively protected enediol **21** and subsequent elongation gave the epoxy enoate **22** which was converted to the acetate **23**. On treatment with Lewis acid, this epoxide was cleanly rearranged to the aldehyde **24**. We are currently investigating the diastereoselectivity of organometallic additions to **24** and other preparations of compounds such as **25** and ultimately the full bottom half of the tedanolides **26**.



Thus we have examined the Lewis acid promoted rearrangements of several allylic epoxides and their derivatives as a method for the preparation of compounds that can be used in the synthesis of the tedanolides.

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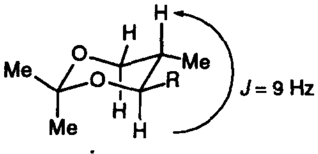
8) Note that the alternative mechanism of migration of the alkenyl group to the tertiary homoallylic cation in **A** would not lead to **8** but rather to the quaternary aldehyde (for examples, see: Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379). Thus while one cannot rule out this mechanism in the other rearrangements reported, e.g., **18** to **20**, we believe that if it did not occur when a tertiary homoallylic cation was possible, it would certainly not occur when a less stable secondary homoallylic cation was involved and thus favor the mechanism described, namely rearrangement via the allylic cation, as shown in **A**.

9) a) We have assigned the stereochemistry based on the 'inside oxygen' model, e.g., via the transition state with the bromide approaching from the less-hindered face in the conformation in which the epoxide oxygen is nearly coplanar with the vinyl hydrogen. For an explanation, see: Haller, J.; Niwayama, S.; Duh., H. Y.; Houk, K. N. *J. Org. Chem.* **1997**, *62*, 5728; Raimondi, L.; Wu, Y. D.; Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1992**, *33*, 4409. b) For other highly diastereoselective cyclizations of this type, see: Jung, M. E.; Karama, U.; Marquez, R. *J. Org. Chem.* **1999**, *64*, 663.

10) For the use of protic acids in this rearrangement, see: D'Amico, D. C. Ph. D. thesis, UCLA, 1994.

11) The relative stereochemistry of these two aldehydes were proven by coupling constants in the ^{1}H NMR spectra of the acetonides **i** and **ii** formed from the diols formed by hydride reduction of **10** and **11**, respectively, followed by acetonide formation.



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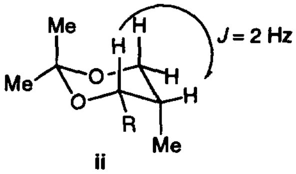

ii