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Ti(III)-Catalyzed Cyclizations of Ketoepoxypolyprenes: Control over the Number of Rings and Unexpected Stereoselectivities

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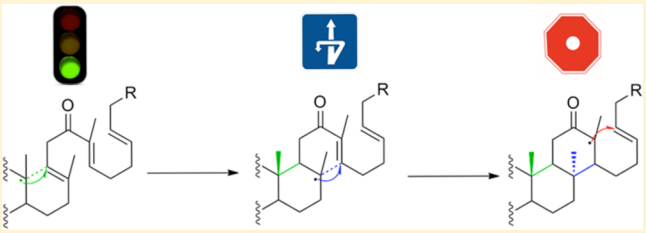
Supporting Information

ABSTRACT: We describe a new strategy to control the number of cyclization steps in bioinspired radical (poly)-cyclizations involving epoxypolyenes containing keto units positioned along the polyene chain. This approach provides an unprecedentedly straightforward access to natural terpenoids with pendant unsaturated side chains. Additionally, in the case of bi- and tricyclizations, decalins with *cis* stereochemistry have been obtained as a consequence of the presence of the ketone. The preferential formation of *cis*-fused adducts was rationalized using DFT calculations. This result is completely unprecedented in biomimetic cyclizations and permits the access to natural terpenoids with this stereochemistry, as well as to non-natural analogues.

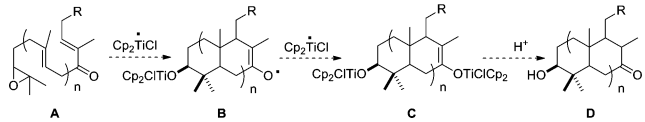


INTRODUCTION

In recent years, bioinspired radical cyclizations have emerged as a powerful tool for the efficient synthesis of different terpenic structures, constituting one of the best ways for the preparation of structures such as these.[1] It is also worth noting that, in many cases, these cyclizations represent a complementary approach to more developed biomimetic cationic cyclizations.[2] Moreover, it is expected that new chemo- and stereoselectivities could be obtained by taking into account the significant differences between their corresponding reactive intermediates and the catalysts used. One of the main differences is the nature of the alkenes present in the polyprenic starting material. Electron deficient alkenes are not usually suitable functionalities for cationic cyclizations of simple polyprenic precursors.[2,3] On the other hand, these electron deficient alkenes can efficiently react with carbon centered radicals.[4] Thus, the expected final products using conventional cationic cyclizations and radical ones might not be the same. Within this context, we focused our attention on Ti(III)-catalyzed radical cyclizations[5−7] of epoxypolyprenes (A) presenting an internal keto functionality in their structures (Scheme 1). We hypothesized that enol radical B, obtained during the bioinspired radical cyclization, could be readily trapped by highly oxophilic radical species Cp_2TiCl.[8,9]

After an acidic quenching, the final (poly)cyclic product would provide a saturated ketone, which could be transformed in other functions present in natural terpenes. Notably, the number of rings in the final carbocycle would depend on the position of the keto group, and not on the number of prenyl subunits in the starting polyprene, as is the case in previous cationic or radical cyclizations.[1,2] Thus, the cyclization might be terminated even in the presence of additional unsaturations. This result would mimic the incomplete polycyclizations, which are responsible for the presence of terpenes with (poly)prenic side chains in nature.

Scheme 1. Working Hypothesis



These compounds are widespread and are present in several natural organisms, such as plants, insects, fungus, and so forth.[10] Moreover, they exhibit diverse and interesting biological properties such as anti-inflammatory, cytotoxic, antifeedant, and antimicrobial effects.[10] All these facts contribute to making them attractive targets in organic synthesis. Nevertheless, efficient methods for their synthesis have remained elusive until now, owing to the fact that the efficient control of the number of cyclization steps is challenging. A remarkable example is the use of allyl silanes by Corey's group to orientate the termination in cationic biomimetic cyclizations.[11] Nevertheless, the preparation of the

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starting materials containing such functionality is not trivial,[11] increasing the complexity and the number of steps in the synthetic sequence. Interestingly, we have also observed that in some substrates tested in this work, the keto group can dramatically affect the stereochemistry of the reaction, resulting in unprecedented bioinspired cyclizations yielding exclusively *cis*-fused decalins.[12] *cis*-Decalins[13] are not very common in terpenes, although it has been very recently suggested that they may possess enhanced biological activities compared with their *trans* analogues.[14]

In this study we conclude that α,β-unsaturated ketones located in suitable positions of an epoxypolyprene chain can be used to control two key features in the synthesis of natural terpenes: (i) the number of carbocycles, and (ii) the stereochemistry of the cyclization. As an example of the usefulness of this new protocol, we have used some of the resulting cyclization products in the synthesis of terpenic structures **1**−**6** (see Figure 1). Thus, functional group

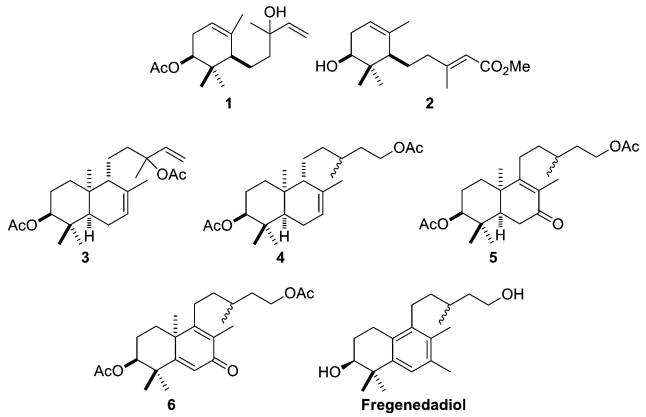


Figure 1. Synthesized compounds **1**−**6**.

interconversions from original saturated ketone to α,β-unsaturated ketone or alkene groups allow the total synthesis of two natural terpenes **1** and **2**,[15,16] the unnatural *cis*-fused terpenes **3**−**5**, and an advanced intermediate **6** in the synthesis of fregenedadiol.[17] Interestingly, more common *trans*-decalines are also available from α,β-unsaturated ketones using known protocols.[18]

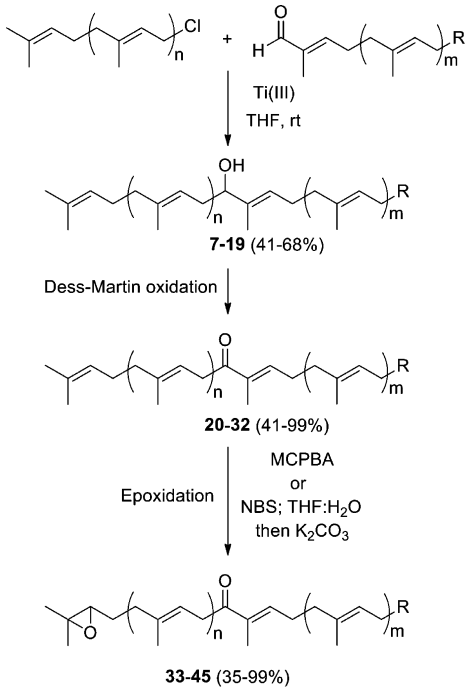
RESULTS AND DISCUSSION

Cyclization Reaction. The required starting epoxypolyprenes were straightforwardly synthesized following the method depicted in Scheme 2. First, we prepared the corresponding hydroxypolyprenes using a modification of our previously described α-prenylation protocol,[7j,19] yielding the corresponding hydroxypolyprenes **7**−**19** (see Scheme 3) (see Supporting Information for experimental details).

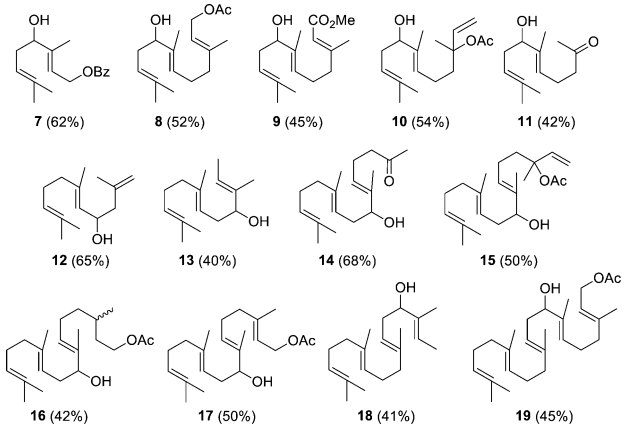
Subsequent hydroxyl group oxidation of allylic alcohols **7**−**19** by Dess-Martin periodinane to yield the corresponding ketones **20**−**32**[20] and regioselective epoxidation using described methods[7] allowed us to prepare a set of starting ketoepoxypolyprenes **33**−**45** with different lengths and functionalities (see Supporting Information for experimental details).

With these starting ketoepoxypolyprenes **33**−**45** in hand, we submitted them to our titanocene(III)-bioinspired cyclization procedure using substoichiometric amounts of Cp_2TiCl.[7] In this case, we selected the usual aprotic combination of

Scheme 2. General Protocol for the Preparation of Starting Ketoepoxypolyprenes 33−45



Scheme 3. Hydroxypolyprenes 7−19 from Ti(III)-Mediated Barbier-Type Reactions



Me_3SiCl/2,4,6-collidine and Mn as a regenerating agent for Cp_2TiCl species since it is compatible with the presence of the oxirane. The results are summarized in Table 1.

The results depicted in Table 1 show that our initial hypothesis was correct, allowing us to prepare different mono-, bi-, and even tricyclic compounds, controlling very efficiently the cyclization sequence. In all cases, we did not detect subsequent additions of the enol radical to other alkenes present in the molecule, even in trace amounts (entries 2−4, 9, 11, and 13), independently of the substitution pattern and functionality of the final side chain. Nevertheless, such an intermediate radical or the final titanocene(IV) enolate is able to react with the carbonyl group present in the side chain of substrate **37**, giving aldol **50** (entry 5). We also tried regioisomeric ketone **38**. In this case, a Michael-type addition exclusively yielded cyclopentane **51** (entry 6). As expected, the relative position of carbonyl group is essential for the regioselectivity of the radical addition.

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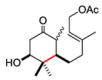
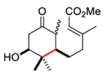
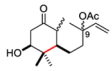
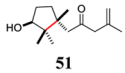
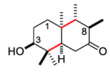
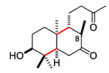
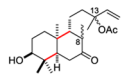
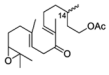
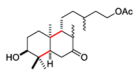
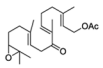
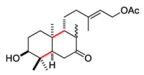
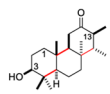
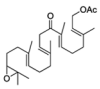
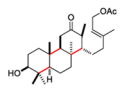
Table 1. Ti(III)-Catalyzed Cyclization of Epoxypolyprenes 33−45[a]

Entry	Starting epoxide	Product[b]	Yield (%)
1	 **33**	 **46**	99[c]
2	 **34**	 **47**	64[c]
3	 **35**	 **48**	80
4	 **36**	 **49**	67[d]
5	 **37**	 **50**	59
6	 **38**	 **51**	45
7	 **39**	 **52**	67
8	 **40**	 **53**	60
9	 **41**	 **54**	56[e]
10	 **42**	 **55**	59[e]
11	 **43**	 **56**	50
12	 **44**	 **57**	41
13	 **45**	 **58**	48[f]

[a]Conditions: Cp_2TiCl_2 (0.2 mmol), Mn (8 mmol), 2,4,6-collidine (7 mmol), and TMSCl (4 mmol). [b]Products containing a methyl group in the α position of the ketone (C-6 or C-8) were usually isolated as a mixture of α:β epimers. See SI for details. [c]An additional minor isomer is also observed. See SI for details. [d]1:1 mixture of epimers at C-9. [e]1:1 mixture of epimers at C-13. [f]9:1 mixture of *trans*−*transoid*−*cis* and *trans*−*transoid*−*trans* isomers.

Furthermore, the yields observed were comparable to and even higher than those obtained in the parent bioinspired protocol.[1,7] The cyclization process is also highly stereoselective with the exception of the methyl group in vicinal position to the ketone group, which was usually obtained as a mixture of epimers. This presents a minor drawback, however, since this position is usually modified in the subsequent synthetic steps. In monocycles **46**−**49** we mainly observed a *cis*-relationship between the hydroxyl group at C-3 and the side chain at C-5.[7] Remarkably, bicyclic products **52**−**56** presented a *cis*-fused decalin despite the fact that radical additions to double bonds with *E* configuration usually yield *trans* decalines.[1] This unprecedented stereochemistry was confirmed by X-ray analysis of *p*-nitrobenzoate **59**, a simple derivative of **52**. Thus, we could also assign the relative configuration of the side chain at C-9.

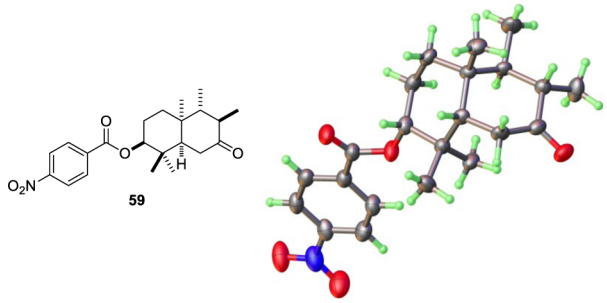


Figure 2. Crystal structure for compound **59**.

Tricyclic products **57** and **58** mainly presented a *trans* fusion between the two first cyclohexanes, and a *cis* fusion between the second and third cyclohexane rings (see Supporting Information for experimental details), suggesting that the *cis* stereochemistry is intrinsic to the radical addition reaction when the ketone group is present. The reason for this surprising stereoselectivity was not clear. The use of different titanocene(III) catalysts with different steric or electronic characteristics always yielded the *cis*-fused compounds. However, in the presence of another functional group in the same position, such as acetate, *trans*-fused structures were obtained.[7j]

Theoretical Calculations. To shed light on this unexpected chemo- and stereoselectivity, we made use of theoretical calculations (see Supporting Information for experimental details) carried out at the DFT-B3LYP level[21−23] with the Gaussian 09 program.[24] The geometries were fully optimized by the gradient technique using polarized 6-31G* basis set for all the atoms.[25] This theoretical level has been extensively used to rationalize titanocene(III) chemistry.[7a,d,f,k,9a,b,d] The nature of the optimized structures, either transition states or intermediates, was assessed through a frequency calculation, and the changes of Gibbs free reaction energies (ΔG values) were obtained by taking into account zero-point energies, thermal motion, and entropy contribution at standard conditions (temperature of 298.15 K, pressure of 1 atm). We have concentrated our discussion on the corresponding enthalpic values.

A key point of this theoretical study is the suitable selection of the titanocene(III) active species in the catalytic cycle. Using epoxypolyprene **I** as model, we explored the coordination capabilities of epoxide and ketone groups toward different oxophilic titanocene(III) complexes. Taking into account that THF is used as solvent, the presence of a THF molecule as ligand has also been considered to maintain all the potential

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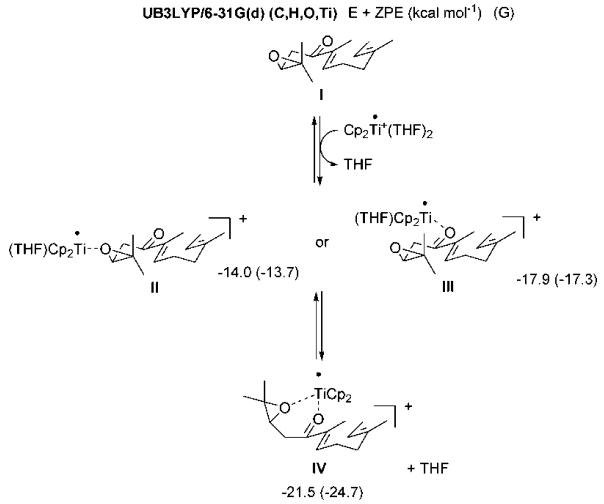
intermediates coordinatively saturated, thus avoiding any artificial bias during the calculations.[26,27] Cationic complex $Cp_2Ti^+(THF)_2$ resulted as the best ligand for compound **I**.[28,29] Moreover, Gansäuer's group has experimentally demonstrated that coordination of epoxides to Cp_2TiCl is accompanied by dissociation of the chloride anion to form the true cationic active species.[30] Therefore, we selected titanocene(III) cationic complexes as the active species in our catalytic cycle. In this case, we also guarantee a homogeneous treatment of the energies, avoiding artificial charge separations. After an exhaustive sampling of structures presenting different conformations and binding geometries, we could conclude that complex **III** is slightly favored (3.6 kcal mol^{-1}) in free energy terms (Scheme 4). As expected, the complex possessing both

Scheme 4. Calculated Minimum Energy Structures II–IV of Epoxypolyprene I and $Cp_2Ti^+(THF)_2$

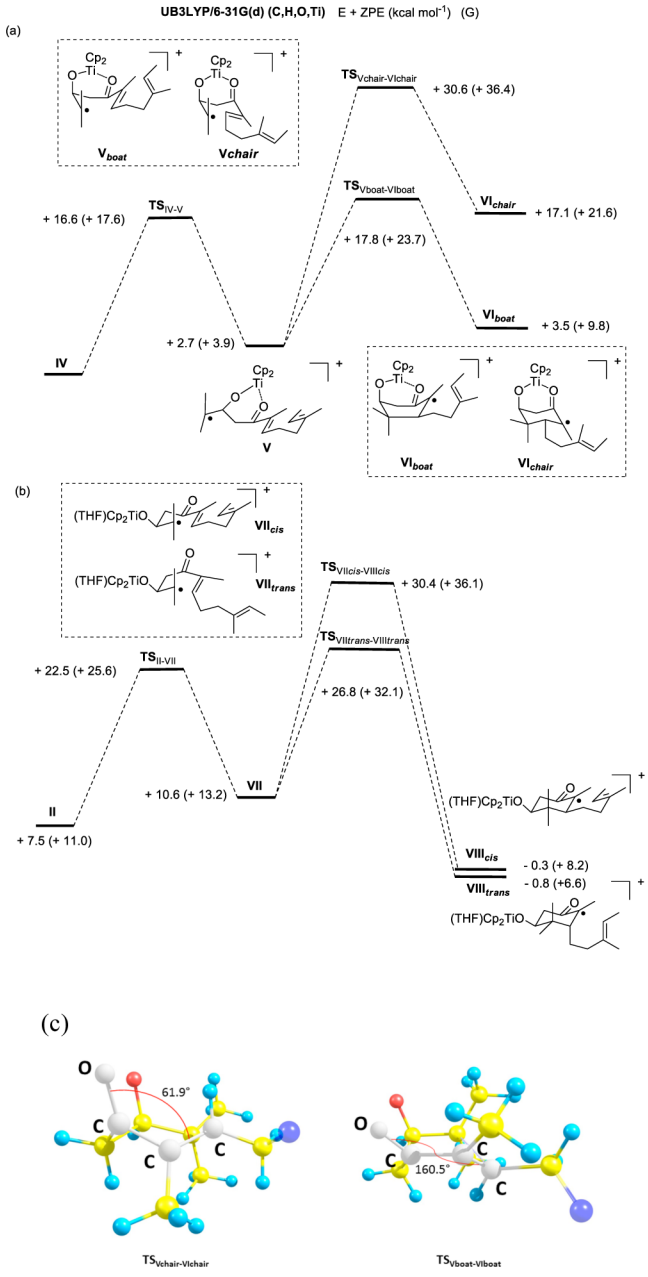


groups coordinated simultaneously to Cp_2Ti^+ (**IV**) is the most favorable one by 11 kcal mol^{-1} and can be considered the resting state of the system.[8,31]

Homolytic epoxide opening of such complexes (**II**–**IV**) leads to a tertiary radical able to undergo 6-*endo*-trig radical cyclizations to yield monocyclic radicals. Taking into account the thermodynamic stability of **IV** we initially focused our attention in such intermediate. Homolytic epoxide opening of **IV** to yield radical **V** is slightly endothermic and takes place with a calculated activation energy of 16.6 kcal mol^{-1} (Scheme 5a). Then, we explored different cyclization processes from radical **V** to monocyclic radical type **VI**. For this rigid structure, we could only find one chairlike and one boat-like transition state. The lowest energy for the transition state was found for templated structure $\mathbf{VI}_{boat}$ (17.8 kcal mol^{-1}). This cyclization is slightly endothermic (3.5 kcal mol^{-1}), in clear contrast with the thermodynamically unfavorable monocycle $\mathbf{VI}_{chair}$ (17.1 kcal mol^{-1}). These calculated values can be explained based on the geometrical constraints of intermediates **V** (Scheme 5c). In the transition state from $\mathbf{V}_{boat}$ to $\mathbf{VI}_{boat}$ the geometry of the system allows an efficient conjugation between the alkene and the titanoce(IV)-activated carbonyl group and, therefore, the radical addition is highly favored. On the other hand, in the transition state from $\mathbf{V}_{chair}$ to $\mathbf{VI}_{chair}$ the alkene is rotated and the conjugation is disrupted, disfavoring the radical addition.

Taking into account the modest binding energies calculated before (Scheme 4), a dynamic situation is expected at room

Scheme 5. Activation and Reaction Energies Calculated for Cyclization Reactions of the Model Radicals[a]



[a](a) **V**, (b) **VII**, and (c) geometrical details of transitions states $\mathbf{V}_{chair}$ to $\mathbf{VI}_{chair}$ and $\mathbf{V}_{boat}$ to $\mathbf{VI}_{boat}$ (some atoms have been omitted for clarity). Energies are referenced to resting state **IV** from Scheme 4. TS = transition state, ZPE = zeropoint energy.

temperature. Within this context, a Curtin-Hammett scenario could be operative. In this sense, we also studied the behavior of energetically unfavorable nontemplated radical **VII**, which is derived from complex **II** (Scheme 5b) to rule out such a possibility. The lowest activation energy (16.2 kcal mol^{-1} referred to **VII**) corresponds to a monocyclization process yielding monocyclic radical $\mathbf{VIII}_{trans}$, which possesses the opposite stereochemistry to that experimentally observed. However, the difference between the lowest activation energies for both reaction pathways is less than 2 kcal mol^{-1}. Consequently the experimental results, in which the final monocyclic radical presents a *cis* relationship between the

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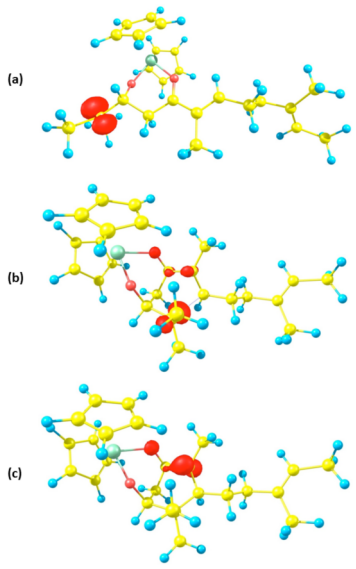
hydroxyl group at C-3 and the side chain at C-5, can be explained based on a template effect derived from the coordination capabilities of the titanium center. Such a reaction pathway is globally favored by 9 kcal mol^{-1}. Spin density of key monocyclic **VI**$_{boat}$ was then calculated showing that the electron is mainly located at the carbon atom and could undergo subsequent radical additions (Scheme 6).

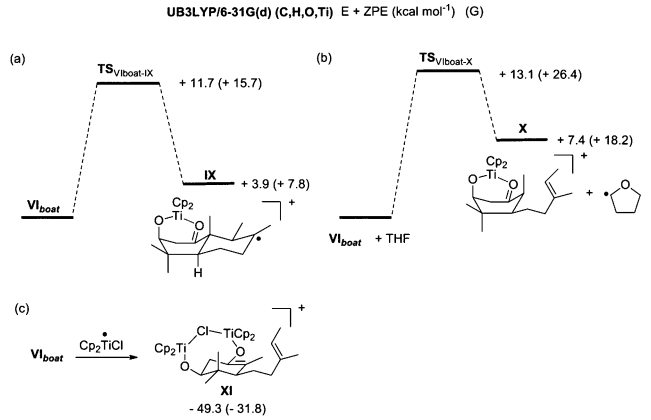
Scheme 6. Calculated Spin Densities[a]



[a](a) **V**, (b) **TS-V**$_{boat}$**-VI**$_{boat}$ and (c) **VI**. The isodensity surfaces represented correspond to a cut-off value of 0.018 e·bohr^{-3}.

At these points, we explored three subsequent reactions of this enol radical (Scheme 7): (a) a second radical addition, (b)

Scheme 7. Activation and Reaction Energies Calculated for Reactions of the Model Radical VI$_{boat}$[a]

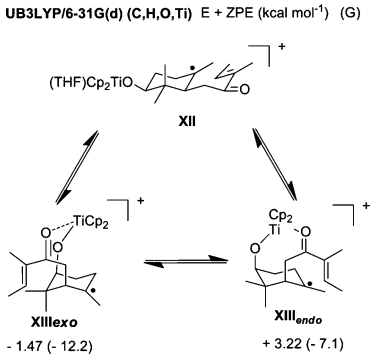


[a]TS = transition state, ZPE = zeropoint energy.

a hydrogen-atom transfer from THF, and (c) a reaction with another titanocene(III) radical center. In the first case, the templated structure **VI**$_{boat}$ can only cyclize by the β-face to yield the bicyclic radical **IX**. This reaction is slightly endothermic (3.9 kcal mol^{-1}) and presents a moderate activation energy (11.7 kcal mol^{-1}). With this calculated data, we can consider that the cyclization reaction is in fact reversible[32] and the monocyclic radical **VI**$_{boat}$ dominates the equilibrium. On the other hand, the solvent (THF) can be considered as a hydrogen-atom source and the enol radical could be directly deactivated by a hydrogen-atom transfer reaction. We explored such a possibility to explain the incapacity of intermediate **VI**$_{boat}$ to continue the cyclization process. We found a viable transition state in which the hydrogen atom is transferred to the carbon atom.[33] Such reaction gave an energetically disfavored result (7.4 kcal mol^{-1}) and could only explain the experimental results if we assume that the resulting THF-derived radicals diffuse in the solvent and are irreversibly trapped. As we proposed in our working hypothesis, the direct reaction of templated enol radical **VI**$_{boat}$ with Cp_2TiCl, present in the reaction media, is barrierless and highly exothermic (−43.9 kcal mol^{-1}). This favorable process joined to the stabilization of the radical by the carbonyl group could also explain why subsequent cyclizations were never observed. Finally, the cycle can proceed by reaction of the titanocene(IV) alkoxides **XI** by other oxophilic species such as TMSCl. The final Ti(IV) chlorides can be reduced by manganese dust, thus closing the catalytic cycle.

All the previous findings can be extended to the rest of the described cyclizations. Nevertheless, the reason for the observed *cis* stereoselectivity in the bi- and tricyclization processes is not clear. In this case, we used model monocyclic radical **XII** in our calculations. This species is in equilibrium with two Ti-templates **XIII**. Such species are energetically favored in free energy terms, specially the *exo* form **XIII**$_{exo}$ (−12.2 kcal mol^{-1}). Interestingly, the penalty cost to dissociate the carbonyl group is low, allowing interconvertion from **XIII**$_{exo}$ to **XIII**$_{endo}$ at room temperature, via radical **XII** or even through a direct rotation (Scheme 8). In Scheme 9, we summarized the

Scheme 8. Calculated Energies for the Proposed Ti-Templated Radical Intermediates, XIII$_{exo}$ **and XIII**$_{endo}$**, on the Stereoselective *cis* Bicycle Formation Pathway Using Intermediate XII as Reference**[a]



[a]ZPE = zeropoint energy.

activation energies for the formation of bicyclic products **XIV** and **XV** from both potential intermediates **XII** and **XIII**$_{endo}$. As it can be seen, cyclization of **XII** mainly would lead to *trans*-decalins in contrast with the observed stereochemistry. Intermediate **XIII**$_{endo}$ can only evolve to the final *cis* product. Interestingly, in this case we could find two transition states leading to two diastereoisomers. The computed energy for the transition state to yield **XV**$_b$, which presents the experimentally observed stereochemistry, is only 6.9 kcal mol^{-1}.

On the other hand, the observed *cis* ring closing in the formation of the tricycle cannot be due to any template effect, which is not plausible from a structural point of view. To study

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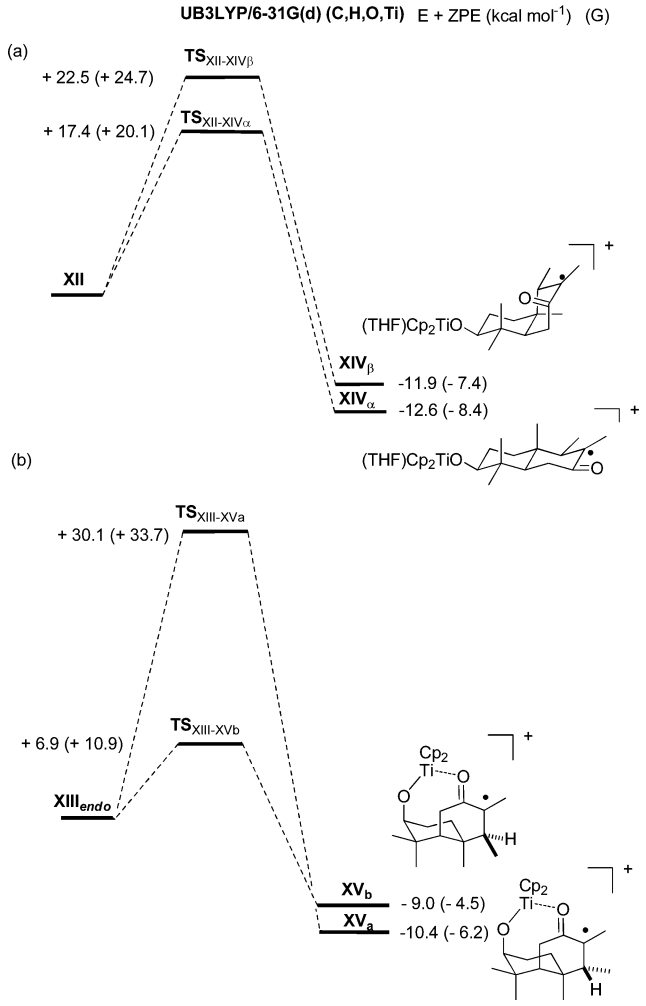
Scheme 9. Activation and Reaction Energies Calculated for Reactions of the Model Radicals XII and XIII[a]



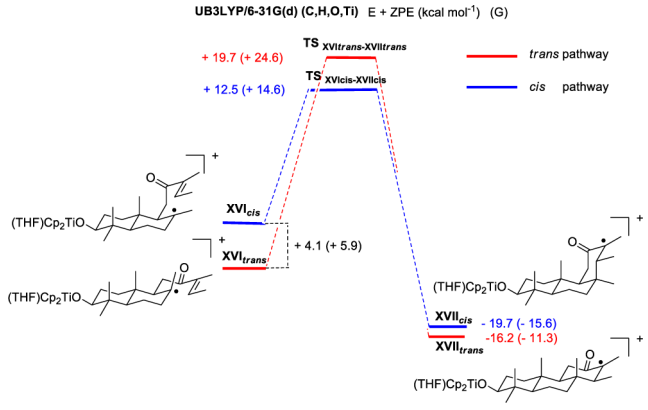
[a]TS = transition state, ZPE = zeropoint energy.

this situation we used model bicyclic radical compound **XVI**. Remarkably, the side chain presenting the ketone group adopts less easily the required *trans* 6-membered transition state once the bicycle (*trans*) is formed. We calculated both reaction mechanisms as shown in Scheme 10. Once again, the *cis* pathway was favored ($\mathbf{XVI}_{cis}$ to $\mathbf{XVII}_{cis}$) due to a low-energy transition state (12.5 kcal mol^{-1}), even if a prearrangement (of about 4.1 kcal mol^{-1}) is required.[34]

To sum up, theoretical calculations revealed that the presence of the ketone group is relevant for two processes. First, it is able to stabilize transient radicals and also to react with oxophilic radical species in the reaction media, thus avoiding subsequent cyclization reactions. Second, it forces the corresponding side chain to follow a reaction pathway through the β-face, promoting the *cis* stereochemistry in the final cyclization reaction. The reason for this preferred stereochemistry is a combination of template (for the bicyclic structures, see above) and/or conformational effects (for the tricyclic structures).

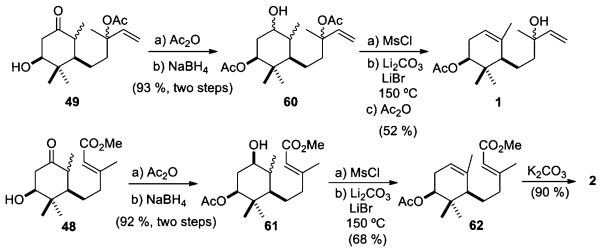
Synthetic Applications. Monocyclic structures **46**–**49** are versatile synthons and they can be easily transformed into different terpenic substructures. Thus, the synthesis of sesquiterpene **1**, isolated from the plant *Atermisia chamaemelifolia*,[15] started from monocycle **49** (Scheme 11). It was

Scheme 10. Activation and Reaction Energies Calculated for Reactions of the Model Radicals XVI[a]



[a]TS = transition state, ZPE = zeropoint energy.

Scheme 11. Synthesis of Sesquiterpenes 1 and 2

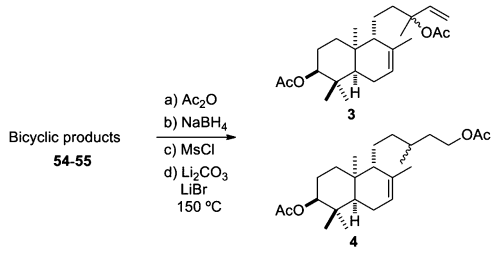


transformed in the diacetate **60** in two steps with excellent global yield. Subsequently, the hydroxyl group was mesylated and the mesyl group eliminated by basic treatment, yielding the corresponding trisubstituted alkene in good yield (61%, two steps). Finally, selective acetylation of secondary hydroxyl group gave **1**, in only 5 steps from **49** and in a 48% overall yield. Sesquiterpene **2**, obtained from the plant *Celistopholis glauca*,[16] was prepared from cyclization product **48** using a similar procedure in only 5 steps (57% overall yield). Gratifyingly, this new strategy allows access to elusive natural terpenoids with excellent yields and a reasonable number of synthetic steps, thus demonstrating the usefulness of our methodology.

A similar synthetic sequence allowed us to prepare the *cis*-fused terpenic structures **3** and **4**, which are structurally related to existing natural labdanes (Scheme 12).[35,36] As expected, comparison between their ^{1}H and ^{13}C NMR spectra and bibliographic *trans* stereoisomers showed differences between the natural compounds and our synthetic analogues.

Beyond elimination processes, the dehydrogenation of cyclohexanones present in compounds **46**–**58** might also

Scheme 12. Synthesis of *cis*-Fused Compounds 3 and 4



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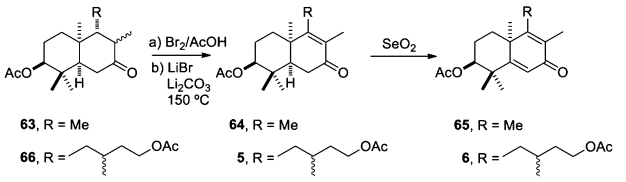
yield interesting terpenic building blocks. Thus, for example, we explored the possibility with model substrate **63** (Scheme 13).

Scheme 13. Transformation of 63 and 66 into Natural Related structures



Two conjugated double bonds can be introduced sequentially in the structure using Br_2 in AcOH and SeO_2 (see Supporting Information for experimental details). Compounds **64** and **65** are related with dri-8-en-7-one[37] and dri-5,8-dien-7-one,[38] interesting building blocks for drimane synthesis. The same sequence was carried out with compound **66**. α,β-Unsaturated ketone **5** was obtained in good yield and is structurally related with known labdanes, such as rhinocerotinoic acid.[39] The second oxidation step yielded compound **6**, an advanced precursor for the synthesis of fregenedadiol,[17] a bicyclic diterpene containing an aromatic ring.

CONCLUSIONS

To sum up, in this paper we have described a new strategy to control Ti(III)-catalyzed bioinspired radical cyclizations using α,β-unsaturated ketones placed in suitable positions in the starting ketoepoxypolyenes. These starting materials are easily prepared using previously described titanocene(III)-mediated Barbier-type prenylations. This method allowed us to control the number of cyclizations, yielding the corresponding cyclic products with complete selectivity and high yields. Preparing such structures is challenging using other classical biomimetic cyclization processes. The presence of ketone groups in the final cyclization products facilitates the installation of tri- or tetrasubstituted alkenes usually present in natural terpenes. This alkene regioselectivity is also complementary to the exocyclic regioselectivity observed in the parent Cp_2TiCl-catalyzed reaction. This procedure has allowed us to synthesize the natural sesquiterpenoids **1** and **2**, in a few steps and with acceptable yields, meeting the demand for selectivity and atom and step economy required for any modern synthesis.[40] Additionally, the presence of ketone groups in the polyene leads to the formation of *cis*-fused decalins from *E*-alkenes, which is unprecedented in the field of biomimetic radical cyclizations. A possible explanation has been explored by means of DFT calculations, which showed that either template or conformational effects could operate to give this preferred stereochemistry. This fact is especially relevant for the exploration of new compounds with important biological activities.

EXPERIMENTAL SECTION

General Details. Deoxygenated solvents and reagents were used for all reactions involving Cp_2TiCl. THF was freshly distilled from Na. CH_2Cl_2 was freshly distilled from P_2O_5. Products were purified by flash chromatography on Merck silica gel 50. Yields refer to analytically pure samples. NMR spectra were recorded in NMR 300, 400, and 500 MHz spectrometers.

General Procedure for Ti^{III}-Catalyzed Bioinspired Cyclizations. Strictly 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). Then, a solution of epoxypolyprene (1 mmol), 2,4,6-collidine (7 mmol) in THF (2 mL), and Me_3SiCl (4 mmol) were added and the mixture was stirred for 16 h. The reaction was then quenched with 2 N HCl and extracted with EtOAc. The organic layer was washed with brine, dried (anhyd Na_2SO_4), and the solvent removed. Products **46**−**58** were isolated by flash chromatography of the residue (hexane/EtOAc) and characterized by spectroscopic techniques. Results are depicted in Table 1. See SI for more experimental details.

ASSOCIATED CONTENT

Supporting Information

General experimental details. Synthesis of all new substrates and compounds **1**−**6**. ^1H NMR and ^{13}C NMR spectra of all new compounds. Computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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2,4,6-collidine yielded the same stereoselections (but lower yields) that those observed using the catalytic protocol with added 2,4,6-collidine. These results rule out any potential interference of 2,4,6-collidine with active species in the catalytic cycle and, therefore, was not considered during the calculations.

(28) Neutral complex $Cp_2TiCl(THF)$ presented somewhat worse initial coordination capabilities than cationic $Cp_2Ti^{+}(THF)_2$ by 3.3 kcal mol^{-1}. See Supporting Information.

(29) Theoretical studies support the existence of such cationic species when Cp_2TiCl is generated from the mixture of Cp_2TiCl_2 and Zn dust: ref 9e. Although in our case, we usually use manganese dust as coreductant, control experiments showed that the same stereoselection is obtained using Zn dust as coreductant. This fact also supports similar active species in both reactions.

(30) The described experiments were carried out at 10 mM, similar to that used in our experiments: Cangönül, A.; Behlendorf, M.; Gansäuer, A.; van Gastel, M. *Inorg. Chem.* **2013**, *52*, 11859−11866.

(31) In this case we considered the THF molecule in the proximity of the complex. When the THF molecule is removed from the calculated structure **IV** the system resulted in being more favorable by 3.7 kcal mol^{-1} in free energy terms.

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(33) We also found the transition state for the hydrogen-atom transfer to the oxygen atom but the calculated energy is much higher (19.0 kcal mol^{-1}).

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