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# Synthetic Access to Bent Polycycles by Cation-$\pi$ Cyclization

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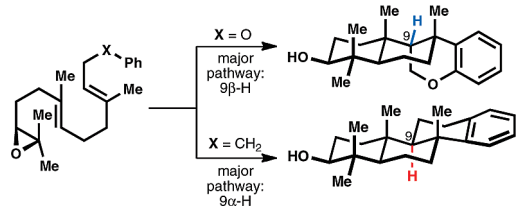
## ABSTRACT




**The presence of an ether oxygen within a chain undergoing cation−polyene cyclization has a profound influence on the stereochemistry of this important construction, apparently due to nucleophilic participation of oxygen in the cyclization process and formation of an oxonium intermediate, leading to bent fused ring systems.**

The carbocation-initiated polycyclization of appropriate polyunsaturated substrates is one of the most powerful molecular constructions in synthetic chemistry. It is also an extremely important biosynthetic process, for instance, in the one-step tetracyclization of (*S*)-2,3-oxidosqualene[1] to a sterol (Figure 1, **1** → **2**). The carbocation−$\pi$-cyclization process is also the dominating pathway for the biosynthesis of cyclic terpenoids. Cationic cyclization has served well for the chemical syntheses of many complex terpenoids, e.g., pentacyclosqualene[2a] (an early example), dammarenediol,[2b] lanostenol,[2c] onocerin,[2d] serratenediol,[2e] $\beta$-amyrins, and lupeol.[2f,g] However, there is still a large gap in efficiency between biosynthetic polycyclizations and present chemical syntheses. Unlike the enzymic cyclizations which proceed with an efficiency of ca. 99% per ring formed, the chemical cyclizations are, at best, only 70−80% efficient per ring formed. This difference arises partly because the cyclization

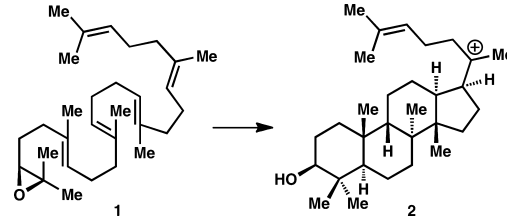



**Figure 1.** Biosynthetic conversion of (*S*)-2,3-oxidosqualene (**1**) to protosteryl cation (**2**).

substrate is held by the enzyme in a prefolded conformational arrangement which selects the proper $\pi$-face of a double bond for attack by the propagating carbocation, minimizing the decrease in the entropy of activation of enzymic cyclization.

Although there is no known way to mimic this template-guided cyclization, the entropic problem may be diminished by conducting cyclization at the lowest possible temperature (to minimize the (positive) $T\Delta S^{\ddagger}$ component of the free energy of activation ($\Delta G^{\ddagger}$)) in $CH_2Cl_2$ with $MeAlCl_2$ as catalyst. Functional groups more basic than epoxide are not tolerated. The studies described herein were undertaken to gain a better understanding of the relationship between substrate structure and $\pi$-facial selectivity and to extend the

(1) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812–2833.

(2) (a) Corey, E. J.; Sauers, R. R. *J. Am. Chem. Soc.* **1957**, *79*, 3925–3926. (b) Corey, E. J.; Lin, S. A. *J. Am. Chem. Soc.* **1996**, *118*, 8765–8766. (c) Corey, E. J.; Lee, J.; Liu, D. R. *Tetrahedron Lett.* **1994**, *35*, 9149–9152. (d) Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290–11291. (e) Zhang, J.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3215–3216. (f) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2009**, *131*, 13928–13929. (g) For a review, see: Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730–4756.

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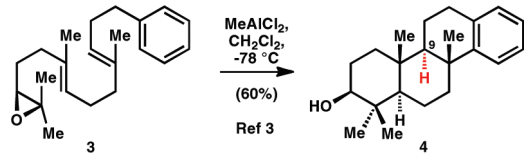



**Figure 2.** *Trans*−*anti*−*trans* cyclization of **3** to **4** producing 9α-H stereochemistry.

scope of cyclization. One motivation for this study was the observation that the common stereochemical pathway for cyclization, exemplified by the conversion of **3** to the A/B/C/*trans*−*anti*−*trans* product **4** (Figure 2),[3] is not universal since cases such as **5** → **6** are known (Figure 3)[4] which would seem to involve cations **7** and **8** and a different π-facial selectivity at the second olefinic linkage. This difference in π-facial selectivity at the double bond involved in closure of the second ring is of great interest since it is clearly a branch point in the biosynthetic cyclizations which lead to sterols or plant triterpenes.[5]

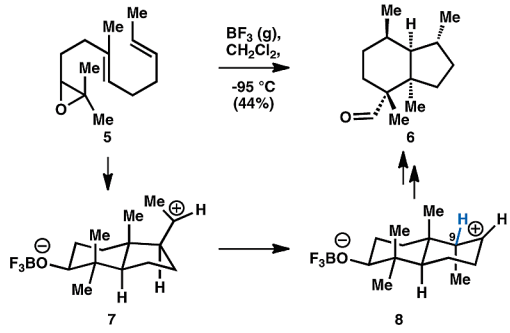



**Figure 3.** Cyclization of **5** to **6** through cation **8**, which possesses 9β-H stereochemistry.

Our initial research of the relationship between the structure of the substrate and the stereochemistry of closure of the second ring in epoxide-initiated cation−olefin cyclizations was conducted with simple epoxyfarnesol derivatives. In the discussion which follows, the two modes of bicyclization will be referred to as the 9α-H or 9β-H pathway, as structurally indicated with formulas **9**−**11** (Figure 4). This phase of our work was carried out with $CH_2Cl_2$ as solvent, and $RAlCl_2$ or $R_2AlCl$ (3 equiv, e.g., $EtAlCl_2$) as catalytic Lewis acid at −78 °C, conditions which generally are most favorable for epoxide-initiated cationic polycyclization reactions.

When the benzoate of 10,11-epoxyfarnesol was examined under standard conditions for cyclization only monocyclic reaction products were obtained. The most obvious explanation for this result is that the Lewis acid coordinates more

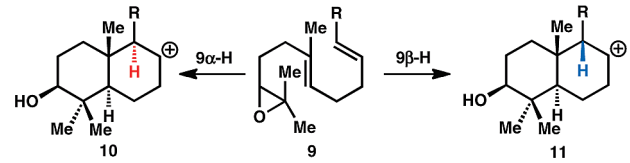
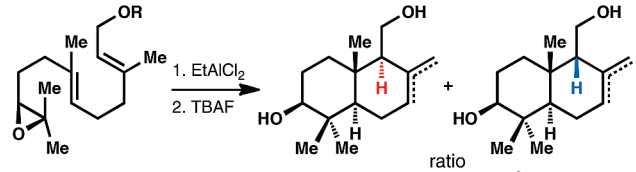



**Figure 4.** Two modes of cyclization for the formation of ring B: the 9α-H or 9β-H pathways.

strongly with the benzoate carbonyl, and essentially completely (with 3 equiv of $EtAlCl_2$), and that coordination removes electron density from the terminating double bond which prevents formation of the second ring. Because of this result, we next examined the two bulky silyl ethers of 10,11-epoxyfarnesol **12a** and **12b** (Scheme 1), the assumption being that Lewis acid complexation with the sterically hindered silyloxy oxygen would not be a complication. Indeed, in each case bicyclization was the principal reaction pathway (70−85% isolated yield of **13** and **14** after desilylation and column chromatography on silica gel). For each of these substrates there was a near balance between 9α-H and 9β-H pathways for cyclization, as indicated in Scheme 1. The 9α-H and 9β-H products each consisted of a mixture of one endo- and one exocyclic olefinic species.[6]

**Scheme 1.** Cyclization of Silyl Ethers **12a** and **12b** To Produce Equimolar Mixtures of 9α-H and 9β-H Products[a]




| | 9α-H products | ratio 13/14 | 9β-H products |
|---|---|---|---|
| **12a**: **R** = *t*-BuMe$_2$Si | **13** | 47:53 | **14** |
| **12b**: **R** = *i*-Pr$_3$Si | **13** | 49:51 | **14** |

[a] Conditions: (1) $EtAlCl_2$ (3 equiv added slowly), $CH_2Cl_2$ (0.01 M), −78 °C, 3 h; (2) TBAF (1.5 equiv), THF (0.5 M), 25 °C, 6 h.

The close similarity of ratios for the 9α-H and 9β-H cyclization pathways came as a surprise, given the considerable number of reported examples in which the 9α-H product is strongly preferred. One possible reason for the exceptional behavior of the substrates **12a** and **12b** becomes apparent when the reported sequence **5** → **6** (presumably via **7** and **8**) is recalled. If it were generally true that the 9β-H pathway is favored for reactions that proceed to bicyclic 6/6-fused product via a bicyclic 6/5-fused intermediate, it is logical to explain the formation of the 9β-H product **14** via the oxonium intermediate **15**, which then converts to **16** (Figure 5). To test whether the 9β-H pathway is made more favorable if the incipient ring B is generated via a 5-membered-like precursor, cyclization of the corresponding allylsilane **17** was examined (Scheme 2).

(3) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8865–8869.
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(6) For details of analyses and quantitative data, see the Supporting Information.

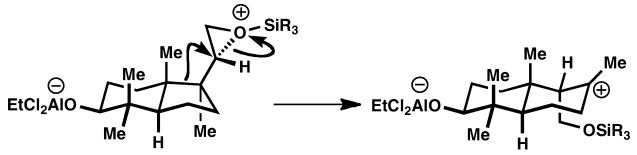
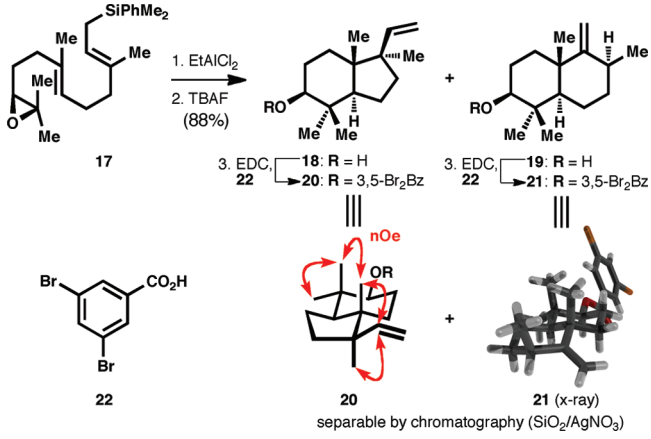



**Figure 5.** Intermediacy of an oxygen-stabilized secondary cation **15** may explain the formation of 9$\beta$-H products.

The substrate **17** was synthesized from 9,10-epoxyfarnesyl benzoate by coupling with the reagent derived from dimethylphenylsilyllithium and copper(I) cyanide. Cyclization of **17** under the conditions developed for **12a** and **12b** and subsequent desilylation with TBAF afforded an equimolar mixture of two products which were chromatographically separated after conversion to their 3,5-dibromobenzoates **20** and **21** (chromatography on $AgNO_3$-impregnated silica gel). The stereochemistry of the decalin product **19** corresponds to the usual 9$\alpha$-H cyclization (confirmed by X-ray crystallographic analysis of **21**, mp 144−146 °C), whereas that of the hydrindane **18** corresponds to the $\pi$-facial selection of the 9$\beta$-H geometry (confirmed by NOE studies of **20**). This result for **18** is consistent with the proposal that cyclization via a 5-membered B-ring structure can involve the opposite $\pi$-face selectivity to that which is generally found for 6-membered B-ring formation.

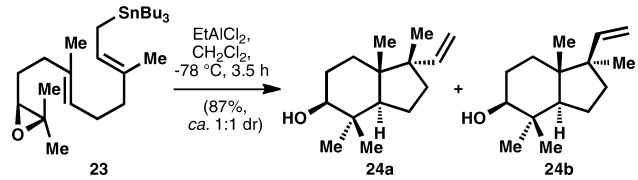
**Scheme 2.** Cyclization of Silane **17** Giving Rise To Hydrindane **18**, Which Possesses 9$\beta$-H sStereochemistry[a]




[a] Conditions: (1) $EtAlCl_2$ (3 equiv added slowly), $CH_2Cl_2$ (0.01 M), −78 °C, 3 h; (2) TBAF (1.5 equiv), THF (0.5 M), 25 °C, 6 h; (3) DCC (1.1 equiv), 3,5-dibromobenzoic acid (**22**) (1.1 equiv), DMAP (0.05 equiv), $CH_2Cl_2$ (0.1 M), 25 °C, 1 h.

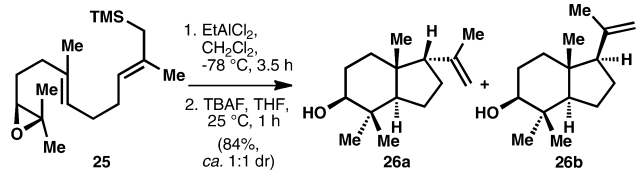
Further studies uncovered a surprising effect of $\pi$-bond basicity on the stereochemistry of B-ring formation. The more $\pi$-basic tri-*n*-butylstannyl analogue **23** of the allylic silane **17** underwent cyclization under the standard conditions to produce a 1:1 mixture of the two diastereomeric bicyclic structures **24a** and **24b** (Scheme 3). This complete lack of $\pi$-face selectivity in the formation of ring B may well be a consequence of a much earlier transition state for ring B closure, i.e., a much longer incipient C−C bond in the transition state.

**Scheme 3.** Cyclization of Allylstannane **23** To Form a Mixture of Diastereomers **24a** and **24b**



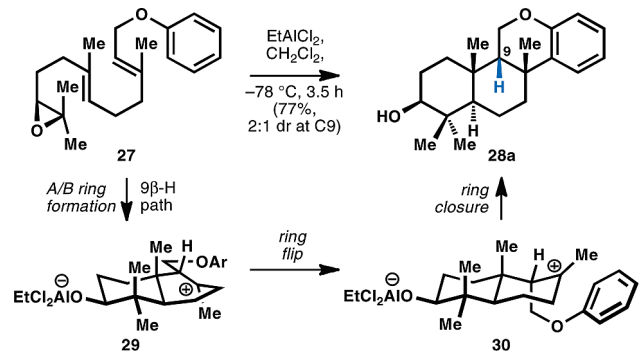

Behavior similar to that just described for **23** was observed in the cyclization of epoxide **25** which leads to a 1:1 mixture of **26a** and **26b** (Scheme 4). In this case also, there is no $\pi$-face selectivity in the formation of ring B, probably for the same reason: a longer C−C bond in the transition state for B-ring closure and a small energy difference between the diastereomeric transition states.[7]

**Scheme 4.** Cyclization of Allylsilane **25** To Form a Mixture of Diastereomers **26a** and **26b**




It was found that 9,10-epoxyfarnesyl phenyl ether **27** underwent efficient conversion to the tetracyclic product **28a** in a single step (Scheme 5). Evidently, the phenolic oxygen is sufficiently nonbasic to allow monocoordination of $EtAlCl_2$ to the more basic epoxide function, in contrast to the benzyl and cinnamyl ethers, which gave essentially no polycyclic products under identical reaction conditions. Of great interest is the fact that cyclization of **27** favored the 9$\beta$-H pathway

**Scheme 5.** Cyclization of Phenyl Ether **27** To Produce Predominantly 9$\beta$-H Product **28a**



in preference to the 9α-H path, since **28a** predominated over the C9 diastereomer **28b** by 2:1 (see the Supporting Information). The major tetracyclic product was isolated by chromatography after conversion to the 3,5-dibromobenzoate (51% overall yield from **27**). The assignment of stereochemistry to **28a** and **28b** was made unambiguously by $^1$H NMR measurements at 500 MHz and NOE correlations. It should be noted that decalin cation **29** must undergo a conformational change[8] from initially formed boatlike conformer **29** to the chair form **30** before closure of ring C to produce tetracycle **28a**.

The contrast between the cyclization pathways **27** → **28a** and **3** → **4** (Figure 6) provides another indication of the importance of the lone pairs of oxygen in influencing the balance between the 9α-H and 9β-H modes of reaction.

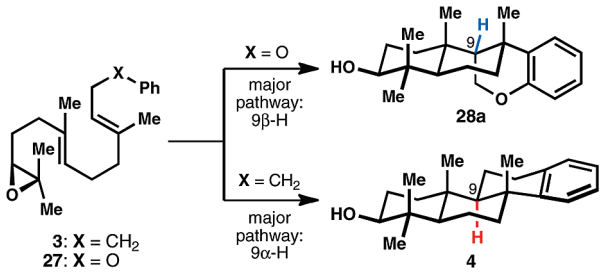
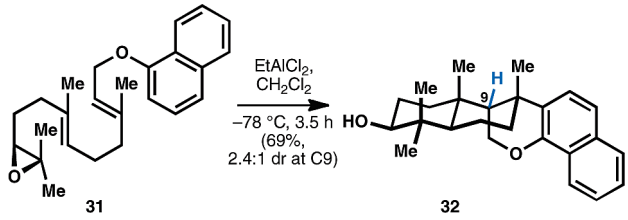



**Figure 6.** Cyclization of **27** → **28a** compared to the cyclization of **3** → **4**.

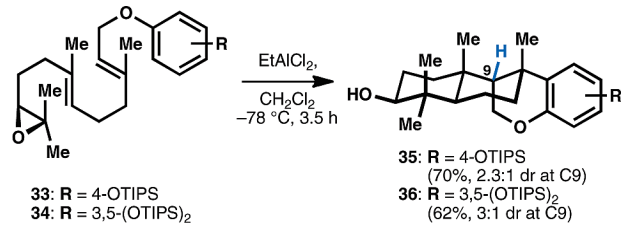
Cyclization of the analogous 1-naphthyl ether **31** also proceeded cleanly and afforded the pentacycle **32** as the major product (Scheme 6). A slight increase in the diastereoselectivity of cyclization (9β-H/9α-H, 2.4:1) was observed relative to the cyclization of phenyl ether **27** (9β-H/9α-H, 2:1).

**Scheme 6.** Cyclization of **31** To Produce Pentacycle **32**



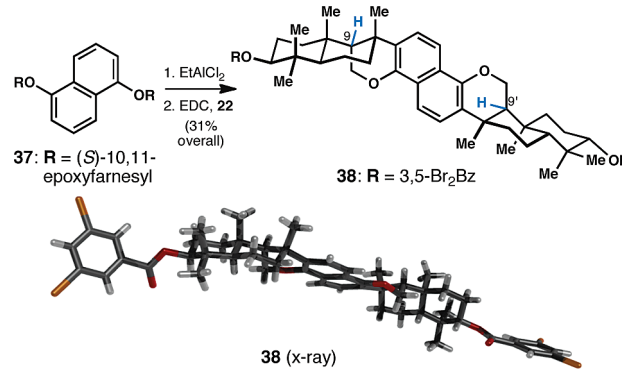

Additional oxygen substitution on the aryl moiety is also tolerated in the cationic polycyclization process and as such can provide useful reactive centers for elaboration to more complex structures (Scheme 7). The farnesyl ether derived from hydroquinone (**33**) underwent efficient cyclization to tetracycle **35** in good yield and in 2.3:1 excess over the 9α-H epimer (70% combined yield of diastereomers). Similarly, the phloroglucinol-derived bis-triisopropylsilyl (TIPS) ether **34** underwent cyclization to the corresponding tetracycle **36** with a 9β-H to 9α-H ratio of 3:1 (total yield 62%).

**Scheme 7.** Oxygen Substitution on the Arene Is Tolerated under Cyclization Conditions




We also investigated the cyclization of the difarnesyl 1,5-naphthyl ether **37** (Scheme 8) which was synthesized in one step from 1,5-dihydroxynaphthalene and (*S*)-10,11-epoxyfarnesyl bromide. Treatment of **37** with $EtAlCl_2$ (6 equiv) in $CH_2Cl_2$ at −78 °C led to a mixture of diols, which were converted to the corresponding 3,5-dibromobenzoates and purified by chromatography to give octacycle **38** (31% from **37**), the structure of which was confirmed by NMR and single-crystal X-ray analysis.[8]

**Scheme 8.** Bidirectional Cyclization of **37** To Octacycle **38**




The unique twisted, rigid octacyclic structure of **38**, prepared in just a few steps from farnesol and commercially available 1,5-dihydroxynapthalene, would be difficult to make by other methods.[9] It further demonstrates the power of cationic polycyclization methodology to produce a wide range of interesting structures.

**Acknowledgment.** We thank the NIH for a Postdoctoral Fellowship to R.A.S. and Dr. Shao-Liang Zheng (Harvard) for X-ray diffraction analysis.

**Supporting Information Available:** Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) A less likely extreme case can also be visualized in which electron transfer occurs from the π-electron-rich terminating C=C subunit to the monocyclic carbocation (without stereoselectivity) to give a diradical that collapses to the 1:1 mixture of **24a** and **24b**.

(8) Corey, E. J.; Wood, H. B. *J. Am. Chem. Soc.* **1996**, *118*, 11982–11983.

(9) Corey, E. J.; Luo, G.; Lin, L. S. *Angew. Chem., Int. Ed.* **1998**, *37*, 1126–1128.