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Radical Reduction of Epoxides Using a Titanocene(III)/Water System: Synthesis of β-Deuterated Alcohols and Their Use as Internal Standards in Food Analysis

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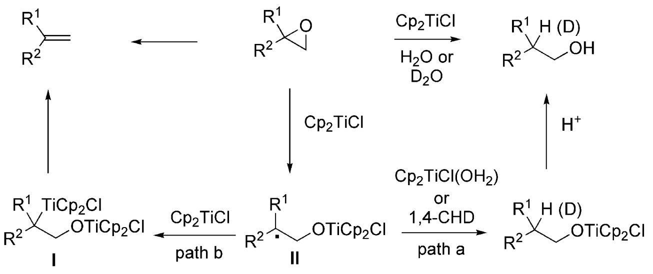
We describe a comprehensive study into the Cp_2TiCl-mediated reductive epoxide ring opening using either water as a hydrogen source or deuterium oxide as a deuterium source. The remarkable chemical profile of this reaction allows access to alcohols with anti-Markovnikov regiochemistry from different epoxides. The use of D_2O as a deuterium source leads to an efficient synthesis of β-deuterated alcohols, including a deuterated sample of tyrosol, a bioactive compound contained in the leaves of the olive, which was successfully applied as an internal standard in food analysis.

Introduction

In the early 1990s, RajanBabu and Nugent described the synthesis of alcohols from epoxides mediated by a titanium(III) complex (Cp_2TiCl) in the presence of 1,4-cyclohexadiene (1,4-CHD), a common hydrogen-atom donor.[1] This protocol usually yields less-substituted alcohols under mild reaction conditions (Scheme 1, path a).[1,2] Nevertheless, their reported yields ranged from excellent (95%) to poor (6%), depending upon the substitution pattern of the starting epoxides, which tended to limit the synthetic viability of this procedure. In the reduction reaction of monosubstituted epoxides the deoxygenating side reaction generally becomes the preferred pathway (Scheme 1, path b). Another limitation of this transformation is the toxic, expensive, and/or foul-smelling nature of the hydrogen-atom donor used, such as 1,4-CHD, Bu_3SnH, or *tert*-butyl thiol. Although the reaction was improved by Gansäuer et al.,[2] its main drawbacks remain.

We reported in a recent publication that water, a ubiquitous source of hydrogen atoms, can transfer hydrogen atoms to carbon-centered radicals in the presence of titanocene(III) complexes.[3] To explain this process, we assume that (aqua)titanocene(III) complexes, generated in situ, are the real hydrogen-atom donors. This idea is supported by theoretical calculations,[3] and Newcomb et al. have determined a rate constant of 1.0×10^5 $\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ for the reduction of secondary radicals by titanocene(III)/water mixtures[4a] that is only one order of magnitude lower than that corresponding to $HSnBu_3$ ($k = 1.4 \times 10^6$ $\mathrm{M}^{-1}\,\mathrm{s}^{-1}$).[4b]



Scheme 1. Radical epoxide opening mediated by Cp_2TiCl.

The use of water as a safe, inexpensive alternative to conventional hydrogen-atom donors in this transformation entails advantages from both practical and economic points of view. It is also worth noting that the use of deuterium oxide, a relatively inexpensive, commercially available deuterium source,[5] affords β-deuterated alcohols, which are not easily obtained by other methods, in a very simple and straightforward way.[6]

Additionally, the use of water can also overcome the formation of undesired deoxygenated compounds. The formation of these byproducts is commonly related to the presence of bimetallic species **I** in the reaction medium (Scheme 1), which are derived from a heterocoupling radical process between carbon-centered radical **II** and Cp_2TiCl. This process can, therefore, be avoided by lower-

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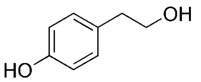
ing the concentration of free Cp_2TiCl and by increasing the concentration of the hydrogen-atom-transfer (HAT) reagent. Within this context, we have recently reported that titanocene(III) reacts almost quantitatively with water to form an aqua complex, which consequently decreases the concentration of free Cp_2TiCl.[3]

In view of all these precedents we have focused our study upon the remarkable capacity of titanocene(III)/water mixtures to synthesize alcohols by the reductive radical opening of epoxides. We also describe an easy, efficient synthesis of β-deuterated alcohols by using D_2O as a deuterium-atom source. These deuterated derivatives, which present almost the same physical and chemical properties as their non-deuterated analogues, have many potential applications. For example, they are used as internal standards in the analysis of complex mixtures, which is of great interest to the food and pharmaceutical industries.[7] They are also used in the study of mechanisms, kinetics, and metabolic routes in chemistry and biochemistry.[8] Therefore, the development of simple and efficient methods to introduce deuterium atoms into organic molecules is an important goal in organic synthesis.[8]

Olive leaves have traditionally been used as a folk remedy for combating fevers and other diseases such as malaria and thus the characterization, biosynthesis, and biotransformation of phenolic and other polar compounds from the leaves and fruit of the olive tree is of considerable interest nowadays in research into natural plant profiles. With this in mind, we also report on an initial study into the use of a β-deuterated alcohol, synthesized according to the method described here, as an internal standard in the analysis of extracts from olive-tree leaves.

We initially turned our attention to tyrosol (**1**, Scheme 2), a phenolic antioxidant that has been related to lower the incidence of heart disease and certain cancers.[9] For our needs we chose high-performance liquid chromatography (HPLC) allied with mass spectrometry (MS) detection, using electrospray ionization (ESI) as an interface, because of its extremely efficient resolution and characterization of a wide range of polar compounds.

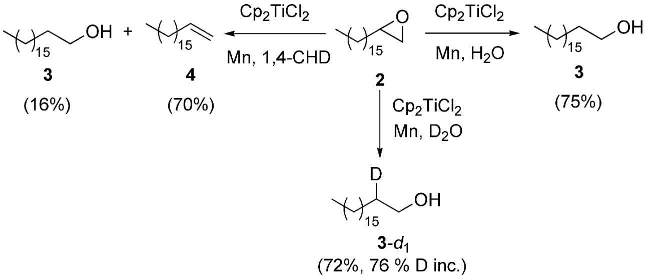


1

Scheme 2. Chemical structure of tyrosol (**1**).

Results and Discussion

Initially we chose simple monosubstituted epoxide **2** to find the best reaction conditions for this transformation despite the fact that it is considered an unsuitable substrate for the reduction reaction. In fact, when we reduced epoxide **2** under the conditions described by RajanBabu and Nugent[1] using 1,4-CHD as the hydrogen-atom donor, we obtained desired alcohol **3** at a yield of only 16% (Scheme 3). The main product was alkene **4** (70%), which is derived from a deoxygenation reaction.[10] A 75% yield of alcohol **3** could be obtained on the other hand under our aqueous conditions by using an optimized mixture of Cp_2TiCl_2 (2.5 equiv.), Mn dust (8 equiv.), and water (10 equiv.; Scheme 3).[11] It is worth noting that under these new conditions alkene **4** was not detected. These results support the idea that our procedure is safer, cheaper, and more efficient than that of RajanBabu and Nugent[1] for this kind of substrate and thus overcomes some of their main drawbacks. Epoxide **2** can also be deuterated with our protocol by using deuterium oxide instead of water. Both the yield (72%) and incorporation of deuterium (76%) obtained indicate that this process represents an efficient way of preparing β-deuterated alcohols.

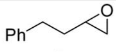
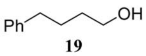
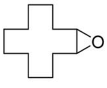
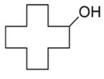
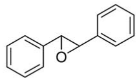
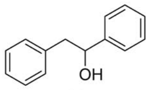
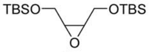
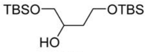
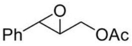
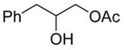
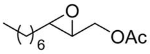
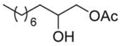
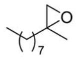
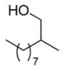
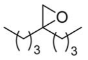
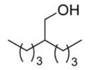
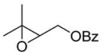
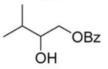
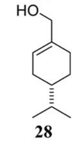
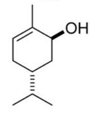
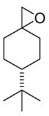
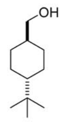
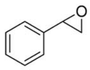
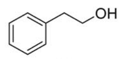
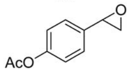
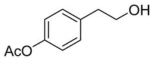


Scheme 3. Study of the reductive opening of **2** by using H_2O, D_2O, or 1,4-cyclohexadiene (1,4-CHD) as hydrogen-/deuterium-atom sources.

With this valuable information in our hands we prepared epoxides **5**–**18** to study the scope of this reduction reaction by using water as the hydrogen source or deuterium oxide as the deuterium source. We conducted the corresponding reactions under the optimized conditions described above (Table 1).[11]

In all cases the yields for the epoxide reductions were good to excellent (70–98%) with the only exception of substrate **18** (Table 1, Entry 14). Mono- (Table 1, Entries 1, 13, and 14), di- (Table 1, Entries 2–8, 10, and 12), and trisubstituted epoxides (Table 1, Entries 9 and 11) could be used as starting materials, showing that our method is not conditioned by the substitution pattern in the starting epoxides. The only limitation seems to be the susceptibility of the phenyl-substituted epoxides to cationic opening due to the pK_a value of 6.76 that was determined for the mixture of Cp_2TiCl, water, and $MnCl_2$.[11,13] Thus, **18** gave only a low yield of corresponding alcohol **32**. Another important feature of this reaction is that less-substituted alcohols are always obtained (Table 1, Entries 1, 7–14), showing anti-Markovnikov regiochemistry. Therefore, this method may be considered as offering a successful alternative to the hydroboration/oxidation reaction. This is due to the formation of the more stable radical in the Ti-mediated epoxide opening in most cases.[14] When asymmetric 1,2-disubstituted epoxides were used the same trend was observed. For example, for substrate **9** (Table 1, Entry 5) we obtained the alcohol derived from the reduction of the benzylic position. Nevertheless, when differences in the stability of both potential radicals were not significant a mixture of products could be

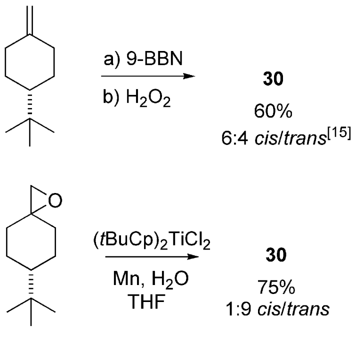
Table 1. Ti^{III}-mediated epoxide ring opening in the presence of H_2O or D_2O.

Entry	Substrate	Product	% Yield[a]	% Yield[b] (% D inc.)
1	 **5**	 **19**	79	40 (87)
2	 **6**	 **20**	95	97 (55)[c]
3	 **7**	 **21**	88	56 (94)
4	 **8**	 **22**	79	92[d]
5	 **9**	 **23**	98	78 (70)
6	 **10**	 **24**	71	50 (86)
7	 **11**	 **25**	89	100 (39)[c]
8	 **12**	 **26**	75	89 (84)
9	 **13**	 **27**	77	69 (88)
10	 **14**	 **28**	87	81 (68)
11	 **15**	 **29**	82	44 (71)
12	 **16**	 **30**	70[e]	73[e] (64)[c]
13	 **17**	 **31**	82	30 (74)
14	 **18**	 **32**	27	36 (85)

[a] Epoxide (1 mmol), Cp_2TiCl_2 (2.5 mmol), Mn dust (8 mmol), and water (10 mmol). [b] Epoxide (1 mmol), Cp_2TiCl_2 (2.5 mmol), Mn dust (8 mmol), and D_2O (10 mmol). [c] Deuterium incorporation was determined on the basis of the $[M - 18]^+$ peak (see ref.[12]). [d] A good mass spectrum for the determination of D-incorporation could not be obtained. [e] A 3:7 mixture of *cis*/*trans* stereoisomers.

expected. In these cases, the presence of functional groups may exert a template effect and direct the homolytic opening to one sole position, yielding only one product (Table 1, Entry 6).

It is noteworthy that the main product in the reduction of epoxide **16** was anti-Markovnikov alcohol **30** (Scheme 4) as a 3:7 mixture of *cis*/*trans* stereoisomers.[2e] This alcohol presents the opposite stereochemistry to those obtained by hydroboration/oxidation reaction of the corresponding alkene.[15] Changes in the reaction conditions did not improve this remarkable stereochemistry, but the use of a bulkier titanocene(III) complex [$(t\mathrm{BuCp})_2TiCl_2$] did provide an excellent yield (75 %) and stereoselectivity (1:9, *cis*/*trans*). This result opens the possibility of developing new titanocene(III) complexes to synthesize alcohols from epoxides, which not only offers an alternative to the hydroboration/oxidation reaction but also provides complementary stereochemistry, which is difficult to achieve using other methods.



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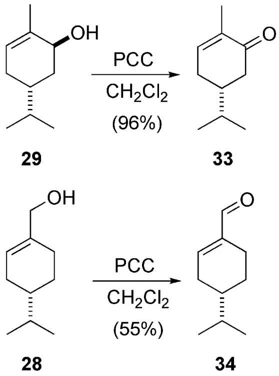
Scheme 4. Hydroboration/oxidation vs. reductive Ti^{III} epoxide opening to yield **30**.

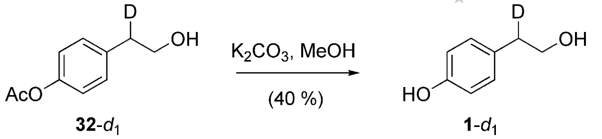
When the radical generated was vicinal to a four-membered ring (Table 1, Entries 10 and 11) epoxide opening products **28** and **29** were obtained, which are derived from the opening of the four-membered rings and subsequent reduction of the stabilized tertiary radicals. This suggests that under our aqueous conditions the reaction rate for four-membered ring cleavage in epoxides **14** and **15** is faster than the corresponding reduction processes. Recently, Fernández-Mateos et al. were able to determine the rate constant for the ring opening of a bicyclic cyclobutylcarbinyl model that generates a trisubstituted radical. The value, $k = 1.1 \times 10^7\ s^{-1}$, corresponds to a fast reaction.[16] The rate constant for the reduction by a (aqua)titanocene(III) complex of trisubstituted radicals is not available for comparison, but previous results reported by Newcomb et al. indicate that the rate constant for the reduction of a disubstituted radical by titanocene/water mixtures is $1 \times 10^5\ \mathrm{M}^{-1}\,s^{-1}$,[4a] which is smaller than that for the opening of the bicyclic four-membered ring and which would justify our results. Interestingly, alcohols **28** and **29** (carvotanacetol) are valuable compounds in the foodstuffs and pharmaceutical industries,[17] imparting as they do an intense mint flavor/odor. Some simple derivatives, such as carvotanacetone (**33**)[18] and phellandral (**34**),[19] are also natural products appreciated by these industries. From alcohols **28** and **29**, odorous compounds **33** and **34** (Scheme 5) can be obtained by simple oxidation with PCC.[11]



Scheme 5. Preparation of carvotanacetone (**33**) and phellandral (**34**).

To our satisfaction, the results obtained in the reductive epoxide ring opening mediated by Cp_2TiCl using D_2O as the deuterium source were on the whole quite good, with yields only slightly lower than those obtained using water as the hydrogen source. The incorporation of deuterium was excellent in many examples (Table 1, Entries 1, 3, 6, 8, 9, and 14) despite the relatively high isotopic effects associated with these reactions. Nevertheless, the reasons for the observed variations in deuterium incorporation are still not clear. The non-deuterated products are apparently derived from HAT processes from the solvent (i.e., THF).[20] In fact, HAT side processes from the solvent (i.e., THF) to secondary radicals have been described under very similar reaction conditions.[21] The efficiency of HAT from the $Cp_2TiCl(D_2O)$ complex is also expected to vary for different substrates, and as a consequence, deuterium incorporation will also vary as a result of the fact that in HAT reactions a relationship exists between the activation energy of the process and the nature of the C–H bond formed.[22] Nevertheless, steric and polar effects also have to be taken into account. In any case, these reaction conditions constitute an excellent procedure for the preparation of various kinds of β-deuterated alcohols.

Although the yield of deuterated **32**-d_1 was not completely satisfactory, we focused our attention on it. A simple deacetylation reaction (K_2CO_3/HOMe, 40%) yielded deuterated tyrosol (**1**-d_1)[6b] from commercial acetoxystyrene in only three steps in an overall yield of 10.5%. As mentioned above, tyrosol (**1**) is very important to the food industry, and so analytical chemists have become interested in its use in food analysis. We went on to use deuterated tyrosol (**1**-d_1) in a real analysis of olive-leaf extracts (Scheme 6). The results expressed in mg analyte/g of dry weight olive-leaves was 0.2 ± 0.05 mg/g of **1** in the leaf extracts.[11] It is the first time that the concentration of this bioactive compound has been determined in an olive-leaf extract by using a deuterated internal standard.



Scheme 6. Preparation of deuterated tyrosol (**1**-d_1).

It is noteworthy that the reduction reaction can also be carried out with the use of only substoichiometric amounts of the titanocene(III) complex. In this case, a titanocene(III) regenerating agent is required. Among these, only the combination of 2,4,6-coll·HCl and Mn dust, developed by the group of Gansäuer,[2,23] gave satisfactory results (Table 2). For deuteration experiments, 2,4,6-coll·DCl, prepared from 2,4,6-collidine and DCl/7.6 N D_2O, was used as the regenerating agent. The catalytic process seems to take place with the same trends as the stoichiometric protocol. The yields in many cases are similar (Table 2, Entries 1, 4 and 6) or even better (Table 2, Entry 7) than those conducted under stoichiometric conditions. The results also showed that the catalytic version works with mono- (Table 2, Entries 1 and 2), di- (Table 2, Entries 3–6), and trisubstituted epoxides (Table 2, Entry 7). The isolation of the corresponding deuterated alcohols with good-to-high deuterium incorporation highlighted once again the fact that our method constitutes an efficient deuteration procedure for the synthesis of β-deuterated alcohols, resulting in some cases in better deuterium incorporation than under stoichiometric conditions. Although the reasons for this are not clear, the presence of undetermined quantities of adventitious deuterium oxide in 2,4,6-coll·DCl might offer an explanation. Also worth remarking upon is the fact that excellent yields of odorous compounds **28** and **29** were obtained at gram scale (86 and 89%, respectively, from 1 g of starting material).[11]

Table 2. Epoxide ring opening catalyzed by Ti^{III} in the presence of H_2O or D_2O.

Entry	Substrate	Product	% Yield[a]	% Yield[b] (% D inc.)
1	**2**	**3**	78	60 (65)
2	**5**	**19**	56	61 (80)
3	**6**	**20**	46	40 (85)
4	**7**	**21**	86	61 (96)
5	**12**	**26**	60	48 (78)
6	**14**	**28**	87	60 (53)
7	**15**	**29**	91	54 (62)

[a] Epoxide (1 mmol), Cp_2TiCl_2 (0.2 mmol), Mn dust (8 mmol), water (10 mmol), and 2,4,6-coll·HCl (2 mmol). [b] Epoxide (1 mmol), Cp_2TiCl_2 (0.2 mmol), Mn dust (8 mmol), D_2O (10 mmol), and 2,4,6-coll·DCl (2 mmol).

Conclusions

We have described a comprehensive study of radical reductive epoxide ring opening promoted by Cp_2TiCl under mild reaction conditions by using innocuous, inexpensive water or deuterium oxide as the hydrogen or deuterium source. The remarkable chemical profile of this reaction allowed us to access alcohols with anti-Markovnikov regiochemistry from epoxides with different substitution patterns, thus improving upon the previously reported methods. The stereochemistry obtained by using this protocol is also complementary to that obtained with the hydroboration/oxidation reaction. Moreover, the use of D_2O as the deuterium source allows efficient synthesis of β-deuterated alcohols, improving the known procedures for the preparation of these kinds of compounds. We went on to follow this procedure for the preparation of a deuterated sample of tyrosol (**1**-d_1), used as an internal standard in the analysis of foodstuffs, from olive-leaf extract. We have also described an efficient catalytic protocol by using substoichiometric quantities of Ti^{III} to prepare multigrams of the odorous compounds carvotanacetone (**33**) and phellandral (**34**), thus opening the way for possible industrial applications of our procedure.

Experimental Section

General Details: Solvents and additives were thoroughly deoxygenated prior to all reactions with titanocene. Water was purified with a Milli-Q system. Products were purified by flash chromatography on Merck silica gel 50. ^{1}H and ^{13}C NMR spectra were recorded with 400 and 500 MHz spectrometers in $CDCl_3$. Data are reported as follows: chemical shift in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constant (Hz), and integration. Peak assignments were made with the aid of the DEPT method. The stereochemistry of the new stereogenic centers derived from the inclusion of a deuterium atom in the structure was not determined.[24] The following known compounds were isolated as pure samples and showed ^{1}H and ^{13}C NMR spectra matching those of the reported compounds: **5**,[25] **7**,[26] **8**,[27] **9**,[28] **11**,[28] **13**,[10] **16**,[10] **18**,[29] **21**-d_1,[26a] **22**,[30] **23**,[31] **24**,[32] **25**,[33] **26**,[34] **27**,[35] **28**,[36] **31**-d_1,[37] **32**,[38] **33**,[18] **34**,[19] and **1**-d_1.[6b]

General Procedure for the Epoxidation of Alkenes with *m*-CPBA: A sample of *m*-CPBA (2 mmol, 70% purity) was added to a solution of alkene (1 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred at room temperature until the starting material was consumed (checked by TLC). CH_2Cl_2 was then added, and the solution was washed with 2 N NaOH, dried with anhydrous Na_2SO_4, and concentrated. Products **5**–**10**, **13**, and **18** were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopic techniques.

Epoxide 10: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.31 (dd, J = 12.2, 3.2 Hz, 1 H, CH*H*OAc), 3.88 (dd, J = 12.2, 6.3 Hz, 1 H, C*H*HOAc), 2.94–2.89 (m, 1 H, C*H*O-), 2.80 (td, J = 5.5, 2.0 Hz, 1 H, C*H*O-), 2.05 (s, 3 H, -OCH_3), 2.06 (m, 2 H, CH_2), 1.53 (dd, J = 13.2, 7.2 Hz, 2 H, CH_2), 1.45–1.34 (m, 2 H, CH_2), 1.32–1.17 (m, 8 H, CH_2), 0.84 (t, J = 6.7 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$; DEPT): δ = 170.7 (C), 64.8 (CH_2), 56.7 (CH), 55.3 (CH), 31.8 (CH_2), 31.6 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 25.9 (CH_2), 22.7 (CH_2), 20.8 (CH_3), 14.1 (CH_3) ppm. HRMS (ESI+): calcd. for $C_{12}H_{23}O_3$ [M + H]$^+$ 215.1647; found 215.1638.

General Procedure for the Preparation of Epoxides from Ketones: To a solution of ketone (1 mmol) and CH_2Br_2 (2 mmol) in THF (15 mL) cooled to –78 °C was dropwise added BuLi (2.5 M in hexane, 1.1 mmol) for 5 min. The mixture was stirred for 5 min at –78 °C and then for 24 h at room temperature. AcOEt was added, and the organic layer was washed with a saturated solution of NH_4Cl, dried with anhydrous Na_2SO_4, and concentrated. Products **11**, **12**, and **16** were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopy.

Epoxide 12: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.57 (s, 2 H, CH_2O), 1.64–1.46 (m, 4 H, CH_2), 1.37–1.25 (m, 8 H, CH_2), 0.90 (m, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$; DEPT): δ = 59.7 (C), 52.8 (CH_2), 34.1 (CH_2), 27.2 (CH_2), 23.0 (CH_2), 14.2 (CH_3) ppm. HRMS (ESI+): calcd. for $C_{10}H_{21}O$ [M + H]$^+$ 157.1592; found 157.1587.

General Procedure for Ti^{III}-Mediated Epoxide Ring Opening with H_2O as Hydrogen Source (GP 1): Thoroughly deoxygenated THF (20 mL) was added to a mixture of Cp_2TiCl_2 (2.5 mmol) and Mn dust (8 mmol) under an Ar atmosphere, and the suspension was stirred at room temperature until it turned lime green (after about 15 min). A solution of epoxide (1 mmol) and H_2O (10 mmol) in THF (1 mL) was added, and the mixture was stirred for 24 h, after which the reaction was quenched with a saturated solution of $KHSO_4$ and extracted with EtOAc. The organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated. Products **3** and **19**–**32** were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopy. Yields are reported in the text and set out in Table 1.

General Procedure for Ti^{III}-Mediated Epoxide Ring Opening with D_2O as Deuterium Source (GP 2): Thoroughly deoxygenated THF (20 mL) was added to a mixture of Cp_2TiCl_2 (2.5 mmol) and Mn dust (8 mmol) under an Ar atmosphere, and the suspension was stirred at room temperature until it turned lime green (after about 15 min). A solution of epoxide (1 mmol) and D_2O (10 mmol) in THF (1 mL) was added, and the mixture was stirred for 24 h, after which the reaction was quenched with a saturated solution of $KHSO_4$ and extracted with EtOAc. The organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated. Deuterated products **3**-d_1 and **19**-d_1–**32**-d_1 were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopy. Yields are reported in the text and set out in Table 1.

General Procedure for Ti^{III}-Catalyzed Epoxide Ring Opening with H_2O as Hydrogen Source (GP 3): Thoroughly deoxygenated THF (20 mL) was added to a mixture of Cp_2TiCl_2 (0.2 mmol) and Mn dust (8 mmol) under an Ar atmosphere, and the suspension was stirred at room temperature until it turned lime green (after about 15 min). A solution of epoxide (1 mmol), collidine·HCl (7 mmol), and H_2O (10 mmol) in THF (1 mL) was added, and the mixture was stirred at room temperature for 24 h, after which the reaction was quenched with a saturated solution of $KHSO_4$ and extracted with EtOAc. The organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated. Products **3**, **19**–**21**, **26**, **28**, and **29** were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopy. Yields are reported in the text and set out in Table 2.

General Procedure for Ti^{III}-Catalyzed Epoxide ring Opening with D_2O as Deuterium Source (GP 4): Thoroughly deoxygenated THF (20 mL) was added to a mixture of Cp_2TiCl_2 (0.2 mmol) and Mn dust (8 mmol) under an Ar atmosphere, and the suspension was stirred at room temperature until it turned lime green (after about 15 min). A solution of epoxide (1 mmol), collidine·DCl (7 mmol), and D_2O (10 mmol) in THF (1 mL) was added, and the mixture was stirred at room temperature for 24 h, after which the reaction was quenched with a saturated solution of $KHSO_4$ and extracted with EtOAc. The organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated. Deuterated products **3**-d_1,

19-*d*$_1$–**21**-*d*$_1$, **26**-*d*$_1$, **28**-*d*$_1$, and **29**-*d*$_1$ were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopic techniques. Yields are reported in the text and set out in Table 2.

Compound 3-*d*$_1$: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.62 (d, *J* = 6.4 Hz, 2 H, C*H*$_2$OH), 1.60–1.48 (m, 1 H, C*H*D), 1.35–1.20 (m, 30 H, C*H*$_2$), 0.87 (t, *J* = 6.6 Hz, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$; DEPT): δ = 63.1 (CH$_2$), 32.5 (m, CHD), 32.1 (CH$_2$), 29.9 (CH$_2$), 29.8 (CH$_2$), 29.8 (CH$_2$), 25.7 (CH$_2$), 22.8 (CH$_2$), 14.3 (CH$_3$) ppm. HRMS (ESI+): calcd. for $C_{18}H_{35}D$ [M – H$_2$O]$^+$ 253.2880; found 253.2906.

Compound 19-*d*$_1$: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.31–7.26 (m, 2 H, aromatic C*H*), 7.21–7.16 (m, 3 H, aromatic C*H*), 3.65 (d, *J* = 6.3 Hz, 2 H, C*H*$_2$OH), 2.65 (t, *J* = 7.3 Hz, 2 H, PhC*H*$_2$CH$_2$), 1.73–1.57 (m, 3 H, CH$_2$C*H*$_2$C*H*D) ppm. ^{13}C NMR (100 MHz, CDCl$_3$; DEPT): δ = 142.4 (C), 128.5 (CH), 128.4 (CH), 125.9 (CH), 62.8 (CH$_2$), 32.4 (CH$_2$), 32.0 (m, CHD), 27.6 (CH$_2$) ppm. HRMS (ESI+): calcd. for $C_{10}H_{13}DO$ [M]$^+$ 151.1107; found 151.1114.

Compound 20-*d*$_1$: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.64 (br. s, 1 H, C*H*OH), 1.74–1.55 (m, 1 H, C*H*D), 1.54–1.21 (m, 20 H, C*H*$_2$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$; DEPT): δ = 69.2 (CH), 32.5 (CH$_2$), 32.1 (m, CHD), 24.2 (CH$_2$), 23.8 (CH$_2$), 23.4 (CH$_2$), 23.4 (CH$_2$), 23.3 (CH$_2$), 23.3 (CH$_2$), 23.2 (CH$_2$), 20.9 (CH$_2$), 20.9 (CH$_2$) ppm. HRMS (ESI+): calcd. for $C_{12}H_{23}DO$ [M]$^+$ 185.1890; found 185.1888.

Compound 22-*d*$_1$: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.90–3.75 (m, 3 H, C*H*$_2$O), 3.55 (ddd, *J* = 16.5, 10.0, 5.8 Hz, 2 H, C*H*$_2$O), 1.73–1.57 (m, 1 H, C*H*D), 0.89 [s, 18 H, (C*H*$_3$)$_3$C], 0.01 (m, 12 H, C*H*$_3$Si) ppm. ^{13}C NMR (100 MHz, CDCl$_3$; DEPT): δ = 70.9 (CH), 67.3 (CH$_2$), 61.2 (CH$_2$), 35.3 (m, CD), 26.1 (CH$_3$), 26.0 (CH$_3$), 18.5 (C), 18.4 (C), –5.2 (CH$_3$), –5.2 (CH$_3$), –5.3 (CH$_3$), –5.3 (CH$_3$) ppm.

Compound 23-*d*$_1$: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.40–7.11 (m, 5 H, aromatic C*H*), 4.22–3.90 (m, 3 H, C*H*$_2$OAc and C*H*OH), 2.84–2.71 (m, 1 H, PhC*H*D), 2.09 (s, 3 H, OC*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$; DEPT): δ = 171.3 (C), 137.3 (C), 129.4 (CH), 128.7 (CH), 126.8 (CH), 70.7 (CH), 67.8 (CH$_2$), 39.9 (m, CHD), 20.9 (CH$_3$) ppm. HRMS (ESI+): calcd. for $C_{11}H_{11}DO_2$ [M – H$_2$O]$^+$ 177.0900; found 177.0910.

Compound 24-*d*$_1$: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 4.11 (dd, *J* = 11.3, 2.5 Hz, 1 H, C*H*HOAc), 3.93 (dd, *J* = 11.3, 7.5 Hz, 1 H, CH*H*OAc), 3.80 (br. s, 1 H, C*H*OH), 2.07 (s, 3 H, OC*H*$_3$), 1.48–1.38 (m, 1 H, C*H*D), 1.35–1.18 (m, 12 H, C*H*$_2$), 0.85 (t, *J* = 6.4 Hz, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$; DEPT): δ = 171.4 (C), 70.0 (CH), 68.9 (CH$_2$), 33.2 (m, CHD), 31.9 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.3 (CH$_2$), 25.4 (CH$_2$), 22.7 (CH$_2$), 21.0 (CH$_3$), 14.2 (CH$_3$) ppm. HRMS (ESI+): calcd. for $C_{12}H_{21}DO_2$ [M – H$_2$O]$^+$ 199.1698; found 199.1699.

Compound 25-*d*$_1$: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.42 (d, *J* = 10.5 Hz, 1 H, C*H*HOH), 3.32 (d, *J* = 10.5 Hz, 1 H, CH*H*OH), 1.26–1.13 (m, 14 H, C*H*$_2$), 0.86–0.75 (m, 6 H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$; DEPT): δ = 68.4 (CH$_2$), 35.5 (m, CD), 33.2 (CH$_2$), 32.0 (CH$_2$), 30.1 (CH$_2$), 29.7 (CH$_2$), 29.5 (CH$_2$), 27.1 (CH$_2$), 22.8 (CH$_2$), 16.6 (CH$_3$), 14.2 (CH$_3$) ppm. LRMS (ESI+): *m*/*z* (%) = 155 (3) [M – H$_2$O]$^+$, 154 (8), 127 (4), 112 (9), 98 (15), 70 (65), 57 (100), 55 (86).

Compound 26-*d*$_1$: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.51 (s, 2 H, C*H*$_2$OH), 1.39–1.17 (m, 12 H, C*H*$_2$), 0.88 (t, *J* = 7.0 Hz, 6 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$; DEPT): δ = 65.8 (CH$_2$), 30.6 (CH$_2$), 29.2 (CH$_2$), 23.2 (CH$_2$), 14.2 (CH$_3$) ppm (one carbon signal was not observed). HRMS (ESI+): calcd. for $C_{10}H_{19}D$ [M – H$_2$O]$^+$ 140.1550; found 140.1560.

Compound 27: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.04 (d, *J* = 8.2 Hz, 2 H, aromatic C*H*), 7.55 (m, 1 H, aromatic C*H*), 7.42 (t, *J* = 11.1 Hz, 2 H, aromatic C*H*), 4.44 (ddd, *J* = 11.5, 3.0, 1.2 Hz, 2 H, C*H*$_2$OBz), 3.72 (m, 1 H, C*H*OH), 1.90–1.79 [m, 1 H, C*H*(CH$_3$)$_2$], 1.02 (d, *J* = 6.8 Hz, 3 H, CHC*H*$_3$), 0.99 (d, *J* = 6.8 Hz, 3 H, CHC*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$; DEPT): δ = 167.0 (C), 133.2 (CH), 130.0 (C), 129.7 (CH), 128.5 (CH), 74.9 (CH), 67.9 (CH$_2$), 31.3 (CH), 18.8 (CH$_3$), 17.9 (CH$_3$) ppm. HRMS (ESI+): calcd. for $C_{12}H_{17}O_3$ [M + H]$^+$ 209.1178; found 209.1171.

Compound 27-*d*$_1$: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.04 (d, *J* = 8.3 Hz, 2 H, aromatic C*H*), 7.55 (t, *J* = 7.4 Hz, 1 H, aromatic C*H*), 7.43 (t, *J* = 7.7 Hz, 2 H, aromatic C*H*), 4.44 (dd, *J* = 11.5, 3.0 Hz, 1 H, C*H*HOBz), 4.29 (dd, *J* = 11.5, 7.4 Hz, 1 H, CH*H*OBz), 3.72 (dd, *J* = 7.2, 2.8 Hz, 1 H, C*H*OH), 2.30 (br. s, 1 H, O*H*), 1.01 (s, 3 H, CHC*H*$_3$), 0.99 (s, 3 H, CHC*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$; DEPT): δ = 167.0 (C), 133.2 (CH), 130.0 (C), 129.7 (CH), 128.5 (CH), 74.8 (CH), 67.9 (CH$_2$), 31.3 (m, CD), 18.7 (CH$_3$), 17.7 (CH$_3$) ppm. HRMS (ESI+): calcd. for $C_{12}H_{13}DO_2$ [M – H$_2$O]$^+$ 191.1057; found 191.1063.

Compound 28-*d*$_1$: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.66 (br. s, 1 H, C*H*=C), 3.97 (br. s, 2 H, C*H*$_2$OH), 2.42–1.90 (m, 3 H, C*H*$_2$ and C*H*), 1.80–1.35 (m, 2 H, C*H*$_2$), 1.30–1.15 (m, 2 H, C*H*$_2$), 0.88 (s, 6 H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$; DEPT): δ = 137.5 (C), 123.0 (CH), 67.4 (CH$_2$), 40.3 (CH)*, 40.2 (CH), 32.3 (CH), 31.7 (m, CD), 28.7 (CH$_2$)*, 28.7 (CH$_2$), 26.5 (CH$_2$), 26.2 (CH$_2$)*, 26.1 (CH$_2$), 20.0 (CH$_3$)*, 19.9 (CH$_3$), 19.8 (CH$_3$)*, 19.6 (CH$_3$) ppm (asterisks refer to minor isomers). HRMS (ESI+): calcd. for $C_{10}H_{17}DO$ [M]$^+$ 155.1420; found 155.1422.

Compound 29-*d*$_1$: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.57–5.50 (m, 1 H, C*H*=C), 3.95 (br. s, 1 H, C*H*OH), 2.01 (dd, *J* = 12.9, 9.0 Hz, 1 H, C*H*H), 1.85 (d, *J* = 13.2 Hz, 1 H, CH*H*), 1.76 (s, 3 H, C*H*$_3$), 1.73–1.57 (m, 1 H, CH$_2$C*H*CH$_2$), 1.45 (dd, *J* = 12.0, 9.6 Hz, 1 H, C*H*H), 1.33 (ddd, *J* = 12.9, 3.8, 2.9 Hz, 1 H, CH*H*), 0.88 (s, 3 H, C*H*$_3$), 0.86 (s, 3 H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$; DEPT): δ = 134.6 (C), 125.8 (CH), 68.8 (CH), 35.5 (CH$_2$), 34.0 (m, CD), 29.1 (CH$_2$), 21.0 (CH$_3$), 19.9 (CH$_3$), 19.5 (CH$_3$) ppm. HRMS (ESI+): calcd. for $C_{10}H_{17}DO$ [M]$^+$ 155.1420; found 155.1420.

Compound 30-*d*$_1$: Mixture of 3:7 *cis*/*trans* isomers. Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.61 (s, 2 H, *cis* isomer, C*H*$_2$OH), 3.41 (s, 2 H, *trans* isomer, C*H*$_2$), 1.84–1.73 (m, 2 H, C*H*$_2$), 1.61–1.37 (m, 2 H, C*H*$_2$), 1.08–0.85 (m, 5 H, C*H*$_2$ and C*H*), 0.83 [s, 9 H, *trans* isomer, (C*H*$_3$)$_3$C], 0.82 [s, 9 H, *cis* isomer, (C*H*$_3$)$_3$C] ppm. ^{13}C NMR (100 MHz, CDCl$_3$; DEPT): δ = 68.8 (CH$_2$, *trans* isomer), 63.8 (CH$_2$, *cis* isomer), 48.5 (CH$_2$, *cis* isomer), 48.4 (CH$_2$, *trans* isomer), 40.7 (CH), 40.5 (m, CD), 32.7 (C, *cis* isomer), 32.6 (C, *trans* isomer), 30.1 (CH$_2$, *cis* isomer), 30.0 (CH$_2$, *trans* isomer), 27.7 (CH$_3$, *trans* isomer), 27.6 (CH$_3$, *cis* isomer), 27.5 (CH$_2$, *cis* isomer), 26.9 (CH$_2$, *trans* isomer), 22.2 (CH$_2$) ppm. LRMS (ESI+): *m*/*z* (%) = 153 (3) [M – H$_2$O]$^+$, 138 (5), 114 (22), 96 (81), 82 (32), 67 (35), 57 (100), 55 (46).

Compound 32-*d*$_1$: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.21 (d, *J* = 8.2 Hz, 2 H, aromatic C*H*), 7.01 (d, *J* = 8.2 Hz, 2 H, aromatic C*H*), 3.80 (d, *J* = 6.4 Hz, 2 H, CHDC*H*$_2$OH), 2.86–2.77 (m, 1 H, C*H*DCH$_2$OH), 2.28 (s, 3 H, OC*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$; DEPT): δ = 169.8 (C), 149.3 (C), 136.3 (C), 130.1 (CH), 121.7 (CH), 63.5 (CH$_2$), 38.6 (m, CHD), 21.2 (CH$_3$) ppm. HRMS (ESI+): calcd. for $C_{10}H_{11}DO_3$ [M]$^+$ 181.0849; found 181.0852.

Oxidation of 28 and 29 with PCC: A solution of allylic alcohol (1 mmol) in CH_2Cl_2 (20 mL) was treated with a sample of PCC (2 mmol) for 3 h at room temperature. Et_2O (40 mL) was added, and the mixture was washed with 2 N NaOH (2×), 2 N HCl (2×) and then with a saturated solution of $NaHCO_3$. The organic layer was dried with anhydrous Na_2SO_4, and the solvent was removed. The residue was submitted to flash chromatography (hexane/EtOAc, 9:1) to yield ketone **33**[18] (146 mg, 96%) or aldehyde **34**[19] (84 mg, 55%).

Synthesis of Deuterated Tyrosol (1-*d*$_1$): A sample of K_2CO_3 (82 mg, 0.58 mmol) was added to a solution of alcohol **32**-*d*$_1$ (36 mg, 0.2 mmol) in MeOH (5 mL), and the mixture was stirred for 24 h at room temperature. AcOEt (20 mL) was added, and the organic layer was washed with water, dried with anhydrous Na_2SO_4, and concentrated. The residue was submitted to flash chromatography (hexane/EtOAc, 1:1) to give **1**-*d*$_1$[6b] (13 mg, 40%) as a colorless oil.

Supporting Information (see footnote on the first page of this article): Optimization of reaction conditions, analysis of tyrosol, and ^{1}H and ^{13}C NMR spectra of all described and new compounds.

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