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Effects of Solvents and Water in Ti(III)-Mediated Radical Cyclizations of Epoxygermacrolides. Straightforward Synthesis and Absolute Stereochemistry of (+)-3α-Hydroxyreynosin and Related Eudesmanolides

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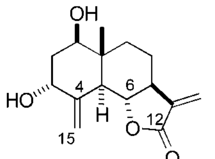
The Cp_2TiCl-mediated rearrangement of 1,10-epoxy-11*β*,13-dihydrocostunolide (**4**) was carried out using different solvents and additives to develop an expeditious procedure for the synthesis of natural eudesmanolides via free-radical chemistry. In the nonhalogenated solvents THF, benzene, and toluene the transannular cyclization, initiated by the homolytic opening of the oxirane ring, selectively led to the desired exocyclic alkene **5**. When water was added to THF, however, the main product was reduced eudesmanolide **8**. Experiments with D_2O confirmed that the H-4 of **8** comes from water. To rationalize these results, a mechanistic hypothesis based on a water-solvated Cp_2TiCl complex is proposed. Finally, the usefulness of Cp_2TiCl for the synthesis of natural eudesmanolides has been proved using this reagent in the key step for the chemical preparation of (+)-3α-hydroxyreynosin (**1**) and (+)-reynosin (**17**). These syntheses confirmed the chemical structure of **1** and established the absolute stereochemistry of the natural products **1** and **17**. The results obtained suggest that the combination of the biomimetic strategy employed, with Ti(III)-mediated free-radical chemistry, may come to represent a general method for the enantiospecific synthesis of more than 170 natural eudesmanolides containing an exocyclic double bond between C-4 and C-15.

Introduction

Sesquiterpene lactones form an important class of natural products with antitumoral, phytotoxic, antimicrobial, and other biological properties.[1] Eudesmanolides represent one of the main skeletal types of sesquiterpene lactones.[1] Within this group there are more than 170 natural products, such as (+)-3α-hydroxyreynosin (**1**) (a 12,6-eudesmanolide) or (+)-8*β*-hydroxyasterolide (**2**) (a 12,8-eudesmanolide), that contain an exocyclic double bond between C-4 and C-15.[2]



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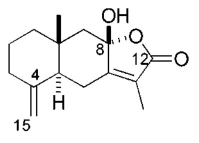

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The chemical structure and biological activity of this kind of terpenoid have attracted the attention of chemists, and during the last three decades many efforts have been made to synthesize several of them.[3] Nevertheless, the processes developed so far generally require numerous steps and provide poor overall yields. Despite these discouraging results, some studies into the zoopharmacognosy, pharmacology, and neurotoxicology of sesquiterpene lactones published in 1995[4] aroused new interest in this class of natural products, and subsequently, novel methods have been applied to the synthesis of eudesmanolides.[5] However, an expeditious procedure for synthesizing complex eudesmanolides has still to be reported.

Following a biomimetic strategy, we, among other researchers, have used accessible germacrolides and 1,10-epoxygermacrolides as raw material for the enantiospecific synthesis of various eudesmanolides.[6] Nevertheless, via carbocationic chemistry, the conventional acid-promoted transannular cyclization of germacrolides and 1,10-epoxygermacrolides results in eudesmanolide mixtures in which the exocyclic alkene either is one of the

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Table 1. Relative Proportions[a] (%) of Compounds 4−8 Obtained after Acid-Induced and Cp_2TiCl-Promoted Transannular Cyclizations of 4 in Different Solvents

entry	reagent (equiv)	solvent	additive (equiv)	**4**	**5**	**6**	**7**	**8**
1	TsOH (0.5)	CH_2Cl_2			8	82	10	
2	BF_3 (0.6)	CH_2Cl_2			40	57	3	
3	$MnCl_2$ (1.5)	THF			19	63	18	
4	Cp_2TiCl (3.3)	THF			91	6		3
5	Cp_2TiCl (3.3)	PhH			84	12		4
6	Cp_2TiCl (3.3)	$PhCH_3$			86	4		10
7	Cp_2TiCl (3.0)	PhH	1,4-C_6H_8[b] (30.0)		86	8		6
8	Cp_2TiCl (1.1)	PhH		12	36	29	8	15
9	Cp_2TiCl (3.3)	CH_2Cl_2			40	49	8	3
10	Cp_2TiCl (3.3)	CCl_4			40	55	5	
11	Cp_2TiCl (3.3)	THF	H_2O (28.0)		13	8	8	71

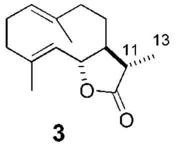
[a] Relative proportions were determined on the basis of the ^{1}H NMR spectra of the mixtures formed in every experiment. [b] 1,4-C_6H_8 = 1,4-cyclohexadiene.

minor components or is absent altogether.[1a,6,7] Furthermore, the palladium(II)-promoted rearrangement of germacrolides leads to similar results, probably via carbocationic chemistry also.[8] In the mid-1990s, RajanBabu and Nugent reported the selective generation of free radicals from epoxides using bis(cyclopentadienyl)titanium(III) chloride.[9] This method has since been applied to useful synthetic transformations, including the synthesis of five-membered carbocyclic rings by the usual 5-*exo* cyclization mode of hexenyl radicals.[10,11] Moreover, some of us have recently found that when applied to acyclic epoxypolyprenes Cp_2TiCl leads to six-membered carbocyclic rings bearing exocyclic double bonds.[12] We therefore decided to extend titanium(III) chemistry to the sesquiterpene lactone field to develop a straightforward procedure for the synthesis of eudesmanolides such as **1** and **2**.

Results and Discussion

Epoxygermacrolide **4**, obtained by selective oxidation of 11β,13-dihydrocostunolide (**3**), was first treated with Bronsted and Lewis acids (Table 1, entries 1−3) to observe its behavior under the usual acidic treatment. Under these conditions, mixtures of dihydroreynosin[13] (**5**), dihydrosantamarin[14] (**6**), and artesin[15] (**7**) were obtained even when the relatively weak Lewis acid $MnCl_2$ was used. Endocyclic regioisomer **6** was always the main product.

Subsequently, the reaction between **4** and Cp_2TiCl was carried out in different solvents, with and without additives (Table 1, entries 4−11). In all cases, Cp_2TiCl was first generated in situ by stirring Cp_2TiCl_2 and Mn dust into THF[16] (some attempts in other solvents were unsuccessful) until the mixture turned lime green. The THF was then either kept (entries 4 and 11) or pumped off and replaced by a second solvent (entries 5−10) before the addition of substrate **4** and the optional additive (either 1,4-cyclohexadiene or water). The reaction of **4** with an excess of Cp_2TiCl in THF, benzene, or toluene (Table 1, entries 4−6) led selectively to the desired exocyclic alkene **5**. Low amounts of **6** and **8** may be due to the presence of $MnCl_2$ (formed during Cp_2TiCl_2 reduction) and moisture (see discussion below), respectively. Thus, **5** was isolated (80% yield) from the experiment summarized in entry 4. Its IR and ^{1}H NMR spectra matched those of natural dihydroreynosin found in the plant *Michelia compresa*.[13]



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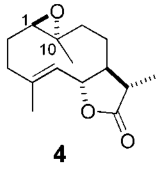

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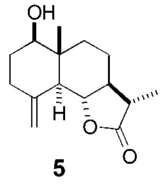

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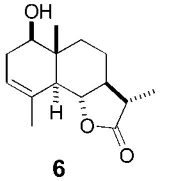

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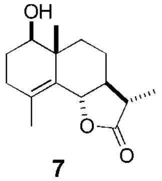

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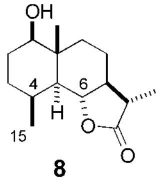

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The regio- and stereoselectivities of this reaction are noteworthy because, in previously reported transannular cyclizations of cyclodecenone radicals, a mixture of *cis*- and *trans*-decalones (derived from a 6-*endo*/*exo* cyclization) and a product derived from a 5-*exo* cyclization were obtained.[17] In our experiments only *trans*-decalins were formed, and we found no products from a 5-*exo* transannular cyclization. Products derived from the trapping, reduction, or other reactions of a hypothetical C-10-centered free radical were not detected either. These facts can be rationalized by a concerted mechanism leading directly to the tertiary radical **10** (Scheme 1).

It is known that germacrolides such as **3** in solution adopt the preferred "UU" conformation depicted in Scheme 1.[18] It is therefore possible that oxirane **4** retains such a preferred conformation, an idea which is sup-

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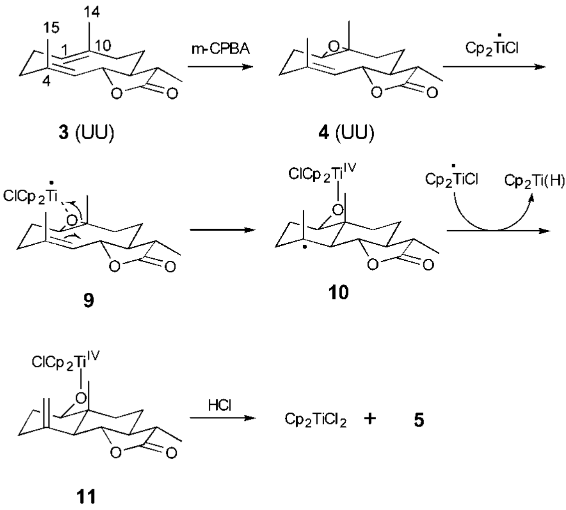
Scheme 1

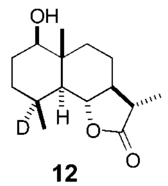


ported by the NOE observed between the hydrogens of the C-14 and the C-15 methyl groups. In the UU conformation the interatomic distance between C-5 and C-10 (about 2.8 Å, as measured with the aid of Dreiding's models) allows a transannular overlap between the π orbital of the C-4−C-5 double bond and the incipient semifilled p orbital which is developing at C-10 by the homolytic cleavage of the oxirane ring. This transannular overlap is in line with the generally admitted transannular interaction between the π orbitals of the C-4−C-5 and the C-1−C-10 double bonds, responsible for the end absorption of the UV spectra of germacrolides such as **3**.[1a] Thus, the free radical **10** (Scheme 1) would be formed directly via a *trans*-fused chair/chair-like transition state, which would control the regio- and stereochemistries observed. Concerted mechanisms have in the past been suggested to explain the high selectivity observed in free-radical-mediated cyclizations directed toward steroid-ring buildings,[19] but these proposals have been the subject of some controversy.[11] Nevertheless, it would seem to us that our experimental results can be more satisfactorily explained by a concerted mechanism than by a sequential one proceeding via a hypothetical C-10-centered free radical.

There is evidence to indicate that after titanocene(III)-mediated 5-*exo* cyclizations the resultant primary radicals are efficiently scavenged by a second equivalent of Ti(III) to afford the corresponding alkyl−Ti(IV) complex.[9] In this way it might be thought that the radical **10** evolves toward **11** by Cp_2TiCl trapping and subsequent β-hydrogen elimination from the alkyl−Ti(IV) species. However, there are several examples of alkyl−Ti(IV) complexes which do not undergo β-hydrogen elimination,[9,20] presumably because the d^0 Ti has no electron density to back-donate into the σ^* orbital of the C−H bond.[20] Moreover, in our case it seems unlikely that the sterically obstructed tertiary radical **10** should be trapped by the bulky Cp_2TiCl. In fact, when 1,4-cyclohexadiene was added to the reaction mixture (entry 7, Table 1), there was no substantial increase in the proportion of reduced product **8**, indicating the difficulties encountered by the hydrogen atom donor in reaching the tertiary radical. (There is an interesting precedent dealing with the low proportion of reduction product derived from a sterically congested tertiary free radical in the presence of 1,4-cyclohexadiene.[21]) Previously reported data indicate that the reaction of a tertiary free radical with Cp_2TiCl is slower than that with 1,4-cyclohexadiene.[16] Consequently, the failure of 1,4-cyclohexadiene in the hydrogenation of free radical **10** practically rules out the possibility that this radical could be trapped by Cp_2TiCl. Recently, Molander and Harris have proposed a disproportionation process to justify the formation of an alkene from a tertiary alkyl radical originated in the presence of samarium(II) iodide.[22] In a similar way, tertiary radical **10** might evolve toward **11** by a disproportionation process favored by the excess of Cp_2TiCl, which would trap a hydrogen atom from the C-15 methyl group, thus producing the exocyclic alkene and $Cp_2Ti(H)Cl$ (see Scheme 2b and discussion below). The high regioselectivity observed may be due to steric and stereoelectronic factors, the former being related to the accessibility of the primary hydrogens of C-15 and the latter to the free rotation around the C-4−C-15 single bond, which would facilitate the orbital overlap between the C−H bonds of the methyl group and the semifilled p orbital at C-4. In any case, a double proportion of Cp_2TiCl would be needed to complete the transformation of **4** into **5** (see Scheme 1). This 2/1 ratio is supported by the results summarized in entry 8 (Table 1): when only 1 mol equiv of Cp_2TiCl was used, a part of oxirane **4** was recovered unchanged. Moreover, increased proportions of **6** presumably derive from the carbocationic opening of **4**, promoted by $MnCl_2$ once Cp_2TiCl has been consumed.

Entries 9 and 10 (Table 1) also show increased proportions of **6**. It seems that chlorinated solvents CH_2Cl_2 and CCl_4 deactivate (at least partially) the Cp_2TiCl complex. In fact, when these solvents were added, the characteristic green color of Cp_2TiCl immediately turned deep orange, probably due to the formation of some Ti(IV) species.

Finally, when water was added to the medium (entry 11), there was an unexpected increase in the proportion of the reduced product **8**, and so this could be isolated (68% yield) and characterized by spectroscopic techniques. The β-axial disposition of the C-15 methyl group was indicated by the coupling constant value between H-4 and H-5 ($J = 4.9$ Hz) and was confirmed by the NOE observed between H_3-15 and H-6. No 4α-methyl epimer of **8** was detected. When D_2O was used instead of H_2O, a mixture of deuterated product **12** and alkene **5** (at relative proportions of 3/1) was obtained. Compound **12** was isolated by flash chromatography and analyzed by spectroscopic techniques. GC−MS analysis indicated a 70% incorporation of deuterium, while HRMS confirmed



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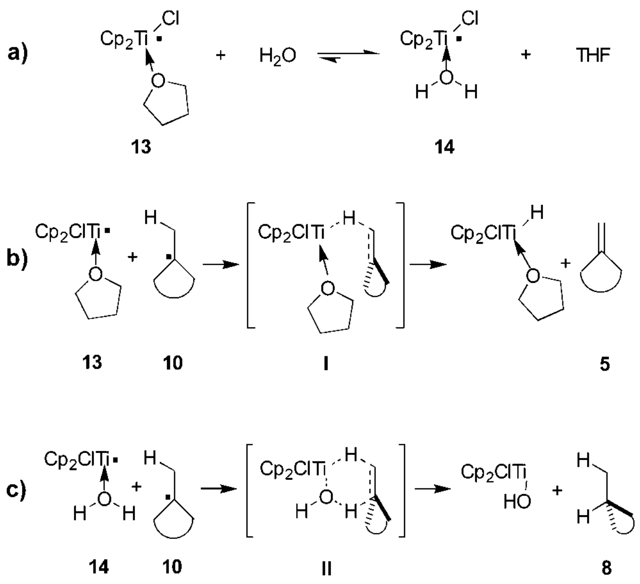
Scheme 2



the molecular formula $C_{15}H_{23}DO_3$. In the ^1H NMR spectrum, the multiplicity of the signals corresponding to H-5 (1.47 ppm, br d, $J = 11.6$ Hz) and H_3-15 (0.99 ppm, br s) indicated that the deuterium atom was located at C-4. This position was confirmed by the ^{13}C NMR spectrum, where C-4 appeared as a small triplet centered at 26.8 ppm with $^1J(^{13}C,D) = 19.6$ Hz. Moreover, the NOE observed between H-6 and H_3-15 indicated that, as in **8**, the C-15 methyl group of **12** was in the β axial position.

Deuterium incorporation in **12** confirmed that H-4 of **8** derives from water. These results were quite intriguing, because it is generally believed that water is stable against free radicals because of its strong O−H bonds.[11] In fact toluene, the benzylic C−H bonds of which are weaker than the O−H bonds of water,[23] was inert under these conditions. Thus, it seems unlikely that water itself could be directly responsible for the reduction of radical **10**. The possible nature of the reductive species and a plausible mechanism for the hydrogen atom transfer were suggested to us by the following observations: first, the solvated character of Cp_2TiCl in electron donor solvents[9,24] and, second, the six-membered transition state proposed by Noyori and co-workers to rationalize the Ru(II)-catalyzed hydrogen transfer between alcohols and carbonyl compounds.[25]

As RajanBabu and Nugent reported, in the solid state Cp_2TiCl exists as a chloride-bridged dimer, but in the presence of THF it dissociates to afford a monomeric species which can be considered as being a "loosely solvated transition-metal-centered radical",[9] represented as **13** in Scheme 2. In a similar way, it seems plausible that in the presence of another electron donor, such as water, the THF unit may be interchanged in an equilibrium leading to **14** (Scheme 2a). When **13** approaches free radical **10**, the overlap between the semifilled titanium d orbital and the σ^* orbital of a C−H bond results in a disproportionation process leading to the exocyclic alkene **5** (Scheme 2b). However, when the water-solvated complex **14** approaches **10** to initiate the disproportionation reaction, the polarized O−H bond is placed in an adequate position to participate in a probably concerted process, involving six electrons, which might take place immediately after or even before the double bond is completely formed (Scheme 2c). This process would result in a net hydrogen atom transfer via the six-membered intermediate **II**. Thus, the reduced product **8** would be formed together with the 16-electron complex Cp_2Ti^{IV}(OH)Cl. The high bond dissociation energy of water (119 kcal mol^{-1})[23] casts serious doubts upon the possibility of an alternative mechanism involving the homolytic cleavage of the O−H bond. Moreover, the proposed mechanism can account for both the reactivity (higher than that of 1,4-cyclohexadiene) and the stereochemistry observed. The former can be justified if the process is regarded as a virtually *intramolecular* reaction. First, the water-solvated complex is anchored to the free radical in an intermediate similar to **I**; then, as the O−H bond has been placed in the adequate position, the hydrogen transfer can start. With respect to the stereochemistry observed, the bulky complex **14** can approach free radical **10** only by the α face, because the access by the opposite face is considerably hindered by the β-oriented C-14 methyl group. Therefore, the titanium atom and the O−H group of the cyclic intermediate **II** are placed in the α face, and thus, the hydrogen atom is introduced in the 4α position.

To the best of our knowledge, this is the first time that a hydrogen atom transfer from water to a carbon-centered free radical has been reported. Whatever the precise mechanism involved might turn out to be, this is a significant finding from both theoretical and synthetic points of view. Water, under carbocationic chemistry conditions, usually acts as an oxidant, that is, transferring a hydroxyl group to the carbocationic center. Our results demonstrate, however, that in Ti(III)-mediated free-radical chemistry water can act in a reductive way, working as a hydrogen atom donor. Therefore, we believe that the generally accepted passivity of water in free-radical chemistry should be carefully revised, especially in the presence of Ti(III)- and other metal-centered free radicals.

Synthesis of (+)-3α-Hydroxyreynosin (1) and (+)-Reynosin (17). (+)-3α-Hydroxyreynosin (**1**) was isolated from *Artemisia ludoviciana* ssp. *mexicana,* a medicinal plant used in Mexico as an antihelmintic and to alleviate stomachache, among other ailments.[26] Compound **1** possesses an α-methylene-γ-lactone group, and since this group is mainly responsible for the cytotoxic activity of sesquiterpene lactones,[1b] it is an interesting candidate for biological screening. Nevertheless, this substance is relatively scarce in nature.[26] The chemical structure of **1** was established by Ruiz-Cancino et al. on the basis of spectroscopic analysis and chemical correlation with santamarin, another eudesmanolide found in the same plant.[26] To confirm the chemical structure of **1**, facilitate further biological analysis, and prove the usefulness of the Ti(III)-based procedure for the synthesis of natural eudesmanolides, we planned the chemical preparation of **1** from costunolide using Cp_2TiCl in the key step.

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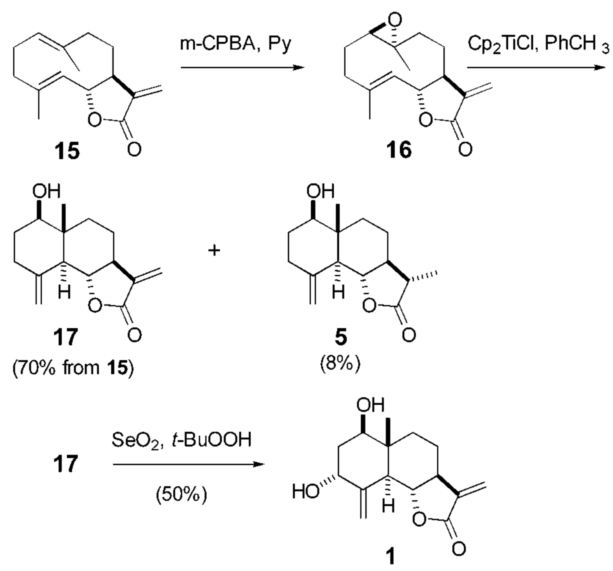
Scheme 3



Racemic costunolide can be obtained by total synthesis,[27] but in this case, to determine the absolute stereochemistry of **1** (see below), we started with (+)-costunolide (**15**) isolated from commercially available Costus Resinoid.[8] Selective oxidation of **15** by treatment with *m*-CPBA in the presence of pyridine (Scheme 3) provided virtually pure **16**[6a] (^{1}H NMR analysis). Treatment of **16** with Cp_2TiCl, in dry toluene, gave a mixture containing (+)-reynosin (**17**) and the hydrogenated derivative **5**. Synthetic **17** was isolated (70% yield from **15**), and its spectroscopic properties, including optical rotation, were in accordance with those of natural (+)-reynosin isolated from *Ambrosia confertiflora*.[28] Reynosin has been synthesized in the past from α-santonin via numerous steps, which only resulted in a 2% overall yield.[3b] It has also been prepared from costunolide via epoxide **16**, but in the reported synthesis the oxirane opening was made with $BF_3{\cdot}OEt_2$,[6a] thus obtaining a mixture of santamarin (ca. 65%) and reynosin (ca. 35%),[6a] and the yield of isolated reynosin was not given. Consequently our Ti(III)-based procedure seems to be the best way so far reported for synthesizing **17**. As far as the hydrogenated product **5** is concerned, it might be due to the reduction of the α-methylene-γ-lactone of **17** (which is a reactive Michael acceptor group) by $Cp_2Ti(H)Cl$ formed from Cp_2TiCl (see Scheme 1). There is little information available concerning the reactivity of $Cp_2Ti(H)Cl$,[29] but the reductive ability of the closely related $Cp_2Zr(H)Cl$ complex (the Schwartz reagent) is well documented.[30] In this way, reduction of **17** to **5** provides additional evidence to support the mechanistic proposal of Scheme 1. Finally, selective allylic oxidation of **17** led to **1** with a moderate yield of 50%. The spectroscopic properties of synthetic **1**, including optical rotation, were in accordance with those reported for natural (+)-3α-hydroxyreynosin,[26] thus confirming the chemical structure of **1**. Inasmuch as the absolute stereochemistry of **15** was previously established by X-ray analysis,[31] the chemical synthesis of **1** and **17** from **15** indicates that the absolute configurations of these natural products are those depicted in this paper.

In summary, we have shown that the combination of a biomimetic strategy with titanium(III)-mediated free-radical chemistry is a useful procedure for the enantiospecific synthesis of **1**, **5**, **17**, and, in principle at least, more than 170 natural eudesmanolides with an exocyclic double bond at $\Delta^{4(15)}$. In addition, as the exocyclic double bond can be further functionalized, this procedure might become a general entry for the synthesis of diverse eudesmanolide types. We have also found that, contrary to general belief, water can act as a reactive hydrogen atom donor in radical chemistry mediated by Ti(III) species. The fact that cheap and environmentally friendly water can be used instead of conventional hydrogen atom donors is of interest from both theoretical and industrial points of view. At the moment we are studying the behavior of water in the presence of Zr(III)-, Hf(III)-, and other transition-metal-centered free radicals. We are also working on the catalytic version of the procedures described here to facilitate the preparation on the gram scale of **1**, **2**, and other bioactive terpenoids which are scarce in nature.

Experimental Section

General Details. All solvents and additives were thoroughly deoxygenated prior to use. NMR signals were assigned with the aid of DEPT and 2D NMR (COSY, HMQC, and HMBC) experiments. The numbering used in the NMR assignments corresponds to the germacrane and eudesmane systems and not the IUPAC nomenclature. Other general experimental details have been reported elsewhere.[32]

(+)-1,10-Epoxy-11*β*,13-dihydrocostunolide (4). This compound was synthesized from 11*β*,13-dihydrocostunolide (**3**), obtained from commercially available Costus Resinoid (Pierre Chauvet S.A., Seillans, France) as follows: the resinoid (16 g) was submitted to flash chromatography (hexane/*t*-BuOMe, 85/15), giving (−)-dehydrocostuslactone[33] (0.7 g) and a mixture (4 g) of (−)-dehydrocostuslactone and (+)-costunolide[34] in a 2/3 ratio, respectively. A 50 mg sample of 10% Pd/C was added to this mixture (dissolved in 100 mL of THF), and the suspension was slowly stirred for 30 min under H_2 at atmospheric pressure. The mixture was then filtered and the solvent removed in vacuo from the filtrate. Flash chromatography (hexane/*t*-BuOMe, 85/15) of the residue afforded 2.5 g of **3**.[34]

Compound **3** (260 mg, 1.12 mmol) dissolved in CH_2Cl_2 (10 mL) was stirred with 70% *m*-CPBA (386 mg, 1.56 mmol) and pyridine (0.2 mL) for 3 h. The solution was then washed with a saturated solution of Na_2SO_3 and brine. The solvent was then removed and the residue (280 mg) analyzed by ^{1}H NMR, which revealed that it was made up of **4** and a trace of pyridine. An analytical sample of **4** crystallized (hexane/*t*-BuOMe) as colorless needles: mp 110−112 °C (lit.[35] mp 105−107 °C); $[\alpha]^{25}_{D}$ −4.9° (*c* 0.01, $CHCl_3$); IR and ^{1}H NMR spectra in ref 35; NOE-dif experiments, proton irradiated (NOEs observed), H_3-14 (H-6, H_3-15), H_3-15 (H-6, H_3-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.3 (C-12), 143.4 (C-4), 124.1 (C-5), 80.5 (C-6), 67.8 (C-1), 61.4 (C-10), 55.2 (C-7), 42.5 (C-11), 39.5 (C-9), 36.2 (C-3), 25.9 (C-8), 24.8 (C-2), 17.7 (C-15), 17.2 (C-14), 13.0 (C-13); HR-

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FABMS *m/z* calcd for $C_{15}H_{22}O_3Na$ 273.1467, found 273.1469. Anal. Calcd for $C_{15}H_{22}O_3$: C, 72.00; H, 8.80. Found: C, 71.75; H, 9.22.

General Procedure 1. Acid-Induced Rearrangements of 4 (Table 1, Entries 1−3). The corresponding acid (0.2 mmol) was added to a solution of **4** (110 mg, 0.44 mmol) in 10 mL of either CH_2Cl_2 or THF (see Table 1). The solution was stirred for 1 h, and the solvent was then removed. The crude residue was dissolved in *t*-BuOMe, and the ethereal solution was washed with $NaHCO_3$-saturated solution and brine before being dried over anhyd Na_2SO_4. The solvent was removed to give a colorless residue which was analyzed by ^1H NMR. Column chromatography (20% $AgNO_3$/silica gel; hexane/*t*-BuOMe, 1/4) of the residue from the experiment of entry 1 afforded 42 mg of **6**[14] and 29 mg of a mixture of **6** and **7**[15] in relative proportions of 2/1, respectively.

General Procedure 2. Cp_2TiCl-Promoted Rearrangements of 4 (Table 1, Entries 4−11). Cp_2TiCl was prepared as follows: rigorously deoxygenated THF (25 mL) was added to a mixture of Cp_2TiCl_2 (212 mg, 0.85 mmol) and Mn dust (125 mg) under an Ar atmosphere, and the suspension was stirred until it turned lime green (after about 20 min). At this point the THF was either kept in the suspension or removed in vacuo and replaced by a second solvent (25 mL), according to the intended reaction conditions (see Table 1). Subsequently, epoxide **4** (70 mg, 0.25 mmol) in the suitable solvent (25 mL), accompanied by an additive in the cases of entries 7 and 11 (Table 1), was added to the green suspension, and the mixture was stirred for 30 min. The solvent was then removed, *t*-BuOMe (30 mL) added, and the solution washed with 10% HCl and brine. The solution was dried over anhyd Na_2SO_4, and the ether was removed, leaving a residue which was analyzed by ^1H NMR spectroscopy. Flash chromatography (hexane/*t*-BuOMe, 2/3) of the residue obtained from the experiment summarized in entry 4 afforded **5** (56 mg, 80% yield), while flash chromatography (hexane/*t*-BuOMe, 1/1) of the residue from the experiment of entry 11 furnished **8** (48 mg, 68% yield).

Data for (+)-11β,13-Dihydroreynosin (5): colorless needles; mp 120−122 °C (lit.[13] mp 129 °C); $[\alpha]^{25}_D$ +98.7° (*c* 0.02, $CHCl_3$); IR and ^1H NMR spectra in ref 13; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.6 (C-12), 143.0 (C-4), 110.0 (C-15), 79.4 (C-6), 77.9 (C-1), 52.3 (C-7), 52.2 (C-5), 42.8 (C-10), 41.1 (C-11), 35.8 (C-9), 33.5 (C-3), 31.0 (C-2), 22.9 (C-8), 12.4 (C-13), 11.5 (C-14).

Data for (+)-4α,11β,13,15-Tetrahydroreynosin (8): colorless needles; mp 150−152 °C; $[\alpha]^{25}_D$ +42.2° (*c* 0.006, $CHCl_3$); IR (film) ν_{max} 3478, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.01 (dd, J = 11.5, 10.3 Hz, 1H, H-6), 3.31 (dd, J = 10.5, 4.2 Hz, 1H, H-1), 2.34 (dq, J = 12.5, 6.9 Hz, 1H, H-11), 1.95 (dt, J = 13.2, 3.1 Hz, 1H, H-9β), 1.85 (dq, J = 12.9, 3.3 Hz, 1H, H-8α), 1.50 (dd, J = 11.5, 4.9 Hz, 1H, H-5), 1.23 (d, J = 6.9 Hz, 3H, H-13), 1.02 (s, 3H, H-14), 1.00 (d, J = 7.6 Hz, 3H, H-15); NOE-dif experiments, proton irradiated (NOEs observed), H-1 (H-5), H-6 (H-11, H_3-14, H_3-15); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.8 (C-12), 80.3 (C-6), 79.6 (C-1), 53.5 (C-7), 50.0 (C-5), 42.0 (C-11), 41.9 (C-10), 39.6 (C-9), 30.5 (C-2), 27.1 (C-4), 26.5 (C-3), 23.4 (C-8), 15.1 (C-15), 15.0 (C-14), 12.6 (C-13); EIMS *m/z* 252 $[M]^+$ (0.4), 237 (2.1), 219 (1.3), 193 (14), 166 (47), 165 (25), 161 (13), 148 (100), 133 (22), 122 (38), 81 (59), 68 (36), 55 (53); HRFABMS *m/z* calcd for $C_{15}H_{24}O_3Na$ 275.1623, found 275.1622. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.43; H, 9.52. Found: C, 71.62; H, 9.04.

4α-Deuterio-11β,13,15-Trihydroreynosin (12). Treatment of **4** (100 mg) as described in General Procedure 2, under the experimental conditions summarized in entry 11 (Table 1) but using D_2O (0.4 mL) instead of H_2O, left a residue which was submitted to flash chromatography (hexane/*t*-BuOMe, 1/1). In this way products **5** (12 mg) and **12** (34 mg) were isolated. Data for compound **12**: ^1H and ^{13}C NMR spectra matched those of **8** except for the significant signals referred to in the Results and Discussion; NOE-dif experiments, proton irradiated (NOEs observed), H-1 (H-5), H-6 (H-11, H_3-14, H_3-15); EIMS *m/z* 253 $[M]^+$ (0.7), 238 (2.0), 220 (1.5), 194 (16), 167 (59), 165 (34), 162 (15), 149 (100), 134 (24), 122 (48), 81 (55), 68 (57), 55 (58); HRFABMS *m/z* calcd for $C_{15}H_{23}DO_3Na$ 276.1686, found 276.1679.

Costunolide 1,10-Epoxide (16). Following the same procedure described for the synthesis of **4**, compound **16**[6a] was obtained in quantitative yield, starting with (+)-costunolide (**15**) isolated from commercially available Costus Resinoid:[8] IR, ^1H NMR, and mass spectra of **16** in refs 6a and 13; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1 (C-12), 144.4 (C-4), 139.7 (C-11), 124.0 (C-5), 119.6 (C-13), 80.8 (C-6), 67.6 (C-1), 51.0 (C-7), 39.3 (C-9), 36.1 (C-3), 25.3 (C-8), 24.8 (C-2), 17.7 (C-15), 17.1 (C-14).

(+)-Reynosin (17). Strictly deoxygenated THF (25 mL) was added to a mixture of Cp_2TiCl_2 (372 mg, 1.51 mmol) and Mn dust (270 mg) under an Ar atmosphere, and the suspension was stirred until it turned lime green (after about 20 min). THF was then pumped off, deoxygenated toluene (25 mL) and epoxide **16** (125 mg, 0.5 mmol) dissolved in toluene (25 mL) were added, and the mixture was stirred for 30 min. Toluene was then removed in vacuo, *t*-BuOMe added, and the ethereal solution washed with 10% HCl and brine. The organic layer was dried over anhyd Na_2SO_4 and the solvent removed. Flash chromatography (hexane/*t*-BuOMe, 2/3) of the residue gave **17** (88 mg, 70% yield) and **5** (10 mg, 8%). Synthetic **17** was obtained as a white solid: $[\alpha]^{25}_D$ +96° (*c* 0.005, EtOH) (natural reynosin:[28] $[\alpha]^{25}_D$ +180°); IR and ^1H NMR spectra in refs 28 and 3b; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7 (C-12), 142.5 (C-4), 139.3 (C-11), 117.2 (C-13), 110.7 (C-15), 79.7 (C-6), 78.3 (C-1), 53.0 (C-5), 49.6 (C-7), 43.0 (C-10), 53.7 (C-9), 33.6 (C-3), 31.3 (C-2), 21.5 (C-8), 11.7 (C-14).

(+)-3α-Hydroxyreynosin (1). Compound **17** (60 mg, 0.24 mmol) in CH_2Cl_2 (6 mL) was added to a solution of SeO_2 (15 mg, 0.12 mmol) and *t*-BuOOH (0.22 mL of a 5−6 M solution in decane) in CH_2Cl_2 (2 mL). The mixture was stirred for 26 h, then diluted with CH_2Cl_2, and washed with brine. The organic layer was dried over anhyd Na_2SO_4 and the solvent removed. The residue was submitted to flash chromatography (*t*-BuOMe), affording **1** (32 mg, 50% yield) and **17** (5 mg, 8%). Synthetic **1** was obtained as a white solid: mp 230−232 °C; $[\alpha]^{25}_D$ +90.7° (*c* 0.004, acetone) (natural 3α-hydroxyreynosin:[26] mp 236−237 °C, $[\alpha]^{25}_D$ +73°); ^1H NMR (CD_3COCD_3, 300 MHz) δ 5.93 (d, J = 3.2 Hz, 1H, H-13a), 5.45 (d, J = 3.2 Hz, 1H, H-13b), 5.04 (br s, 1H, H-15a), 4.85 (br s, 1H, H-15b), 4.27 (q, J = 2.9 Hz, 1H, H-3), 4.08 (t, J = 10.9 Hz, 1H, H-6), 3.95 (br s, 1H, OH), 3.89 (dt, J = 11.7, 5.0 Hz, 1H, H-1), 3.71 (d, J = 5.3 Hz, 1H, OH), 2.77 (d, J = 11.1 Hz, 1H, H-5), 2.64 (tq, J = 11.1, 3.2 Hz, 1H, H-7), 1.95 (ddd, J = 13.6, 4.7, 2.6 Hz, 1H, H-2α), 0.79 (s, 3H, H-14); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 170.8 (C-12), 147.6 (C-4), 141.2 (C-11), 116.1 (C-13), 111.2 (C-15), 80.0 (C-6), 73.6 (CH), 73.2 (CH), 50.4 (C-5), 48.2 (C-7), 44.0 (C-10), 39.5 (C-2), 36.5 (C-9), 22.1 (C-8), 11.1 (C-14); HRFABMS *m/z* calcd for $C_{15}H_{20}O_4Na$ 287.1259, found 287.1260.

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