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Tetrahydropyran Formation by Rearrangement of an Epoxy Ester: A Model for the Biosynthesis of Marine Polyether Toxins

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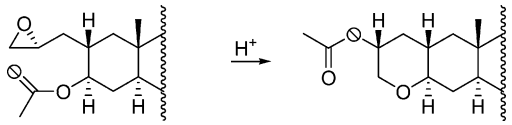
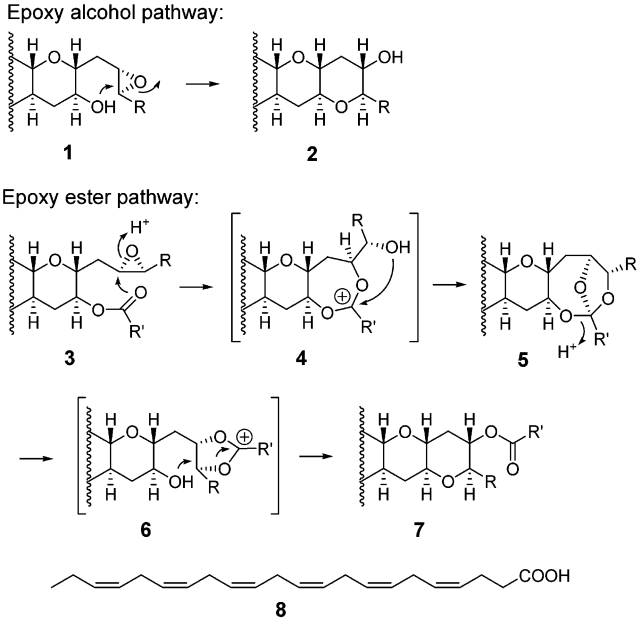


Acid-catalyzed rearrangement of the (*S*)-epoxide derived from 2α-allyl cholestanyl acetate resulted in a 1:1 mixture of a steroidal tetrahydrofuran and a steroidal tetrahydropyran. Formation of a six-membered ring supports the hypothesis that epoxy ester−orthester−cyclic ether rearrangement may be involved in the biosynthesis of ladder-type marine polyether toxins. This reaction represents a new biomimetic preparation of medium ring cyclic ethers.

A consideration of the mechanisms of biosynthetic processes can be instructive to organic chemists engaged in the synthesis of complex natural products. Several biomimetic approaches have been published on the synthesis of the trans-fused cyclic ether rings found in ladder-type polyether marine toxins.[1] Although there is a lack of knowledge regarding the biosynthetic formation of cyclic ethers in "red tide" dinoflagellates, the Westley−Cane hypothesis as extended by Nakanishi and Shimizu is the prevailing theory.[2,3] This proposes *endo*-cyclization of an intramolecular alcohol nucleophile and an electrophilic epoxide in the ether bond-forming step (**1**, Scheme 1, epoxy alcohol pathway). The alcohol (**2**) thus generated can then react with another epoxide group to form another ether ring. It is unknown whether this occurs in a stepwise fashion or via a polyepoxide intermediate. Synthetic strategies based on this hypothetical biosynthetic mechanism have been reported;[4] however, other more unusual mechanisms in which the epoxide serves as the nucleophilic agent,[4,5] or that involve the intermediacy of hypothetical metallooxetane species,[6] have also provided the basis for biomimetic approaches.

SCHEME 1. Biosynthetic Hypotheses for Cyclic Ether Formation in Ladder-Type Polyether Toxins



We have recently proposed a new biosynthetic mechanism for cyclic ether formation (Scheme 1, epoxy ester pathway) involving acid-catalyzed rearrangement of an epoxy ester (**3**) to a bicyclic orthoester (**5**), which subsequently rearranges to a cyclic ether (**7**).[7] This mechanism can be regarded as a variant of the epoxy alcohol mechanism in which the epoxide electrophile (**1**) has been replaced with a dioxolanium ion electrophile (**6**) in the ether bond-forming step. However, this reaction differs significantly in its stereochemical course, requiring the *cis* geometry of the olefinic precursor instead of the *trans*, because both centers of the epoxide undergo inversion. Interestingly, the required precursor for the most regular segments of polyether toxins, i.e., those parts consisting of only 6-membered rings, such as rings H−K of gymnocin-A (Chart 1),[8] would be an *all-cis* skipped polyolefin resembling the ω-3 fatty acids produced by marine dinoflagellates (e.g., DHA, **8**). Also, as has been pointed out by Townsend,[9] a mechanism requiring *cis*-olefins has the advantage that the precursors would be *all-cis*, whereas a mechanism involving *trans*-double bonds

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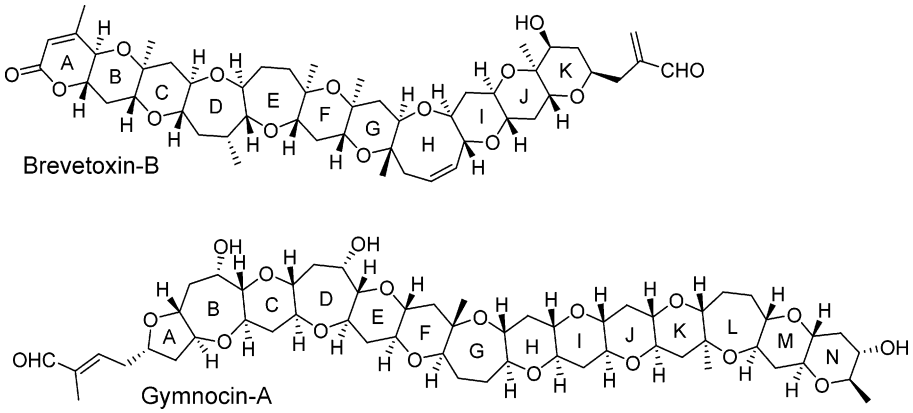
CHART 1

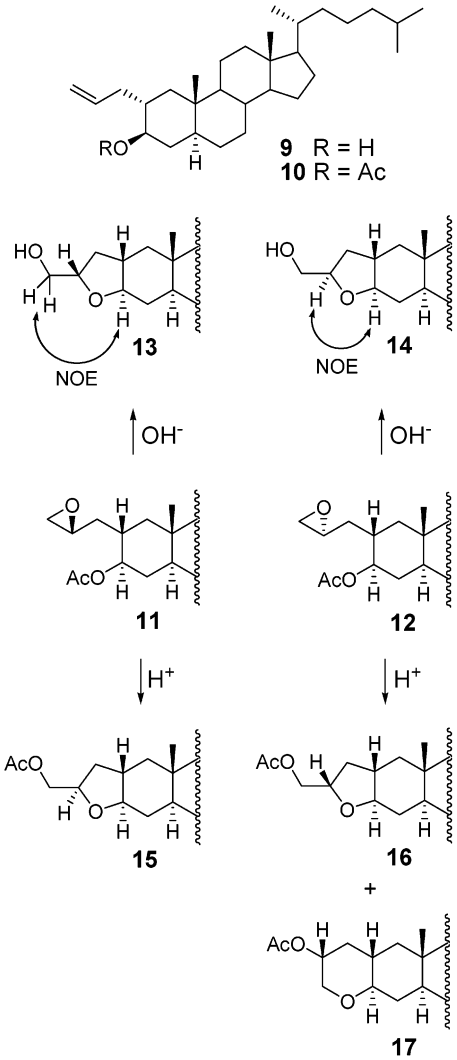


would still require that the unmodified bonds be *cis* (e.g., in rings A and H of brevetoxin-B, Chart 1).[10] A disadvantage of the proposed biogenetic mechanism is that to date only 5-membered ether rings have been prepared by epoxy ester rearrangement,[11] while ladder-type marine toxins contain predominantly 6-membered rings and larger. This study reports the first formation of a 6-membered ether ring via a epoxy ester−orthoester−cyclic ether rearrangement.

To demonstrate that the epoxy ester−orthoester−cyclic ether rearrangement can provide larger ring sizes, a model epoxy acetate (Scheme 2, **12**) was prepared from readily available 2α-allylcholestanol (**9**).[12] It was considered unlikely that a simple acyclic model compound could lead to tetrahydropyrans because previous studies had shown that 1-acetoxy-4,5-epoxyhexanes rearrange exclusively to tetrahydrofurans.[11b,c] Model compound **12** was designed to mimic the hypothetical biosynthetic intermediate **3** and features a 1,2-diequatorial relationship between the two reactive groups.

Treatment of 2α-allylcholestanyl acetate with *m*-CPBA gave a 1:1 mixture of isomeric epoxides (Scheme 2, **11**, **12**) that could not be separated by TLC or HPLC. Attempts to achieve a separation of the corresponding epoxy alcohols failed because they could not be prepared. Thus, *m*-CPBA treatment of 2α-allylcholestanol led to a 1:1 mixture of isomeric tetrahydrofuranyl alcohols (**13**, **14**) instead of the desired epoxy alcohols. The same products were obtained in attempts to deacetylate epoxy acetates **11** and **12** using ethanolic KOH or K_2CO_3 in methanol (Scheme 2). The structures of the tetrahydrofuranyl alcohols were determined as their acetates by 2-dimensional NMR experiments (HMBC and HSQC), and their stereochemical configurations were established by ROESY. The *R*-isomer (**14**) showed ROESY cross-peaks between the signals of the two ether methines at 4.22 and 3.11 ppm (C-3), while the *S*-isomer (**13**) showed correlations between C-3 (3.16 ppm) and the hydrogens of the ester methylene (4.15 and 4.00 ppm).

SCHEME 2. Reactions of Steroidal Model Compounds



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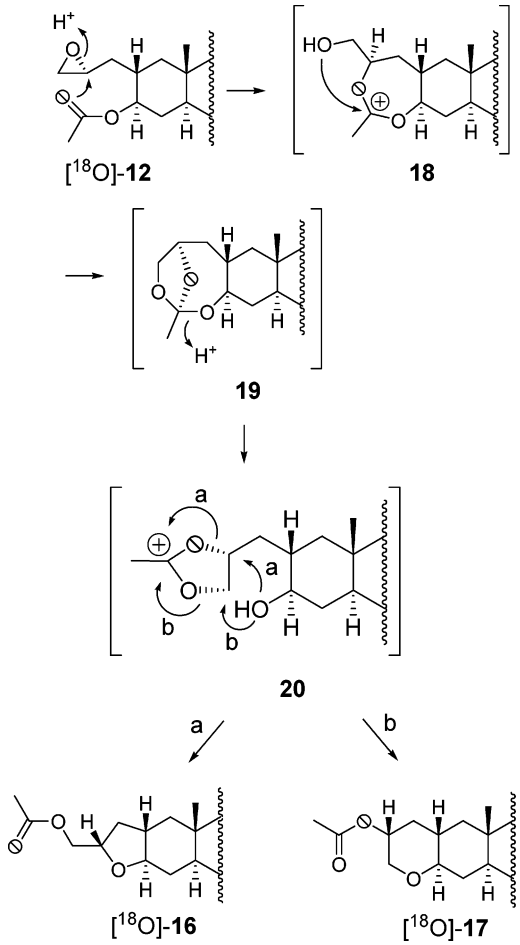
When the mixture of epoxy acetates **11** and **12** was treated with 50 mM TFA/$CDCl_3$, three products were obtained (Scheme 2), the two tetrahydrofuranyl acetates (**15**, **16**) and a tetrahydropyranyl acetate (**17**). Under these conditions, **11** and **12** reacted with half-lives of 9.6 and 3.0 min, respectively. A pure sample of the less reactive isomer (**11**) was obtained by depletion of the more reactive isomer (**12**) under the reaction conditions. Upon saponification of **11**, the *S*-isomer of the tetrahydrofuranyl alcohol (**13**) was formed (Scheme 2), allowing an assignment of the *R*-configuration for **11**. When **11** was subjected to acid-catalyzed rearrangement, the *R*-isomer of the tetrahydrofuranyl acetate (**15**) was formed, consistent with the double-inversion mechanism of the epoxy ester−orthoester−cyclic ether rearrangement. An enriched sample of the desired *S*-epoxy acetate (**12**) was obtained by repeated preparative TLC. Upon saponification, epoxy ester **12** gave the *R*-tetrahydrofuranyl alcohol (**14**), and upon acid-catalyzed rearrangement, it provided a 1:1 mixture of the *S*-tetrahydrofuranyl acetate (**16**) and the tetrahydropyranyl acetate (**17**). The structure of **17** was determined by HMBC and HSQC, and an equatorial orientation was assigned to the acetoxy group on the basis of the splitting pattern of the acetoxy methine (4.83 ppm, dddd, J = 5.3, 5.3, 10.6, 10.6 Hz).

The configuration of the tetrahydropyranyl acetate (**17**) is correctly predicted by the established mechanism of cyclic ether formation from [3.2.1]bicyclic orthoesters.[7] However, in the current rearrangement, the expected [4.2.1]bicyclic orthoesters intermediates (e.g., **19**, Scheme 3) were not detectable. Based on kinetic evidence, we have previously predicted that there would be cases where the orthoester−cyclic ether rearrangement would be faster than the epoxy ester−orthoester rearrangement.[7] To provide additional evidence for the mechanism of the reaction, ^{18}O-labeling experiments were carried out. Acetylation of 2α-allylcholestanol (**9**) with mono-^{18}O-labeled acetic acid, followed by *m*-CPBA epoxidation, provided epoxy esters **11** and **12** labeled in the carbonyl oxygens to the extent of 45%. When the mixture of the ^{18}O-labeled epoxy acetates (**11**, **12**) was subjected to acid-catalyzed rearrangement, the two tetrahydrofuranyl acetates (**15**, **16**) were found to bear the label at the carbonyl oxygen, as shown by an upfield $\delta\Delta$ of 38 ppb in the ^{13}C NMR signals of the carbonyl carbons. In contrast, the ^{18}O-label in the tetrahydropyran (**17**) was shown to be located entirely in the ester oxygen (Scheme 3), based on a $\delta\Delta$ of 14 ppb for the carbonyl signal (170.2 ppm) and a $\delta\Delta$ of 32 ppb for the carbon bearing the acetoxy group (68.7 ppm). These results are completely consistent with rearrangement via a [4.2.1]bicyclic orthoester (**19**, Scheme 3).

This is the first demonstration that a tetrahydropyran can be generated by the epoxy ester rearrangement, which supports the biogenetic hypothesis. Although a carboxylic ester was employed in this experiment, it is possible that the biochemical transformation involves an inorganic ester. Testing of this hypothesis awaits biosynthetic studies. This model study also demonstrates a new method of potential synthetic utility for making six-membered ether rings. Although there is a general *exo* preference for the ether bond forming step (**20**, path a), it is likely that conditions can be found that will favor the *endo* mode, as has been achieved in the case of epoxy alcohol cyclization.[13] Experiments are underway to explore the potential of this biomimetic reaction for the synthesis of medium-ring cyclic ethers.

SCHEME 3. ^{18}O-Labeling Results



Experimental Section

General Methods. ^1H NMR spectra were acquired at 600 MHz and ^{13}C NMR spectra at 151 MHz using $CDCl_3$ as the solvent, unless otherwise specified. TLC was performed on aluminum-backed plates coated with a 0.25 mm layer of Si gel 60 F254.

The acid-catalyzed rearrangements were carried out in NMR tubes using TFA in dry $CDCl_3$. The reactions were followed at 30 °C by ^1H NMR spectroscopy, and the rate of disappearance of substrate over time was measured by integration of isolated NMR signals. The reactions were halted by the addition of triethylamine, and the products were isolated by preparative TLC.

2α-Allylcholestan-3β-yl Acetate (10). Acetylation of 2α-allylcholestan-3β-ol (**9**)[12] (63.2 mg, 0.15 mmol) with a 2:1 mixture of pyridine−acetic anydride (1.5 mL) at 40 °C for 2 h gave, after evaporation of the volatile substances, 67.0 mg of **10** (0.14 mmol, 97% yield). ^1H NMR: 5.72 (1H, dddd, J = 6.7, 7.6, 10.4, 16.6 Hz), 4.97 (1H, br d, J = 10.4 Hz), 4.96 (1H, br d, J = 16.6 Hz), 4.49 (1H, dt, J = 4.8, 10.8 Hz), 2.24−2.19 (1H, m), 2.02 (3H, s), 1.96 (1H, dt, J = 3.2, 12.6 Hz), 0.90 (3H, d, J = 6.5 Hz), 0.865

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(3H, d, J = 6.6 Hz), 0.860 (3H, d, J = 6.7 Hz), 0.82 (3H, s), 0.64 (3H, s). ^{13}C NMR: 170.8, 136.5, 116.0, 56.4, 56.3, 54.3, 44.7, 42.9, 42.6, 40.0, 39.5, 37.2, 37.1, 36.2, 35.9, 35.8, 35.3, 34.1, 31.9, 28.22, 28.20, 28.0, 24.2, 23.8, 22.8, 22.5, 21.3, 21.2, 18.7, 12.9, 12.09, 12.07.

2α-Allylcholestan-3β-yl Acetate Epoxides (11 and 12). A stirred solution of **10** (67.0 mg, 0.14 mmol) in 2 mL of CH_2Cl_2 was treated with 62.0 mg of *m*-CPBA (75%, 0.27 mmol) at 0 °C for 2 h. The reaction mixture was partitioned between 5% NaOH and Et_2O. Purification by silica gel chromatography (hexanes−ethyl acetate 9:1) gave 62.2 mg of a 52:48 mixture of the (*R*)- and (*S*)-epoxy acetates (0.13 mmol, 90% yield).

See below for ^{1}H NMR data. ^{13}C NMR: 170.9, 170.7, 76.9, 56.41, 56.40, 56.29, 56.27. 54.26, 54.24, 51.3, 50.3, 47.6, 46.7, 44.56, 44.54, 43.9, 43.4, 42.6, 39.97, 39.95, 39.5, 36.5, 36.3, 36.2, 36.0, 35.8, 35.4, 35.3, 34.00, 33.99, 31.90, 28.21, 28.19, 28.0, 24.2, 23.8, 22.8, 22.5, 21.30, 21.27, 18.7, 12.9, 12.09, 12.07. Anal. Calcd for $C_{32}H_{54}O_3$: C, 79.96; H, 11.18. Found: C, 79.53; H, 11.36.

2α-Allylcholestan-3β-yl Acetate (*R*)-Epoxide (11). Treatment of the mixed epoxides with 50 mM TFA in $CDCl_3$ until the (*S*)-isomer was gone gave a sample of the less reactive (*R*)-isomer. ^{1}H NMR: 4.49 (1H, dt, J = 4.9, 10.7 Hz), 2.96−2.88 (1H, m), 2.76 (1H, dd, J = 4.1, 4.9 Hz), 2.41 (1H, dd, J = 2.7, 5.1 Hz), 2.03 (3H, s), 0.90 (3H, d, J = 6.5 Hz), 0.863 (3H, d, J = 6.7 Hz), 0.858 (3H, d, J = 6.7 Hz), 0.85 (3H, s), 0.65 (3H, s).

2α-Allylcholestan-3β-yl Acetate (*S*)-Epoxide (12). Repeated fractionation by preparative TLC (hexanes−ethyl acetate 9:1) gave a sample of the slightly less polar (*S*)-isomer. ^{1}H NMR: 4.52 (1H, dt, J = 4.9, 10.7 Hz), 2.99−2.90 (1H, m), 2.71 (1H, dd, J = 4.1, 4.9 Hz), 2.38 (1H, dd, J = 2.7, 5.1 Hz), 2.03 (3H, s), 0.90 (3H, d, J = 6.5 Hz), 0.863 (3H, d, J = 6.7 Hz), 0.858 (3H, d, J = 6.7 Hz), 0.86 (3H, s), 0.65 (3H, s).

***(R)*-THF Alcohol (13).** This was obtained by saponification of the (*S*)-epoxy acetate (**12**) or the (*R*)-THF acetate (**15**) with ethanolic KOH or treatment with K_2CO_3/MeOH. It could also be prepared by *m*-CPBA treatment of 2α-allylcholestan-3β-ol (**9**) as a 1:1 mixture with its (*S*)-isomer (**14**) from which it was separated by preparative TLC (hexanes−ethyl acetate 4:1) as the less polar fraction. ^{1}H NMR: 4.15−4.10 (1H, m), 3.68 (1H, dd, J = 3.4, 11.5 Hz), 3.51 (1H, dd, J = 5.7, 11.5 Hz), 3.13 (1H, dt, J = 4.0, 10.7 Hz), 0.90 (3H, d, J = 6.5 Hz), 0.867 (3H, d, J = 6.7 Hz), 0.863 (3H, d, J = 6.7 Hz), 0.84 (3H, s), 0.66 (3H, s). ^{13}C NMR (75 MHz): 84.6, 78.1, 66.0, 56.4, 56.3, 54.6, 45.7, 42.7, 41.4, 40.5, 40.1, 39.5, 37.7, 36.2, 35.8, 35.5, 34.0, 33.2, 32.2, 28.9, 28.3, 28.0, 24.2, 23.8, 22.8, 22.5, 21.4, 18.7, 14.1, 12.1.

***(S)*-THF Alcohol (14).** This was obtained by saponification of the (*R*)-epoxy acetate (**11**) or the (*S*)-THF acetate (**16**) with ethanolic KOH or treatment with K_2CO_3/MeOH. It could also be prepared by *m*-CPBA treatment of 2α-allylcholestan-3β-ol (**9**) as a 1:1 mixture with its (*R*)-isomer (**13**) from which it was separated by preparative TLC (hexanes−ethyl acetate 4:1) as the more polar fraction. ^{1}H NMR: 4.21−4.15 (1H, m), 3.63 (1H, dd, J = 2.5, 11.6 Hz), 3.52 (1H, dd, J = 7.0, 11.6 Hz), 3.14 (1H, dt, J = 4.0, 10.7 Hz), 0.90 (3H, d, J = 6.5 Hz), 0.867 (3H, d, J = 6.7 Hz), 0.863 (3H, d, J = 6.7 Hz), 0.84 (3H, s), 0.66 (3H, s). ^{13}C NMR (75 MHz): 83.0, 79.3, 65.6, 56.4, 56.3, 54.6, 45.8, 42.7, 41.2, 41.1, 40.1, 39.5, 37.6, 36.2, 35.8, 35.6, 34.0, 33.2, 32.2, 28.9, 28.2, 28.0, 24.2, 23.8, 22.8, 22.5, 21.4, 18.7, 14.0, 12.1.

***(R)*-THF Acetate (15).** This was obtained by the rearrangement of the (*R*)-epoxy acetate (**11**) in 50 mM TFA in $CDCl_3$. It could also be prepared by acetylation of the (*R*)-THF alcohol (**13**). ^{1}H NMR: 4.25−4.20 (1H, m), 4.14 (1H, dd, J = 4.3, 11.4 Hz), 4.00 (1H, dd, J = 6.7, 11.4 Hz), 3.11 (1H, dt, J = 4.1, 10.7 Hz), 2.08 (3H, s), 0.90 (3H, d, J = 6.6 Hz), 0.865 (3H, d, J = 6.7 Hz), 0.861 (3H, d, J = 6.7 Hz), 0.84 (3H, s), 0.66 (3H, s). ^{13}C NMR: 171.1, 84.8, 75.2, 67.3, 56.5, 56.3, 54.6, 45.7, 42.7, 41.2, 40.1, 39.6, 39.5, 37.7, 36.2, 35.8, 35.6, 33.9, 33.5, 32.2, 28.9, 28.3, 28.0, 24.2, 23.9, 22.8, 22.6, 21.4, 21.0, 18.7, 14.1, 12.1. Anal. Calcd for $C_{32}H_{54}O_3$: C, 79.96; H, 11.18. Found: C, 79.68; H, 11.35.

***(S)*-THF Acetate (16).** This was obtained by rearrangement of the (*S*)-epoxy acetate (**12**) in 50 mM TFA in $CDCl_3$ as a 1:1 mixture with the (*R*)-THP acetate (**17**) from which it was separated by preparative TLC (hexanes−ethyl acetate 9:1) as the more polar fraction. It could also be prepared by acetylation of the (*S*)-THF alcohol (**14**). ^{1}H NMR: 4.31−4.26 (1H, m), 4.15 (1H, dd, J = 3.0, 11.7 Hz), 4.00 (1H, dd, J = 7.6, 11.7 Hz), 3.16 (1H, dt, J = 4.2, 10.8 Hz), 2.09 (3H, s), 2.03 (1H, dt, J = 11.7, 6.3 Hz), 0.91 (3H, d, J = 6.6 Hz), 0.870 (3H, d, J = 6.7 Hz), 0.865 (3H, d, J = 6.7 Hz), 0.84 (3H, s), 0.66 (3H, s). ^{13}C NMR: 171.1, 83.2, 76.1, 67.0, 56.4, 56.3, 54.6, 45.7, 42.7, 41.1, 41.0, 40.8, 39.5, 37.6, 36.2, 35.8, 35.6, 34.0, 33.9, 32.2, 28.9, 28.3, 28.0, 24.2, 23.9, 22.8, 22.6, 21.4, 21.0, 18.7, 14.0, 12.1. Anal. Calcd for $C_{32}H_{54}O_3$: C, 79.96; H, 11.18. Found: C, 79.34; H, 11.31.

***(R)*-THP Acetate (17).** This was obtained by rearrangement of the (*S*)-epoxy acetate (**12**, see above). ^{1}H NMR: 4.83 (1H, dddd, J = 5.3, 5.3, 10.6, 10.6 Hz), 4.03 (1H, ddd, J = 2.1, 5.3, 10.6 Hz), 3.19 (1H, dd, J = 10.6, 10.6 Hz), 2.86 (1H, dt, J = 4.5, 10.6 Hz), 2.02 (3H, s), 0.90 (3H, d, J = 6.6 Hz), 0.866 (3H, d, J = 6.6 Hz), 0.862 (3H, d, J = 6.6 Hz), 0.83 (3H, s), 0.65 (3H, s). ^{13}C NMR: 170.2, 82.3, 69.5, 68.7, 56.5, 56.3, 54.4, 45.4, 44.0, 42.6, 40.1, 39.5, 36.6, 36.5, 36.2, 35.79, 35.78, 35.4, 34.3, 32.1, 28.5, 28.2, 28.0, 24.2, 23.8, 22.8, 22.6, 21.3, 21.1, 18.7, 13.3, 12.1. Anal. Calcd for $C_{32}H_{54}O_3$: C, 79.96; H, 11.18. Found: C, 79.75; H, 11.32.

^{18}O Labeling. Acetylation of 2α-allylcholestan-3β-ol (**9**) with mono-^{18}O-labeled acetic acid (48% ^{18}O) was accomplished using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) as previously reported.[7] The resulting 2α-allylcholestan-3β-yl acetate (**10**) contained ^{18}O in the carbonyl oxygen to the extent of 45% as determined by 151 MHz ^{13}C NMR. Epoxidation as described above provided the labeled epoxides **11** and **12**. These contained ^{18}O to the extent of 45% in the carbonyl oxygen. Rearrangement was carried out with 50 mM TFA in $CDCl_3$.

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Supporting Information Available: Kinetic data, ^{1}H NMR spectra of all compounds, and ^{13}C NMR spectra of ^{18}O-labeled compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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