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Mechanistic Studies of the Biomimetic Epoxy Ester−Orthoester and Orthoester−Cyclic Ether Rearrangements†

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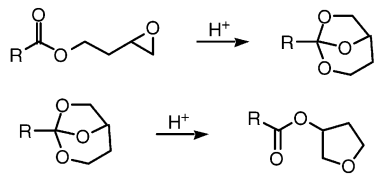
The relative rates of acid-catalyzed rearrangements of epoxy esters to [3.2.1]bicyclic orthoesters, the subsequent rearrangements of these ortho esters to substituted tetrahydrofurans, and the rates of orthoester hydrolysis at pH 4.75 were measured in NMR kinetics experiments. The ease of formation and stabilities of these orthoesters compared favorably with the OBO-type [2.2.2]bicyclic orthoesters typically used as protecting groups of carboxylic acids. Studies with ^{13}C NMR-detected ^{18}O-labeling show that epoxy ester rearrangement takes place preferentially via 6-exo cyclization, although the 7-endo process competes when the distal center of the epoxide is disubstituted. The ortho ester−cyclic ether rearrangement was shown by ^{18}O-labeling to occur exclusively via intermediacy of a five-membered dioxonium ion. The structures of the hydrolysis products also indicate the intermediacy of a dioxolanium ion during hydrolysis. The implications for a hypothetical biosynthesis of marine polyether toxins are discussed.

Introduction

Despite the potential synthetic utility of the epoxy ester−orthoester rearrangement, few studies have explored its mechanism. Examples of the intramolecular formation of orthoesters from epoxy esters, though few in number, have long been known in the natural products literature. Orthoesters have been isolated as unexpected products during the chemical manipulation of labdane,[1] neoclerodane,[2] and taxane diterpenoids[3] as well as during the chemical syntheses of brevicomin,[4] and muscarine.[5] This reaction has also been observed in explorations of zirconocene-catalyzed reactions.[6] More deliberate instances of the epoxy ester−orthoester rearrangement are found in biomimetic studies of natural orthoesters occurring in fungi,[7] fragrances,[8] and plants.[9] We have recently employed the epoxy ester−orthoester rearrangement in biomimetic syntheses of the natural orthoesters ortho esterol B and petuniasteroid D.[10,11] Unlike workers who have used exotic Lewis acids to effect this transformation,[6] we have found that this reaction occurs smoothly in the presence of mild protic acids such as dilute trifluoroacetic acid (TFA) in benzene or chloroform, and we have taken advantage of the stereospecificity of this reaction in a recent synthesis of 2-methylerythritol.[12] The orthoesters thus obtained are capable of subsequent orthoester-cyclic ether rearrangement to give 3-acyloxytetrahydrofurans under acidic conditions.[4,6,8a,13] We report herein experiments conducted to better understand the formation and reactivity of bicyclic orthoesters using simple model compounds.



Results

Measurement of the relative rates of the epoxy ester−orthoester rearrangement and the orthoester−cyclic

† Dedicated to Professor Carl Djerassi in celebration of his 80th birthday.

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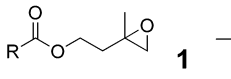
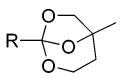
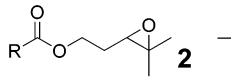
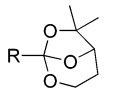
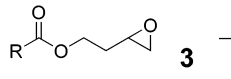
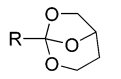
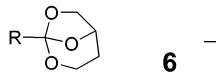
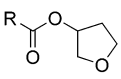
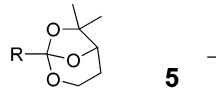
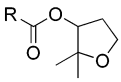
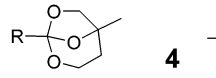
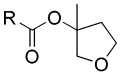
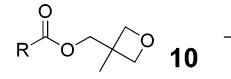
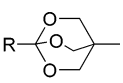
TABLE 1. Relative Rates of Rearrangement of Epoxy Esters and Orthoesters (TFA/$CDCl_3$,30 °C)[a]

		k_{rel}
 **1**	 **4**	22,000
 **2**	 **5**	5,800
 **3**	 **6**	1,300
 **6**	 **9**	160
 **5**	 **8**	69
 **4**	 **7**	23
 **10**	 **11**	1

[a] R = $PhCH_2CH_2$.

ether rearrangement was carried out by NMR kinetics in $CDCl_3$ containing varying concentrations of TFA (Table 1). Rates were measured for the rearrangements of three simple epoxy esters (**1**−**3**), as well as for the subsequent rearrangements of their resulting [3.2.1]-bicyclic orthoesters (**4**−**6**) to 3-acyloxytetrahydrofurans (**7**−**9**). For comparative purposes, the rearrangement of the 3-oxetanemethyl ester **10** to the OBO [2.2.2]bicyclic orthoester **11** was also measured. It proved experimentally difficult to obtain consistent rates for these reactions, but for comparative purposes, relative rates could be obtained by simultaneous measurements of the rearrangements of these compounds in pairs. Thus, the rate of rearrangement of the most reactive compound was measured concurrently with that of the next most reactive compound, and the rearrangement of that compound was in turn measured together with the third most reactive compound at a higher concentration of acid (Figure 1). This method was complicated by the fact that the least reactive epoxy ester **3** and most reactive orthoester **6** stand in a precursor−product relationship. The relative rates in this case were obtained by beginning the measurement of the second reaction only after less than 1% of epoxy ester **3** remained. In this way, it was possible to obtain relative rates for a series of compounds varying greatly in their reactivity (Table 1).

To compare the relative stabilities of orthoesters **4**−**6**, measurements were made of their rates of hydrolysis (Figure 2). Conditions were chosen that allowed the rates to be conveniently measured using ^1H NMR−50 mM NaOAc buffer (pH 4.75)/acetone 1:2 using deuterated solvents. The rates were measured pairwise as before, although in this case the use of a buffer provided highly consistent results. The products of the orthoester hydrolysis reactions (**12**−**20**) were identified, and the product compositions were determined before and after equilibration using 50 mM TFA/$CDCl_3$. (Table 2).

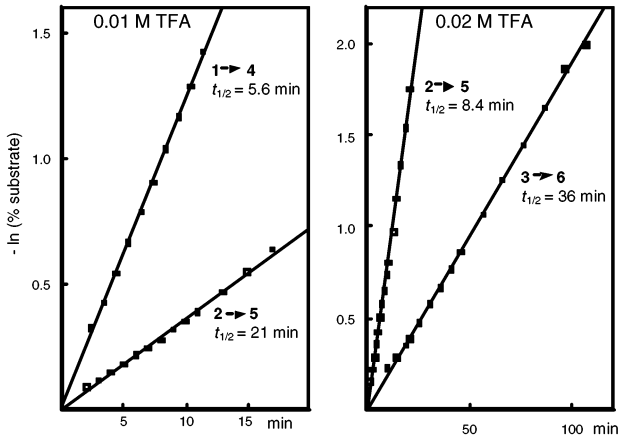


FIGURE 1. Rates of epoxy ester rearrangements (TFA/$CDCl_3$, 30 °C).

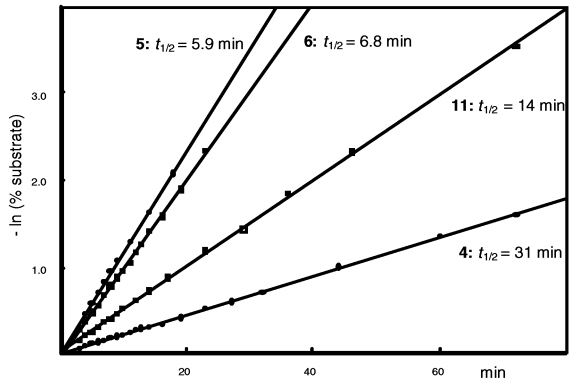


FIGURE 2. Rates of orthoester hydrolysis.

The fates of the oxygen atoms during the epoxy ester−orthoester and orthoester−cyclic ether rearrangements was investigated with ^{18}O-labeled epoxy esters and orthoesters using ^{13}C NMR spectrometry.[14]

Epoxy esters labeled in the carbonyl oxygen (**1a**−**3a**) were prepared by carbodiimide condensation of ^{18}O-labeled hydrocinnamic acid with the appropriate homoallylic alcohols, followed by peracid epoxidation (Scheme 1). All three epoxy esters showed labeling to the extent of approximately 42% as measured by integration of the ^{13}C NMR signals of the carbonyl group, with an upfield $\Delta\delta$ of 38 ppb for the ^{18}O-labeled ^{13}C signals. In the rearrangement of epoxy esters **1a** and **3a** to orthoesters **4a** and **6a**, the ^{18}O-label was found exclusively in the position connecting the orthoester carbon with the bridgehead center (Scheme 2) as shown by upfield shifts in the ^{13}C NMR signals for the bridgehead carbons ($\Delta\delta$ = 32 and 27 ppb, respectively). Upon rearrangement of epoxy ester **2a**, orthoester **5** was found to have ^{18}O-label in two different positions, with 28% ^{18}O-labeling of the bridgehead carbon (**5a**) and 14% labeling of the dimethyl substituted carbon (**5b**) ($\Delta\delta$ = 27 and 32 ppb, respectively). The ^{18}O-labeled signals of the orthoester carbons showed a 21 ppb upfield shift in all three orthoesters.

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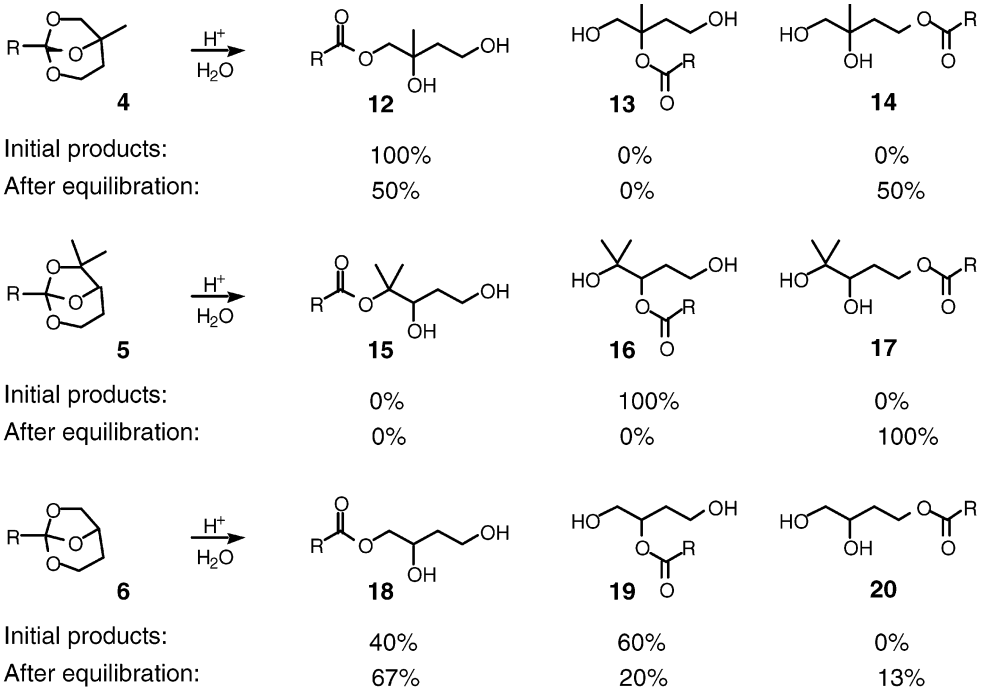
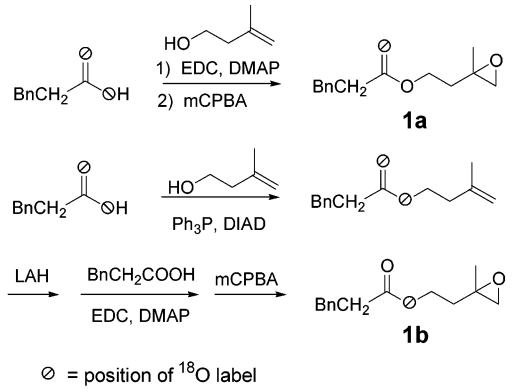
TABLE 2. Products of Orthoester Hydrolysis[a]



[a] R = $PhCH_2CH_2$.

SCHEME 1. ^{18}O-Labeling of Epoxy Ester 1



The ^{18}O-labeled orthoesters thus obtained were rearranged to 3-acyloxytetrahydrofurans (Scheme 2). Rearrangement of **4a** and **6a** led to products containing ^{18}O exclusively in the ester oxygen (**7a** and **9a**), as evident from an upfield shift of the ^{13}C NMR signal of the carbonyl groups by 12 ppb, and of the THF 3-position by 39 and 33 ppb, respectively. Upon rearrangement of the doubly ^{18}O-labeled dimethyl orthoester **5** (**5a** and **5b**), the ester oxygen of **8** was found to be 28% labeled (**8a**), and the carbonyl oxygen 14% (**8b**). The ^{13}C NMR signal of the unlabeled carbonyl carbon was accompanied by two new ^{13}C NMR signals shifted upfield by 15 and 38 ppb in a 58:28:14 ratio, respectively (Figure 3). The ester carbon of the ring showed 28% of its signal shifted upfield by 33 ppb and a smaller, poorly resolved shoulder ($\Delta\delta$ = 5 ppb) due to a two-bond ^{18}O-shift. No ^{18}O-labeling of the ether oxygen was observed in **7a**−**9a**.

To account for the fates of all three oxygen atoms in the rearrangement of **4** to **7**, it was necessary to place the ^{18}O-label in another of the three possible positions. This was achieved by first labeling the homoallylic alcohol with ^{18}O through a Mitsunobu reaction with [^{18}O]-hydrocinnamic acid, followed by LAH reduction (Scheme 1). Re-esterification with unlabeled hydrocinnamic acid, followed by epoxidation gave the epoxy ester **1b** bearing ^{18}O in the ester oxygen to the extent of 28%. The signal of the $-CH_2O-$ carbon was shifted upfield by 30 ppb, and that of the carbonyl group by 15 ppb. After rearrangement to orthoester **4b**, an upfield shift of 20 ppb was measured for the orthoester carbon, and 26 ppb for the oxymethylene group of the longer bridge in the bicyclic orthoester. Orthoester−cyclic ether rearrangement led to 28% ^{18}O-labeling in the ether oxygen of the 3-acyloxytetrahydrofuran (**7b**), as shown by upfield shifts of 18 ppb for C-2, 23 ppb for C-5, and a two-bond shift of 6 ppb for C-3. No shift was seen of the carbonyl signal.

Discussion

Rates of Rearrangement. In our prior studies,[10−12] the epoxy esters bore methyl substituents at the proximal carbon of the epoxide and rearranged with inversion at this center via 6-exo or 5-exo cyclization. Electron-donating alkyl substitutents at the epoxide reaction center are thought to promote acid-catalyzed nucleophilic substitution by stabilizing a partial positive charge in a "borderline S_N2 mechanism"[15] and have been used to direct the regioselectivity of epoxide substitution.[16−18] For this reason, it was not surprising that unsubstituted

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(16) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, *J. Org. Chem* **1985**, *50*, 5687−96.
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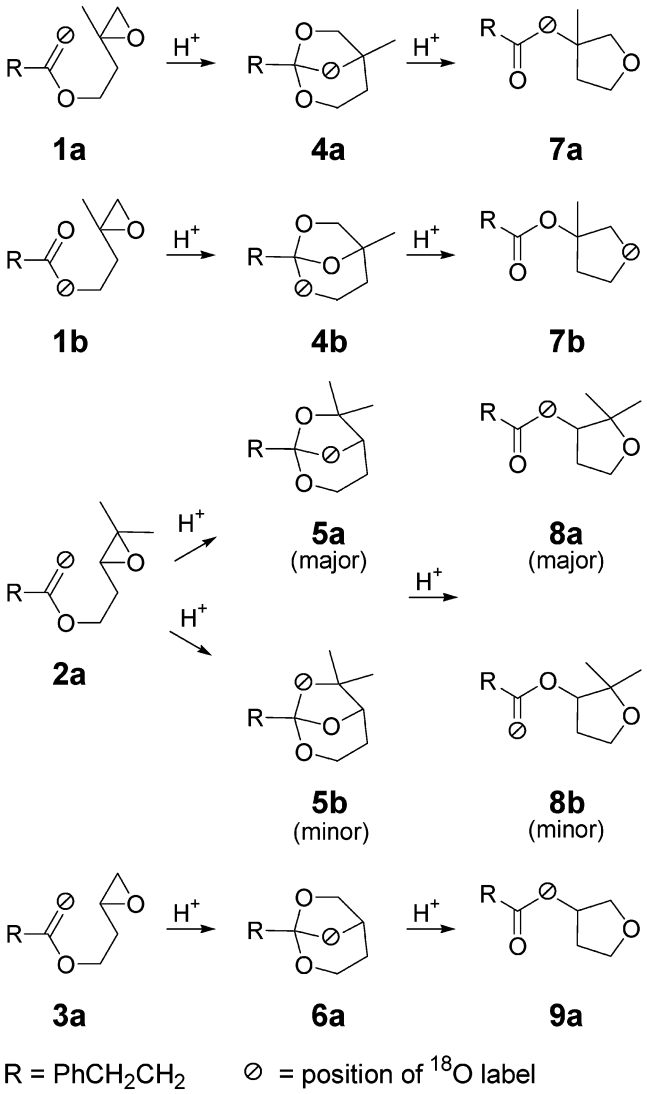
SCHEME 2. Results of ^{18}O-Labeling Experiments



epoxy ester **3** was least reactive ($k_{rel} = 1$) and the epoxy ester bearing a methyl group on the proximal carbon of the epoxide (**1**) was most reactive ($k_{rel} = 16$). More puzzling was the greater reactivity of the dimethyl epoxy ester (**2**, $k_{rel} = 4.3$) compared to the unsubstituted compound (**3**, Table 1) since the substitution is at the distal center of the epoxide. While the rate enhancement may be due in part to conformational effects resulting from methyl substitution, the electronic influence of the substituents activates this molecule to an alternative 7-endo mode of cyclization (see the discussion of ^{18}O results below).

In contrast, the influence of alkyl substitution on the orthoester−cyclic ether rearrangements appeared to be predominantly one of steric hindrance. Here, the monomethyl orthoester (**4**) was least reactive ($k_{rel} = 1$), followed by the dimethyl orthoester (**5**, $k_{rel} = 3.0$) and the unsubstituted orthoester (**6**, $k_{rel} = 7.1$).

Comparison of the rates of epoxy ester−orthoester vs orthoester−cyclic ether rearrangement for the differently

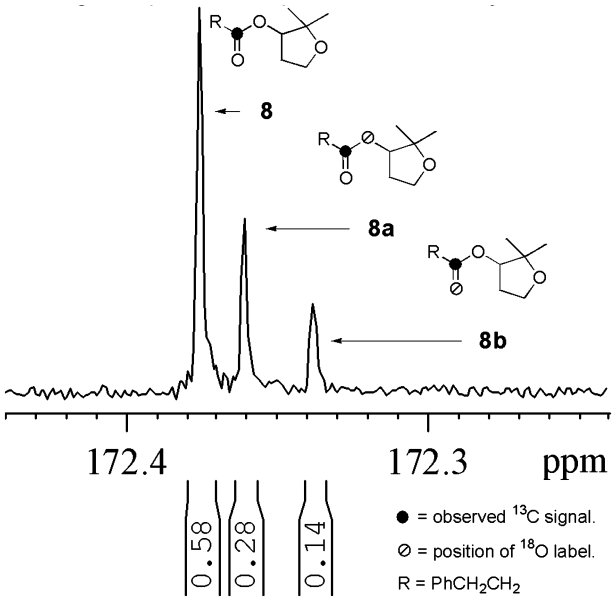


FIGURE 3. ^{13}C NMR signal (151 MHz) of the carbonyl carbon of ^{18}O-labeled **8**.

substituted substrates showed the greatest difference between the rearrangements of the monomethyl-substituted epoxy ester **1** and orthoester **4** ($k_{1\rightarrow4}$ vs $k_{4\rightarrow7} = 950$:1). In comparison, the relative rate was 83:1 for the dimethyl substituted case (**2** → **5** → **8**) and 8.2:1 without methyl substituents (**3** → **6** → **9**). Probably due to the somewhat similar reactivities of **2** and **5**, a previous study using $Cp_2ZrCl_2/AgClO_4$ as the Lewis acid catalyst failed to detect orthoester **6** upon rearrangement of epoxide **3** and only found the acyl tetrahydrofuran **9**.[6d] It is likely that with certain substrates the orthoester−cyclic ether rearrangement can become faster than the epoxy ester−orthoester rearrangement.

Comparisons can also be made between the rates of epoxy ester-orthoester rearrangements and the rate of formation of the OBO [2.2.2]bicyclic orthoester **11** from the 3-oxetanemethyl ester **10**. This rearrangement is commonly employed by synthetic chemists as a protecting group strategy to convert carboxylate groups into orthoesters which are resistant to strongly nucleophilic reagents.[19,20] Although OBO orthoester formation is typically conducted using BF_3−etherate catalysis, in this study the milder TFA catalysis was used to permit comparison with the formation of orthoester **4**, which has been proposed as an alternative to the OBO protecting group.[6] Our results show that under protic acid catalysis (TFA/$CDCl_3$) generation of the [3.2.1]bicyclic orthoester **4** is 2.2×10^4 times faster than the formation of the [2.2.2]bicyclic orthoester **11** (Table 1). The facile formation of **4**, combined with its superior stability to hydrolysis and to orthoester−cyclic ether rearrangement, indicates that bridgehead substituted [3.2.1]bicyclic orthoesters such as **4** might be preferable to OBO orthoesters (e.g., **11**) as protecting groups,[6b,c,19,20] at least in cases

(18) McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodriguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515−2523.

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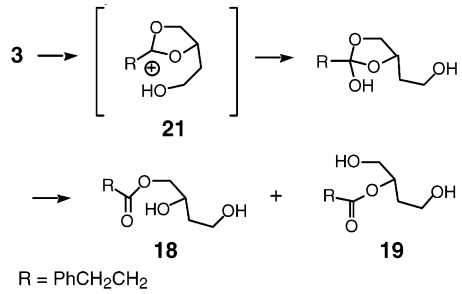
(20) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1999. (b) Kocienski, P. J. *Protecting Groups*; Thieme: New York, 2000.

where the intrinsic chirality of [3.2.1]bicyclic orthoesters is not a problem.[21]

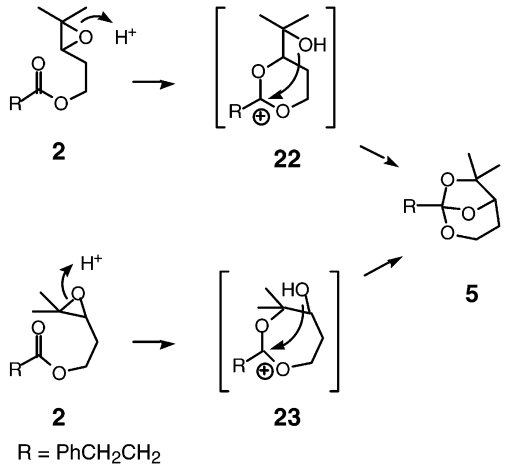
Orthoester Hydrolysis. The hydrolysis of orthoesters is one of the most thoroughly studied reactions in organic chemistry.[22] Mechanistic investigations of this reaction have provided insight into the tetrahedral intermediates in biochemically important reactions such as ester and amide hydrolysis[23,24] and have provided support for stereoelectronic theory.[25] Very few studies, however, have been reported with [3.2.1]bicyclic orthoesters.[26] Under the conditions used in this study, the rate-limiting step of hydrolysis is generally the formation of a dioxonium ion.[27,26b] As in the rearrangement reactions discussed above, no evidence was found in the NMR spectra for the accumulation of any intermediates. The rates of hydrolysis ranged from $t_{1/2} = 6-30$ min (Figure 2). The [3.2.1]-bicyclic orthoesters **5** and **6** are roughly twice as susceptible to hydrolysis as the OBO orthoester **11**, but orthoester **4** proved to be twice as resistant. The stabilizing influence of substitution at the bridgehead position apparent in orthoester **4** vis-à-vis **5** and **6** warrants further investigation. A possible reason for this effect may be that the bridgehead methyl group hinders the rotation of the pendant 2-hydroxyethyl group away from the newly formed dioxonium ion (**21**), thereby favoring the back reaction or hindering the approach of water (Scheme 3).

While the C_3 symmetric [2.2.2]bicyclic OBO orthoester **11** yields only one product upon hydrolysis, there are three possible products for each of the [3.2.1]bicyclic orthoesters (Table 2, **12**−**20**). The observed products are best explained by the intermediacy of a five-membered dioxonium ion (**21**) (Scheme 3). This is most evident in the 3:2 ratio of **18** and **19** in the hydrolysis of orthoester **6**. Even though tertiary esters (**13** and **15**) were not detected in the hydrolysis reactions of orthoesters **4** and **5**, the observed products (**12** and **16**) also fit this pattern. In a previous study using the benzoate analog (R = Ph) of orthoester **6**, the sole hydrolysis product was reported to be the secondary ester **19** (R = Ph).[26c] If this result is correct, the different product preference may be due to an electronic effect of the phenyl substitutent.[28]

SCHEME 3. Proposed Hydrolysis Mechanism for [3.2.1]Bicyclic Orthoesters



SCHEME 4. Alternate Pathways of Epoxy Ester−Orthoester Rearrangement



Equilibration of the initial products of orthoester hydrolysis by acid-catalyzed intramolecular transesterification led to more complex mixtures derived from **4** and **6** (Table 2). For synthetic applications of orthoesters,[12,29] it may therefore be useful to carry out orthoester hydrolysis under buffered conditions where simpler product mixtures are obtained. It is noteworthy that the secondary ester (**16**) obtained from the hydrolysis of **5** could be equilibrated exclusively to the primary ester (**17**).

^{18}O Studies. The ^{18}O-labeling experiments provide insight into the course of the rearrangement reactions (Scheme 2). The rearrangements of ^{18}O-labeled epoxy esters **1a** and **3a** to orthoesters **4a** and **6a** were found to occur entirely via 6-exo cyclization to an intermediate six-membered dioxonium ion. However, the rearrangement product of ^{18}O-labeled epoxy ester **2a** showed ^{18}O-label in two positions (**5a** and **5b**), indicating a 2:1 ratio of 6-exo and 7-*endo* cyclization pathways (Scheme 4). The pathway via the six-membered dioxonium ion **22** remains preferred; however, 7-endo cyclization via a seven-membered dioxonium ion **23** is also observed, apparently because alkyl substitution activates the distal center of

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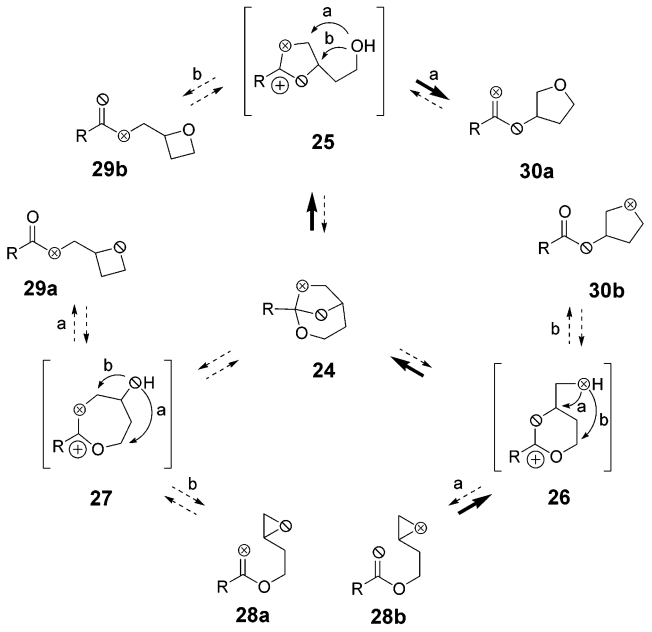
SCHEME 5. Possible Routes of Orthoester−Cyclic Ether Rearrangement Showing the Fates of the Three Orthoester Oxygen Atoms, As Depicted for a General Unsubstituted [3.2.1]Bicyclic Orthoester[a]



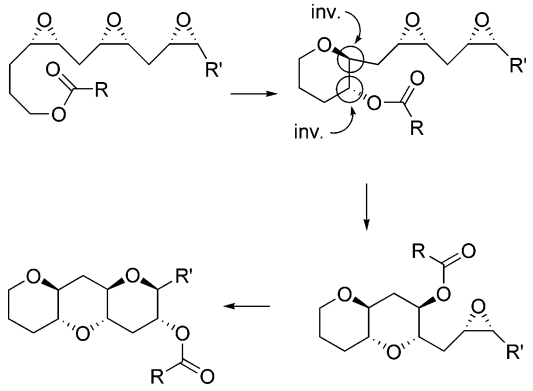
[a] Bold arrows indicate the major reaction pathways observed in these studies.

the intermediate protonated epoxide by stabilizing a partial positive charge.[15−18]

The possible mechanisms of orthoester−cyclic ether rearrangement are somewhat more complicated. To demonstrate the mechanistic course of orthoester−cyclic ether rearrangement, it was insufficient to follow the oxygen atom in the short bridge of a [3.2.1]bicyclic orthoester (**24**, Scheme 5), since its location in the product (**30a** or **30b**) would be the same whether the reaction went through a five-membered (**25**) or a six-membered dioxonium ion (**26**). The fates of all three oxygen atoms, however, could be unambiguously determined by following two of the three oxygen atoms. Thus, rearrangement of the doubly labeled dimethyl orthoester (**5a** and **5b**) can be shown to proceed via the intermediacy of a five-membered dioxonium ion. The reaction follows the same course for the monomethyl orthoester, as shown by the rearrangements of **4a** and **4b**. This evidence contradicts Wipf's depiction of a six-membered dioxonium ion intermediate[6a−c] and agrees with Coxon's interpretations.[13]

In principle, a [3.2.1]bicyclic ortho ester in the presence of acid could be in equilibrium with three different dioxonium ions (**25**−**27**, Scheme 5), and each of these can possibly undergo reversible intramolecular displacement reactions leading to the formation of three different cyclic ethers—an epoxide, an oxetane, or a tetrahydrofuran (**28**−**30**). On the basis of ^{18}O-labeling, no evidence was found for equilibration. Equilibration of orthoester **24** with epoxide **28** could only occur without scrambling of the label if the forward and reverse reactions pass through the same intermediate dioxonium ion (e.g., **24** → **26** → **28b** → **26** → **24**). This rules out the transient formation of epoxide **1** via a seven-membered dioxonium ion during the rearrangement of orthoester **4**. In the case

SCHEME 6. Stereochemical Interrelationships for the Hypothetical Biosynthesis of Marine Polyethers via Epoxy Ester−Orthoester−Cyclic Ether Rearrangements



of the possible equilibration of orthoester **5** with epoxide **2**, even a mechanism involving a common intermediate in the forward and reverse reactions can be ruled out since the rearrangement of epoxide **2** to orthoester **5** takes place by a mixture of 6-exo and 7-endo pathways, and the ratio of ^{18}O in doubly labeled orthoester **5** was found unchanged in THF **8**. Reversibilty in the formation of the tetrahydrofurans (e.g., **30**) is unlikely under our reaction conditions, although it may be possible in the presence of strong Lewis acids, based on acyl group participation during $TiCl_4$-catalyzed THF ring hydrolysis.[30] Oxetanes (**29**) are expected to exhibit reactivities intermediate between epoxides and tetrahydrofurans. Because other oxetanyl esters have been shown to rearrange to [2.2.2]- and [2.2.1]bicyclic orthoesters,[19,31] the possible equilibrium between orthoester **24** and oxetane **29** will most probably lie on the side of the [3.2.1]-bicyclic orthoester (**24**).

Biosynthetic Implications. To what extent does the epoxy ester−orthoester−cyclic ether rearrangement operate in nature? We are aware of only one instance in which a natural cyclic ether has been proposed to arise by this route,[8a] although the ubiquity of epoxides, esters, and acid catalysis suggests that this pathway should be of biosynthetic relevance. We have recently proposed that the oxetane ring of Taxol may originate in this way[31] and would like to speculate here that an iterative version of this mechanism may play a role in the formation of marine polyethers such as brevetoxin. This proposal differs in its stereochemical requirements from the Cane−Westley proposal[32] insofar as the tandem epoxy ester−orthoester−cyclic ether rearrangements proceed with stereochemical inversion at both centers of the epoxide (Scheme 6). Accordingly, the biosynthetic polyepoxy precursor of an all-trans fused polycyclic polyether would be required to have an *all-Z*-conguration, as is also required for the polyolefin precursor if the cyclization occurs according to the Townsend proposal.[33]

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Summary

The epoxy ester−[3.2.1]bicyclic orthoester rearrangement was shown by ^{18}O-labeling to proceed by predominantly via 6-exo cyclization. Competing cyclization by a 7-endo route was noted in a case where methyl substitution activates the distal epoxide reaction center in accordance with a "borderline S_N2 mechanism".[15] Also in accordance with this effect, kinetics measurements showed that the presence of methyl substitution at the proximal center of epoxide **1** leads to a 16-fold acceleration in epoxy ester rearrangement compared to the unsubstituted case. On the other hand, the product of this reaction (orthoester **4**) is stablized by methyl substitution of the bridgehead position, resulting in a greater stability toward acidic hydrolysis. Since the rate of formation of ortho ester **4** was 22 000 times faster than that of the OBO [2.2.2]bicyclic orthoester **11**, and the stability of **4** toward aqueous acid is double that of **11**, the "ABO" bicyclic orthoester (e.g., **4**)[6] appears to be an attractive alternative to Corey's OBO protecting group (e.g., **11**)[13]—at least in cases where its intrinsic chirality is not a problem. The use of exotic zirconocene Lewis acids,[6] however, seems unnecessary, since low concentrations of Brönsted acids (e.g., TFA in benzene or chloroform) provide effective catalysis.

The orthoester−cyclic ether rearrangement was shown by ^{18}O-labeling to proceed entirely via a five-membered cyclic dioxonium ion. The net stereochemical consequence of tandem epoxy ester−orthoester−cyclic ether rearrangement is therefore generally inversion of configuration at both centers of the epoxide ring. A five-membered cyclic dioxonium ion was also indicated in the hydrolysis of the [3.2.1]bicyclic orthoesters.

Experimental Section

^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. NMR assignments are based on DEPT, HMBC, and HSQC experiments. The known epoxy esters **1** and **3**, orthoester **4**, and tetrahydrofuran **9**[6d] were prepared as described for epoxy ester **2**, orthoester **5**, and tetrahydrofuran **8**. The NMR data were in agreement with the published values.

3,4-Epoxy-4-methylpentyl Hydrocinnamate (2). To a stirred solution of 4-methyl-3-penten-1-ol (1.0 g, 10 mmol) in 15 mL of CH_2Cl_2 containing 2.0 mL of pyridine was added dihydrocinnamoyl chloride (2.0 mL, 13 mmol). After 1 h at rt, the reaction mixture was diluted with 30 mL of hexane/EtOAc 2:1 and extracted sequentially with 15 mL portions of saturated aqueous $NaHCO_3$, 5% hydrochloric acid, saturated aqueous $NaHCO_3$, and brine. After drying over Na_2SO_4, the solvents were evaporated under reduced pressure to give 2.07 g (8.9 mmol, 89% yield) of 4-methyl-3-pentenyl hydrocinnamate. ^1H NMR (300 MHz): 7.32−7.16 (5H, m), 5.08 (1H, br t, J = 7.8 Hz), 4.04 (2H, t, J = 7.1 Hz), 2.96 (2H, t, J = 7.8 Hz), 2.63 (2H, t, J = 7.8 Hz), 2.31 (2H, br q, J = 7.1 Hz), 1.71 (3H, s), 1.62 (3H, s). ^{13}C NMR (75 MHz): 172.9, 140.6, 134.6, 128.4, 128.3, 126.2, 119.2, 64.1, 35.9, 31.0, 27.6, 25.7, 17.7.

A stirred solution of 4-methyl-3-pentenyl hydrocinnamate (0.30 g, 1.29 mmol) in 15 mL of dichloromethane was treated with 470 mg (1.9 mmol) of *m*-CPBA (75%) at rt. After 45 min, the reaction was quenched with 5 mL of 5% NaOH and extracted with 20 mL hexane/EtOAc 2:1. The organic layer was extracted with 15 mL of 5% NaOH and, 20 mL of brine and dried over Na_2SO_4. The solvents were removed under reduced pressure to give 311 mg (1.25 mmol, 97% yield) of product. ^1H NMR: 7.31−7.26 (2H, m), 7.22−7.18 (3H, m), 4.27−4.18 (2H, m), 2.96 (2H, t, J = 7.8 Hz), 2.75 (1H, t, J = 6.2 Hz), 2.65 (2H, t, J = 7.8 Hz), 1.91−1.83 (1H, m), 1.83−1.77 (1H, m), 1.30 (3H, s), 1.26 (3H, s). ^{13}C NMR: 172.7, 140.3, 128.4, 128.2, 126.2, 61.7, 61.1, 58.0, 35.7, 30.8, 28.4, 24.6, 18.7. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.56; H, 8.12. Found: C, 72.31; H, 7.98.

Epoxy Esters Bearing ^{18}O in the Carbonyl Group (1a−3a). To a solution of hydrocinnamoyl chloride (168 mg, 1 mmol) in 2 mL of dry dichloromethane was added 18 μL of H_2O (1 mmol, 97 atom % ^{18}O), followed by 418 μL of dry triethylamine (3 mmol) and 4-(dimethylamino)pyridine (12 mg, 0.1 mmol). After standing overnight, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (192 mg, 1 mmol) and 128 μL of 4-methyl-3-penten-1-ol (1.1 mmol) were added, and the mixture allowed to react for 7 h. The mixture was partitioned between ether and water, and the ether layer was dried with Na_2SO_4 and concentrated under a stream of nitrogen. The crude product was purified by silica gel chromatography (hexane/EtOAc 19:1) to yield 4-methyl-3-pentenyl hydrocinnamate (78.3 mg, 34%) bearing ^{18}O in the carbonyl group to the extent of 42%. Epoxidation as described above gave ^{18}O-labeled epoxy ester **2a**. Epoxy esters **1a** and **3a** were prepared in the same way.

3,4-Epoxy-3-methylbutyl Hydrocinnamate Bearing ^{18}O in the Ester Oxygen (1b). To a solution of ^{18}O-labeled hydrocinnamic acid prepared as above (42 mg, 0.28 mmol), 200 μL of 3-methyl-3-buten-1-ol (2 mmol), and triphenylphosphine (132 mg, 0.5 mmol) in 2 mL of dry THF, was slowly added a solution of diisopropylazodicarboxylate (100 μL, 0.51 mmol) in 1 mL of dry THF. After standing overnight, the reaction mixture was purified by silica gel chromatography (hexane/EtOAc 19:1) to yield 3-methyl-3-butenyl hydrocinnamate (47.2 mg, 77%) bearing ^{18}O in both positions of the carboxyl group. The ester was treated with 25 mg of LAH (0.66 mmol) in 5 mL of dry ether. After 3 min, the reaction was quenched with a few drops of brine and filtered through a short column of silica gel. The ether solution was diluted with 5 mL of dichloromethane, and unlabeled hydrocinnamic acid (155 mg, 1.03 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (200 mg, 1.04 mmol), and 4-(dimethylamino)-pyridine (24 mg, 0.20 mmol) were added. After standing overnight, the mixture was partitioned between ether and dilute HCl, dilute NaOH, and brine. The ether layer was dried with Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc 19:1) gave 3-methyl-3-butenyl hydrocinnamate (42.0 mg, 89%) bearing ^{18}O in the ester position to the extent of 28%. Epoxidation as described above gave ^{18}O-labeled epoxy ester **1b**.

4-Methyl-1,3,4-pentanetriol 3-Phenylorthopropionate (5). To a dry NMR tube was added 21.9 mg (0.09 mmol) of **2**, diluted to 665 μL with $CDCl_3$ (filtered through neutral alumina and dried over 3 Å molecular sieves), and treated with 35 μL of 1.0 M TFA in $CDCl_3$. The tube was shaken vigorously and monitored by ^1H NMR. Upon completion, the reaction was quenched by the addition of ca. 50 μL of TEA. The reaction mixture was purified by preparative TLC (1% TEA in hexane/EtOAc 4:1) to yield 20.3 mg of **5** (0.08 mmol, 93%). ^1H NMR: 7.29−7.25 (2H, m, Ph), 7.21 (2H, d, J = 7.4 Hz, Ph), 7.17 (1H, t, J = 7.3 Hz, Ph), 4.21 (1H, dt, J = 4.7, 11.9 Hz, C-1), 4.05 (1H, d, J = 3.7 Hz, C-3), 3.86 (1H, dd, J = 7.5, 11.3 Hz, C-1), 2.81 (2H, dd, J = 6.9, 10.8 Hz, $PhCH_2$), 2.32−2.24 (1H, m, C-2), 2.17−2.06 (2H, m, CH_2CO_3), 1.60 (1H, dd, J = 4.7, 14.0 Hz, C-2), 1.50 (3H, s, Me), 1.34 (3H, s, Me). ^{13}C NMR: 141.8 (Ph), 128.3 (Ph), 128.3 (Ph), 125.8 (Ph), 119.6 (CO_3), 80.8 (C-4), 79.2 (C-3), 58.7 (C-1), 38.1 (CH_2CO_3), 29.7 ($PhCH_2$), 27.4 (Me), 24.9 (C-2), 20.3 (Me). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.56; H, 8.12. Found: C, 72.34; H, 8.04.

1,2,4-Butanetriol 3-Phenylorthopropionate (6). The reaction of 27 mg of epoxy ester **3** (0.12 mmol) in 0.7 mL of 0.05 M TFA in $CDCl_3$ was followed by ^1H NMR. When approximately one-third of **3** remained, the reaction was

quenched by the addition of 3 drops of TEA and purified by preparative TLC (hexane/EtOAc 2:1) to give 8 mg of recovered **3** and 18 mg of **6** (0.08 mmol, 66%). ^{1}H NMR: 7.29−7.24 (2H, m, Ph), 7.21 (2H, d, J = 7.3 Hz, Ph), 7.17 (1H, t, J = 7.4 Hz, Ph), 4.68−4.66 (1H, br m, C-2), 4.13 (1H, dt, J = 4.3, 11.8 Hz, C-4), 4.10 (1H, d, J = 7.4 Hz, C-1), 3.97−3.93 (1H, m, C-1), 3.87 (1H, dd, J = 6.7, 11.4 Hz, C-4), 2.80 (2H, dd, J = 6.3, 11.0 Hz, $PhCH_2$), 2.35−2.28 (1H, br m, C-3), 2.18−2.13 (2H, m, CH_2CO_3), 1.41 (1H, ddd, J = 2.3, 3.8, 13.5 Hz, C-3). ^{13}C NMR: 141.7 (Ph), 128.3 (Ph), 128.3 (Ph), 125.8 (Ph), 119.8 (CO_3), 73.0 (C-2), 69.0 (C-1), 58.6 (C-4), 37.1 (CH_2CO_3), 29.6 ($PhCH_2$), 28.3 (C-3). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.90; H, 7.32. Found: C, 70.68; H, 7.19.

3-Methyl-3-tetrahydrofuranyl Hydrocinnamate (7). Acid-catalyzed isomerization of **4** was carried out as described for **5** using 0.2 M TFA in $CDCl_3$. ^{1}H NMR: 7.31−7.27 (2H, m, Ph), 7.23−7.18 (3H, m, Ph), 3.99 (1H, d, J = 10.0 Hz, C-2), 3.88−3.79 (2H, m, C-5), 3.71 (1H, d, J = 10.0 Hz, C-2), 2.92 (2H, t, J = 7.8 Hz, $PhCH_2$), 2.60 (2H, t, J = 7.8 Hz, CH_2CO_2), 2.33 (1H, ddd, J = 1.9, 7.0, 13.5 Hz, C-4), 1.97 (1H, dt, J = 13.5, 8.0 Hz, C-4), 1.57 (3H, s, Me). ^{13}C NMR: 172.4 (C═O), 140.3 (Ph), 128.4 (Ph), 128.3 (Ph), 126.2 (Ph), 86.4 (C-3), 77.4 (C-2), 67.2 (C-5), 39.3 (C-4), 36.5 (CH_2CO_2), 30.9 ($PhCH_2$), 22.0 (Me). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.78; H, 7.74. Found: C, 71.86; H, 7.69.

2,2-Dimethyl-3-tetrahydrofuranyl Hydrocinnamate (8). Acid-catalyzed isomerization of **5** was carried out using 0.1 M TFA in $CDCl_3$. Evaporation of the solvent gave **8** in quantitative yield. ^{1}H NMR: 7.31−7.26 (2H, m, Ph), 7.22−7.17 (3H, m, Ph), 4.99 (1H, dd, J = 2.7, 6.3 Hz, C-3), 3.91 (1H, dt, J = 8.2, 7.7 Hz, C-5), 3.85 (1H, dt, J = 4.8, 8.6 Hz, C-5), 2.96 (2H, t, J = 7.7 Hz, $PhCH_2$), 2.67 (2H, t, J = 7.7 Hz, CH_2CO_2), 2.39−2.33 (1H, m C-4), 1.87−1.81 (1H, m C-4), 1.19 (3H, s, Me), 1.14 (3H, s, Me). ^{13}C NMR: 172.4 (C═O), 140.3 (Ph), 128.5 (Ph), 128.3 (Ph), 126.3 (Ph), 81.8 (C-2), 79.1 (C-3), 64.5 (C-5), 35.9 (CH_2CO_2), 32.4 (C-4), 30.9 ($PhCH_2$), 26.0 (Me), 21.8 (Me). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.56; H, 8.12. Found: C, 72.39; H, 8.06.

3-Methyl-3-oxetanylmethyl hydrocinnamate (10).[34] Esterification of 3-methyl-3-oxetanemethanol with dihydrocinnamoyl chloride was carried out as described for **2**. ^{1}H NMR: 7.31−7.26 (2H, m), 7.22−7.18 (3H, m), 4.45 (2H, d, J = 5.9 Hz), 4.34 (2H, d, J = 5.9 Hz), 4.15 (2H, s), 2.97 (2H, d, J = 7.7 Hz), 2.69 (2H, d, J = 7.7 Hz), 1.28 (3H, s). ^{13}C NMR (75 MHz): 172.9, 140.3, 128.5, 128.2, 126.3, 79.5, 68.7, 39.0, 21.1.

2-Hydroxymethyl-2-methyl-1,3-propanediol 3-phenylorthopropionate (11).[34,35] Acid-catalyzed isomerization of **10** was carried out as described for **5** using 0.5 M TFA in $CDCl_3$. ^{1}H NMR: 7.28−7.24 (2H, m), 7.21−7.14 (3H, m), 3.93 (6H, s), 2.79−2.74 (2H, m), 2.00−1.96 (2H, m), 0.82 (3H, s). ^{13}C NMR (75 MHz): 141.9, 128.4, 128.3, 125.7, 108.7, 72.6, 38.5, 30.3, 29.6, 14.5.

3-Hydroxy-2-hydroxymethyl-2-methylpropyl hydrocinnamate. Hydrolysis of orthoester **10** (8.6 mg, 0.04 mmol) was carried out in a 2:1 mixture of acetone-d_6 and 50 mM NaOAc/D_2O pH 4.75 buffer. When ^{1}H NMR analysis showed the reaction to be complete, the acetone was removed with a stream of N_2, and the mixture was partitioned beween saturated aqueous $NaHCO_3$ and Et_2O. The crude product was purified by preparative TLC (hexane/EtOAc 1:2) to yield 9.0 mg (0.04 mmol, 97%). ^{1}H NMR: 7.32−7.27 (2H, m), 7.23−7.19 (3H, m), 4.17 (2H, s), 3.49 (2H, dd, J = 3.2, 11.5 Hz), 3.41 (2H, dd, J = 4.2, 11.5 Hz), 2.97 (2H, t, J = 7.6 Hz), 2.70 (2H, t, J = 7.6 Hz), 2.59 (2H, br s), 0.77 (3H, s). ^{13}C NMR: 173.9, 140.1, 128.6, 128.2, 126.4, 67.6, 66.6, 40.7, 35.8, 31.0, 16.7.

2-Methylbutane-1,2,4-triol 1-Hydrocinnamate (12). Hydrolysis of orthoester **4** as above gave **12**. ^{1}H NMR: 7.32−7.27 (2H, m), 7.23−7.19 (3H, m), 4.01 (1H, d, J = 11.2 Hz), 4.00 (1H, d, J = 11.2 Hz), 3.91−3.85 (1H, m), 3.83−3.78 (1H, m), 2.98 (2H, t, J = 7.6 Hz), 2.81 (1H, br s), 2.71 (2H, t, J = 7.6 Hz), 2.41 (1H, br s), 1.77 (1H, ddd, J = 4.5, 7.8, 14.7 Hz), 1.62 (1H, ddd, J = 4.1, 6.7, 14.7 Hz), 1.20 (3H, s). ^{13}C NMR: 172.9, 140.2, 128.6, 128.2, 126.4, 72.4, 71.0, 59.3, 39.0, 35.7, 30.9, 24.3.

4-Methylpentane-1,3,4-triol 3-Hydrocinnamate (16). Hydrolysis of orthoester **5** as above gave **16**. ^{1}H NMR: 7.32−7.27 (2H, m), 7.23−7.19 (3H, m), 4.87 (1H, dd, J = 2.9, 9.9 Hz), 3.59 (1H, dt, J = 11.7, 4.7 Hz), 3.34 (1H, ddd, J = 3.4, 10.0, 11.6 Hz), 2.99 (2H, t, J = 7.6 Hz), 2.75 (2H, t, J = 7.6 Hz), 1.95−1.87 (1H, m), 1.69−1.62 (1H, m), 1.17 (3H, s), 1.15 (3H, s). ^{13}C NMR: 173.6, 140.0, 128.6, 128.2, 126.4, 77.2, 71.3, 58.3, 35.7, 32.2, 30.9, 26.1, 25.4.

4-Methylpentane-1,3,4-triol 1-Hydrocinnamate (17). Treatment of **16** for 21 h at room temperature with 50 mM TFA/$CDCL_3$ yielded **17** in quantitative yield. ^{1}H NMR: 7.31−7.27 (2H, m), 7.22−7.18 (3H, m), 4.37 (1H, ddd, J = 4.9, 9.3, 11.0 Hz), 4.18 (1H, ddd, J = 4.8, 6.0, 11.1 Hz), 3.32 (1H, d, J = 10.7), 2.96 (2H, t, J = 7.7 Hz), 2.66 (2H, t, J = 7.7 Hz), 2.54 (1H, br s), 1.93 (1H, br s), 1.82−1.76 (1H, m), 1.62−1.54 (1H, m), 1.18 (3H, s), 1.14 (3H, s). ^{13}C NMR: 173.4, 140.3, 128.5, 128.4, 126.4, 74.6, 72.6, 62.0, 35.8, 30.9, 30.8, 26.3, 23.4.

Butane-1,2,4-triol 1-Hydrocinnamate (18). Hydrolysis of orthoester **6** as above gave **18**−**20**. Only partial separation could be achieved by TLC. Their NMR data were obtained from a combination of difference spectra and 2D NMR methods (HMBC and HSQC). ^{1}H NMR: 7.32−7.19 (5H, m), 4.13 (1H, d, J = 8.0 Hz), 4.04−4.00 (2H, m), 3.88−3.79 (2H, m), 2.97 (2H, t, J = 7.7 Hz), 2.69 (2H, t, J = 7.7 Hz), 2.57 (1H, br s), 2.10 (1H, br s), 1.69−1.64 (2H, m). ^{13}C NMR: 173, 140, 128, 128, 126, 69.6, 68.5, 60.9, 34.7, 36, 31.

Butane-1,2,4-triol 2-Hydrocinnamate (19). ^{1}H NMR: 7.32−7.19 (5H, m), 5.07−5.02 (1H, m), 3.70−3.60 (3H, m), 3.47 (1H, ddd, J = 4.0, 9.3, 11.6 Hz), 2.98 (2H, t, J = 7.6 Hz), 2.71 (2H, t, J = 7.6 Hz), 2.18 (1H, br s), 1.91 (1H, br s), 1.86−1.79 (1H, m), 1.77−1.70 (1H, m). ^{13}C NMR: 173, 140, 128, 128, 126, 72.9, 64.6, 58.3, 36, 33.7, 31.

Butane-1,2,4-triol 4-Hydrocinnamate (20). ^{1}H NMR: 7.32−7.19 (5H, m), 4.36 (1H, ddd, J = 4.9, 8.9, 11.3 Hz), 4.15 (1H, dt, J = 11.3, 5.4 Hz), 3.66−3.58 (2H, m), 3.46−3.40 (1H, m), 2.96 (2H, t, J = 7.8 Hz), 2.66 (2H, t, J = 7.8 Hz), 2.51 (1H, br s), 1.88 (1H, br s), 1.75−1.63 (2H, m). ^{13}C NMR: 173, 140, 128, 128, 126, 68.9, 66.6, 61.2, 36, 32.3, 31.

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Supporting Information Available: General procedures for NMR kinetics. Graphs for the rearrangements of **4**−**6** and **10**. Spectra of selected ^{13}C NMR signals for ^{18}O-labeled compounds **2a**, **5a**,**b**, **7a**,**b**, **8a**,**b**, and **9a**. 2D NMR spectra (HMBC) for **5**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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