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Titanocene(III)-Catalyzed 6-*exo* Versus 7-*endo* Cyclizations of Epoxypolyprenes: Efficient Control and Synthesis of Versatile Terpenic Building Blocks

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Dedicated to Professor Rafael Robles on the occasion of his retirement

Abstract: In this article, a complete study on the selectivity of titanocene(III) cyclization of epoxypolyprenes is presented. The requirements for the formation of six- or seven-membered rings during these cyclizations are determined, taking into account the different substitution pattern in the epoxypolyprene precursor. Thus, a complete selectivity to 6-*exo* or 7-*endo* cyclization process has been achieved, yielding mono-, bi-, and even tricyclic compounds, constituting a new and efficient access to this type of derivative. Additionally, this procedure opens the possibility to prepare excellent building blocks for the synthesis of polycyclic compounds with a trisubstituted oxygenated function, which is present in several natural terpenes.

Keywords: cyclic compounds · cyclization · natural products · radicals · titanium

Introduction

Natural terpenes are attractive goals in organic synthesis because of their structural complexities, relevant biological activities and also as benchmarks for the development of new synthetic protocols. In this context, bioinspired cationic cyclizations of the corresponding starting polyprenes have been extensively studied (Scheme 1, path A).[1] Nevertheless, cationic cyclizations of simple unfunctionalized polyprenes,[1,2] mainly developed by Goldsmith, Johnson, van Tamelen, and Corey, present some drawbacks in general, such as low yields and/or poor regio- and stereoselectivities. Therefore, extra functional groups able to stabilize carbocationic intermediates are usually required. This requirement is mandatory when the desired target presents a thermodynamically unfavorable exocyclic double bond in the final cyclic product.[3] On the other hand, we can also find in nature compounds presenting a tertiary oxygenated function instead of the corresponding alkene.[4] This functionality is very common in natural terpenes and has been attributed to a trapping of the corresponding cationic intermediate by an external nucleophile (usually a water molecule; Scheme 1, path B).[5] Some selected examples are showed in Figure 1.

It is also worth noting that biomimetic cationic-based protocols for the access to such structures (Scheme 1, path B) are practically unknown owing to all the transient cationic species that can be captured by the external nucleophile, yielding the corresponding mixtures of products.[6] For that reason, compounds containing such a structural moiety have been usually synthesized by using undesirable additional synthetic steps.[7] A recent example is the total synthesis of myrrhanol A, in which this structural motif has been prepared by epoxidation of an exocyclic double bond followed by reduction with $LiAlH_4$.[8] Other interesting solution is based on controlled C–H activation processes of the terpenic parent structures. Unfortunately, this approach is not nowadays general, and all the positions of the terpenic skeleton cannot be functionalized.[9]

This limitation of cationic approaches would be easily overcome by using other propagating species such as carbon-centered radicals, which have shown to be unreactive towards oxygenated functions.[10] The use of bioinspired radical cascade cyclizations of the corresponding polyprenes was introduced by the groups of Breslow and Julia more than forty years ago.[11,12] Inspired by these precedents, our group has developed an efficient and highly stereoselective methodology for the radical cyclization of epoxypolyprenes[10,13] catalyzed by $[TiClCp_2]$[14–17] (Cp = cyclopentadienyl). This radical approach presents complementary features compared with previously known cationic cyclizations:

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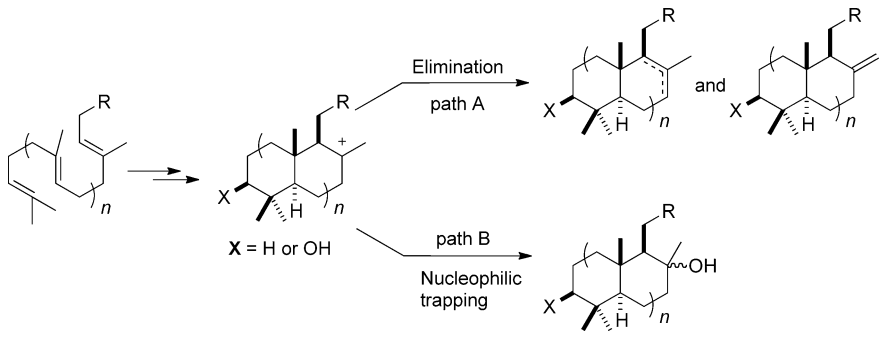


Scheme 1. Usual termination steps in terpene biosynthesis.

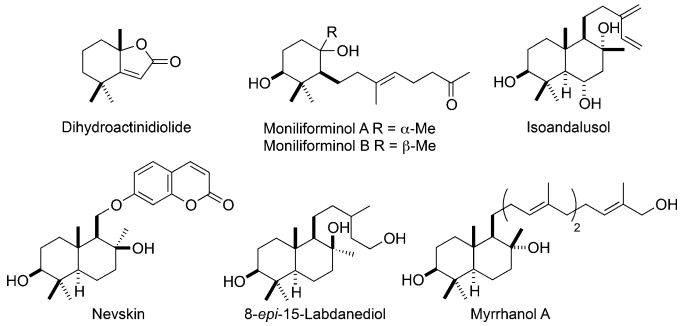


Figure 1. Selected examples of natural terpenoids presenting a trisubstituted oxygenated function.

1) the presence of an exocyclic double bond in the final products and 2) polycyclic compounds containing a 7-membered ring, inaccessible for "classical" cationic procedures, could also be prepared.[18] Consequently, this protocol has allowed the synthesis of several natural terpenes and meroterpenes containing five, six, and seven-member carbocycles.[12b]

The success of our approach resides in the high regioselectivity in the addition of the transient radicals to the corresponding double bonds. Thus, we demonstrated that geranyl, farnesyl, and geranylgeranyl-derived epoxypolyprenes exclusively undergo a sequence of 6-*endo*-trig cyclizations.[13a] On the other hand, the final cyclization of linalyl, nerolidyl, and geranyllinalyl-derived epoxypolyprenes takes place with an unusual 7-*endo*-trig regiochemistry.[18] This unexpected cyclization mode could be explained based on theoretical calculations.[18] In a chair-like transition state, the particular substitution pattern of these starting materials inevitably creates a 1,3-diaxial interaction that presumably rises up the activation energy and, consequently, reduces the reaction rate of the 6-*exo* cyclization process. In contrast, a seven-membered ring can adopt conformations in which this diaxial interaction is released (Figure 2).

Interestingly, if this hypothesis is correct the increase in the steric hindrance in the alkene may disfavor the seven-membered transition state biasing the reaction again to the usual 6-*exo*-trig cyclization mode. In this situation, the final products presenting a substitution pattern consisting on a tertiary oxygenated function could be obtained (Scheme 2).

To our knowledge, methods for the direct and simple preparation of this kind of natural terpenoids are not available. In this article, we have determined the substitution pattern required to control the 6-*exo*-trig versus 7-*endo*-trig cyclization modes, thus preparing new useful and versatile building blocks in terpene synthesis. It is also worth noting that the oxygenated feature may be used for subsequent controlled transformations, thus yielding more elaborated structures.

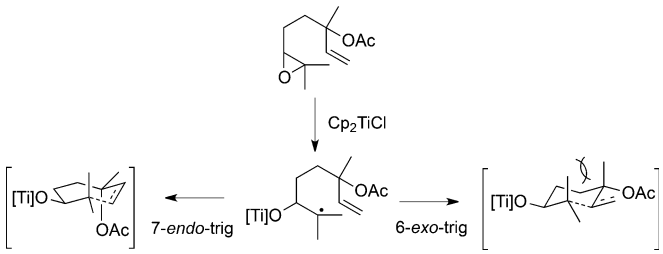
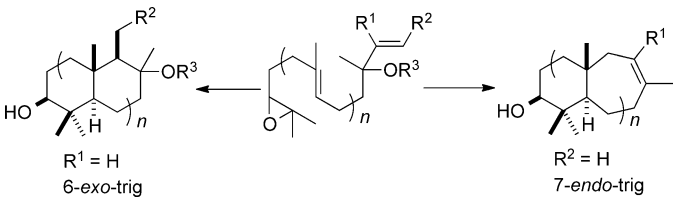


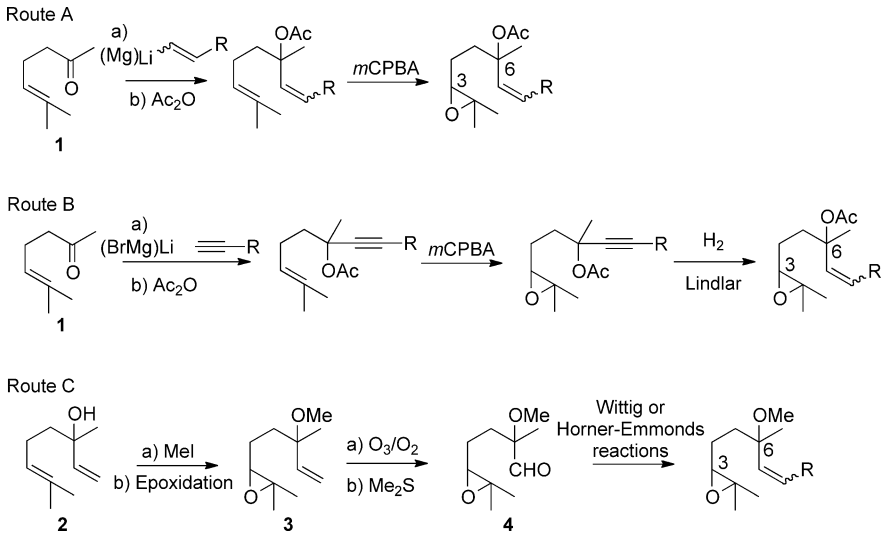
Figure 2. Calculated transition states for 6-*exo* and 7-*endo*-trig cyclizations of 6,7-epoxylinalyl acetate.



Scheme 2. Working hypothesis.

Results and Discussion

We started our study by using simple linalyl-type derivatives **5**–**17** presenting diverse substitution patterns in the terminal alkene. We selected a variety of substituents with different steric and electronic features, which could affect the stability of the transient radical. Therefore, we included as substituents simple alkyl chains (methyl and tetradecyl), oxygenated allylic compounds, aromatic and cyclopropyl rings, a versatile trimethylsilyl group, and carbonyl derivatives.[19] They can be easily prepared using three possible procedures (Scheme 3): A) direct nucleophilic addition of the corresponding alkenyl lithium or magnesium derivative to commercial 6-methyl-5-hepten-2-one (**1**) and subsequent epoxidation, B) addition of the corresponding lithium or Grignard acetylide to ketone **1** and subsequent epoxidation and parti-



Scheme 3. Procedures for the synthesis of starting epoxides **5**–**17**; *m*CPBA = *meta*-chloroperbenzoic acid.

al reduction of the triple bond,[20] and C) ozonolysis of a protected 6,7-epoxylinalyl derivative of **2** followed by Wittig or Horner–Emmons olefination. These starting materials present two stereocenters and are usually prepared as diastereoisomeric mixtures. We took advantage of this fact since we were also interested in the study of the influence of the relative configuration at C3 and C6 on the cyclization reaction. Moreover, the final diastereoisomeric carbocycles could be isolated by using a simple column chromatography separation. The synthesis of diastereo- and enantioenriched starting materials is also possible. Thus, for example, epoxide (+)-(*Z*)-**5** was prepared using commercial enantiopure (−)-linalool by using a sequence of O-methylation, Shi enantioselective epoxidation,[21] ozonolysis, and Wittig reaction with a final diastereomeric excess (*de*) of 82%.

We submitted this collection of epoxides (**5**–**17**) to the Ti^{III}-catalyzed radical cyclization using our previously described procedure.[13a] It is based on the aprotic combination of Me_3SiCl/2,4,6-collidine and Mn, which is compatible with oxiranes and capable of regenerating [$TiCl_2Cp_2$] (Cp = cyclopentadienyl) from both [Ti(H)$ClCp_2$] and oxygen-bonded titanium derivatives, including [Ti(OAc)$ClCp_2$].

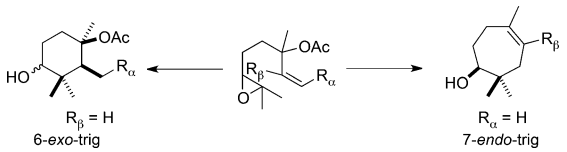
As can be observed in Table 1, complete regiochemical control for the cyclization process is observed in all cases. Substituents in the α position (R_α) always yielded 6-*exo*-trig cyclization products (Table 1, entries 1–10), whereas substituents in β position (R_β) always generated the corresponding 7-*endo*-trig cyclization products (Table 1, entries 12 and 13). The only exception was compound **17** (Table 1, entry 14) in which both cyclizations were hindered, yielding exclusively the uncyclized product **29**.[16i] The configuration of the alkene group does not seem to be relevant for the stereochemistry of the cyclization, because of the same products were obtained from pure (*Z*)-**6** (Table 1, entry 2) and a mixture of stereoisomers (*E,Z*)-**6** (Table 1, entry 3), even with very similar yields. The six-membered carbocycles always showed a *cis* configuration between the side chain at C5 and the oxygenated group at C6, with this latter function being in an axial arrangement.

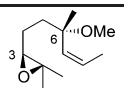
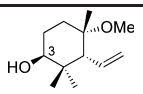
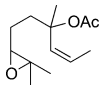
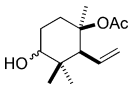
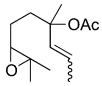
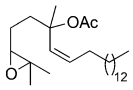
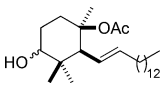
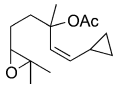
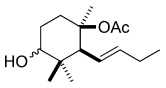
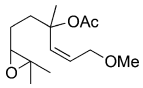
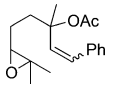
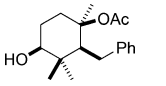
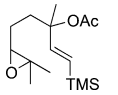
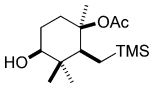
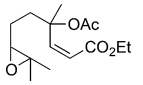
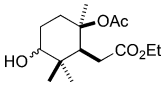
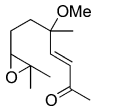
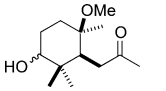
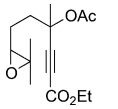
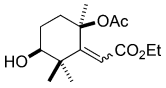
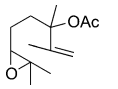
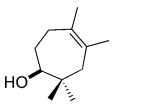
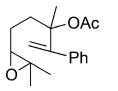
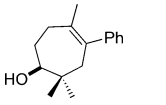
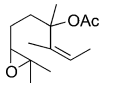
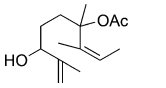
Consequently with the diastereomeric mixtures used as starting materials, two different products with *cis* and *trans* relative configurations between the C3 hydroxyl group and the side chain at C5 can be obtained. In Table 1, entries 2–11, we could observe that *cis* products are predominant, being the exclusive products in some cases (entries 7–8). The *trans* products are only obtained with compounds holding less bulky substituents at C5. Both *cis* and *trans* stereoisomers can be easily isolated and purified in most of cases. These findings are consequent with a six-membered transition state in which the less bulky acetate group at C6 is preferably located in the axial position, yielding two different diastereoisomers derived from the different configuration in the epoxide. This assumption was confirmed by synthesizing enantio- and diastereomerically enriched epoxide (+)-(3*S*,6*S*)-**5** (Table 1, entry 1), which gave the corresponding stereoisomer (−)-(3*S*,6*S*)-**18** in good yield.

The yields were from moderate to excellent in both types of cyclizations. The only exceptions were compounds with aromatic substituents in α-position, which gave very low yields (<10%), probably owing to the fact that generated benzylic radical decomposes very rapidly in the reaction media. Our group has described the benefits of water as an additive in Ti^{III}-mediated transformations, mainly as a radical reducing agent.[17a,22] Consequently with our previous findings,[22] the addition of water (10 equiv) to the reaction media promoted a significant increase in the corresponding yield (Table 1, entry 7, 55%). Product **22**, having an aryl substituent, is interesting because it represents a new direct access to natural meroterpenes. Although cationic and radical approaches to these skeletons have been described, neither of them yielded the oxygenated function at C6. This tertiary acetate could be subsequently used as carbocation precursor to continue increasing the complexity of the molecule.[23]

Regarding the nature of the substituents, we could observe that not only simple alkyl chains but also functionalized ones are substrates of this transformation. The coincidence of the final products in entries 2–3, and 6 (Table 1) is expected considering the known behavior of titanocene complexes towards simple and β-acetoxy substituted alkyl radicals.[10,18] Moreover, the existence of transient radical in

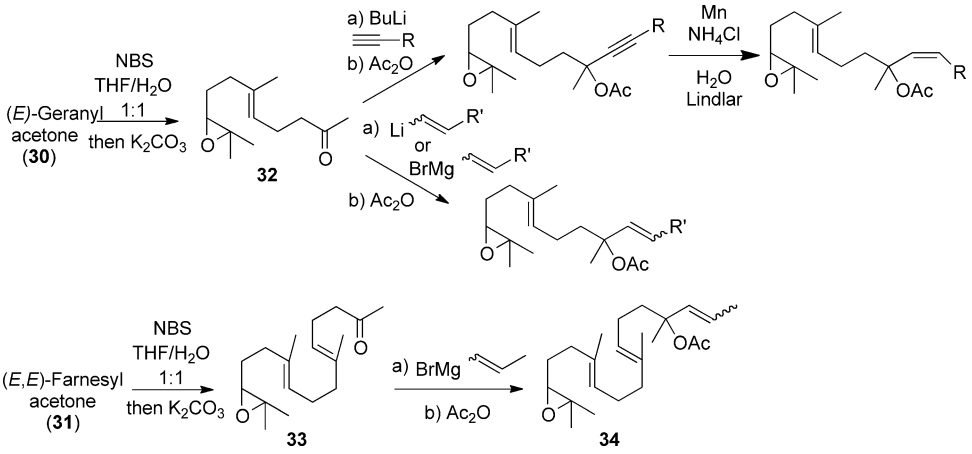
Table 1. Ti^{III}-catalyzed cyclization of epoxides **5**–**17**.[a]



Entry	Epoxide[b]		Cyclization products		Yield [%][c]
1		(+)-(*Z*)-**5**[d]		(−)-**18**	59
2		(*Z*)-**6**		**19**	81[e]
3		(*E*,*Z*)-**6**[f]		**19**	78[e]
4		(*Z*)-**7**		**20**	43[e]
5		(*Z*)-**8**		**21**	73[g]
6		(*Z*)-**9**		**19**	84[h]
7		(*E*,*Z*)-**10**		**22**	55[i]
8		(*E*)-**11**		**23**	43
9		(*Z*)-**12**		**24**	46[e]
10		(*E*)-**13**		**25**	54[e]
11		**14**		**26**	41[i,j]
12		**15**		**27**	76
13		**16**		**28**	89
14		**17**		**29**	93

[a] See the Experimental Section for conditions; [b] 1:1 mixture of diastereoisomers; [c] referred to the starting diastereomeric mixture; [d] 91:9 mixture of (3*S*,6*S*)/(3*R*,6*S*) diastereoisomers; [e] 4:6 mixture of α/β epimers at C3; [f] 55:45 mixture of *E*/*Z* stereoisomers; [g] 45:55 mixture of α/β epimers at C3; [h] 50:50 mixture of α/β epimers at C3; [i] the reaction was carried out in the presence of 10 equiv of water and 1.5 equiv of $[TiCl_2Cp_2]$; [j] 50:50 mixture of *E*/*Z* stereoisomers.

these cyclizations is revealed by the opening of the cyclopropyl ring in Table 1, entry 5.[24] Another characteristic of Ti^{III}-mediated epoxypolyprene cyclizations, which distinguishes them from other simple radical cascade cyclizations, is that the final products present an alkene (Table 1, entries 1–6). Additionally, the trimethylsilyl group is also compatible with the reaction conditions. In this case, only one diastereoisomer was able to cyclize owing to the steric hindrance exerted by the trimethylsilyl group. Finally, a 6-*exo*-dig cyclization (Table 1, entry 11) could also be obtained using compound **14** as starting material.[25] This final cyclic product presents a high degree of functionality that can be used in subsequent synthetic steps.

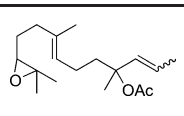
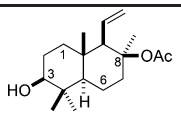
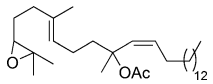
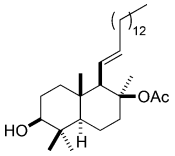
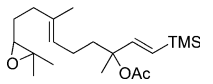
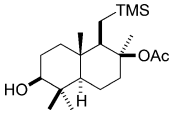
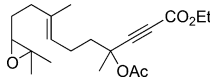
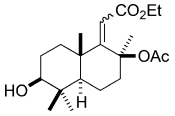
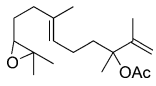
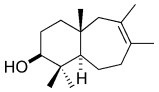
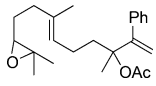
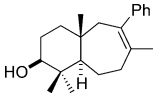
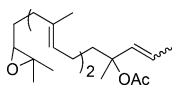
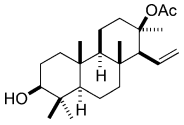


Scheme 4. Synthesis of higher epoxypoliprenes from (*E*)-geranyl acetone (**30**) and (*E*,*E*)-farnesyl acetone (**31**); NBS = *N*-bromosuccinimide.

The excellent results obtained in the study of the monocyclization of epoxides **5**–**17** encouraged us to extend our research to more complex compounds. Thus, we prepared a set of longer-chain epoxypolyprenes following similar methodology previously depicted in Scheme 3, using in this case (*E*)-geranyl acetone (**30**) and (*E,E*)-farnesyl acetone (**31**) as starting materials (Scheme 4).

Epoxides **34**–**40**, structurally similar to **5**–**17**, were submitted to our radical cyclization reaction catalyzed by titanocene(III).[13a] The results are depicted in Table 2.

Table 2. [$TiClCp_2$]-catalyzed radical cyclization of epoxides **34**–**40**.[a]

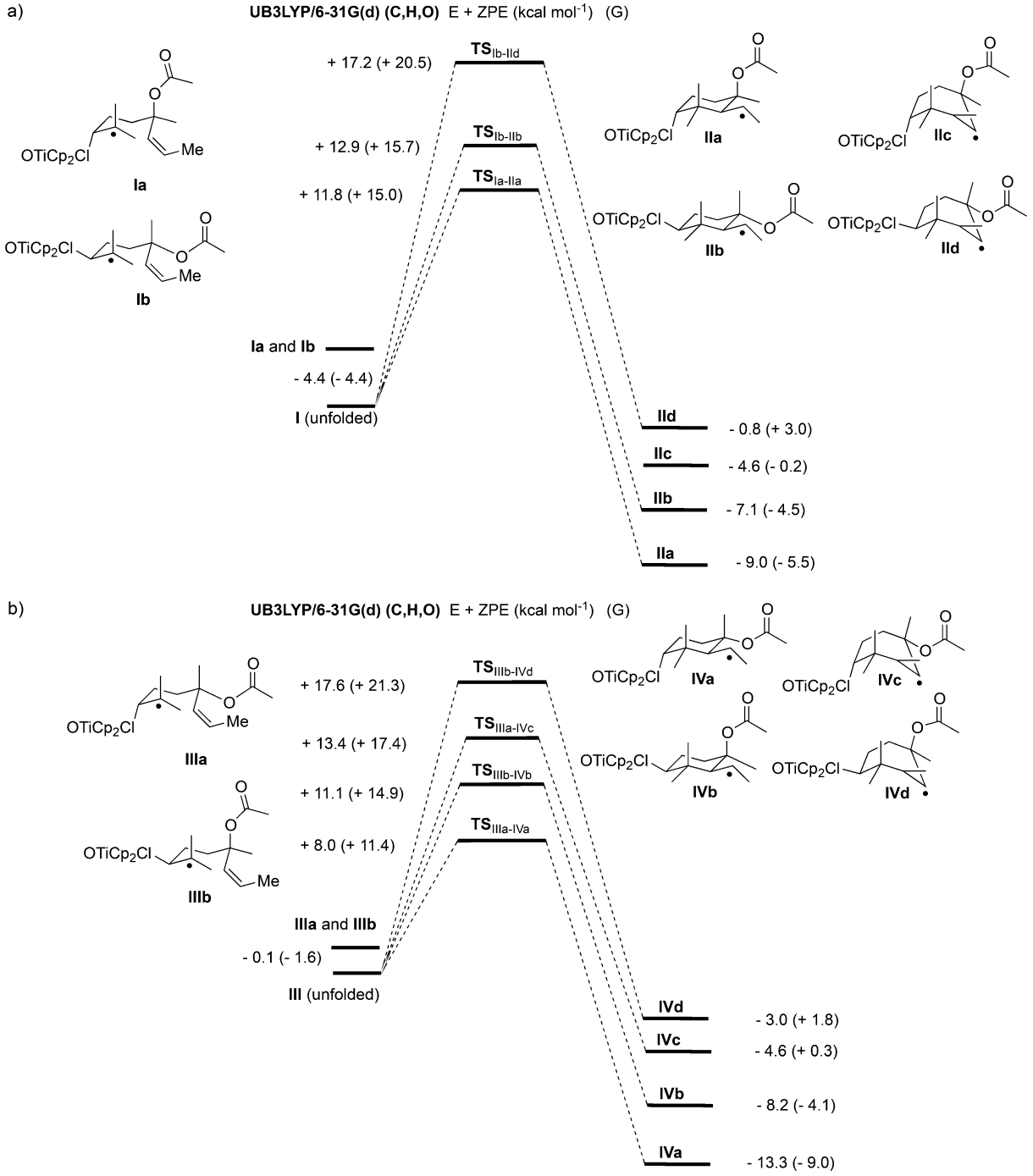
Entry	Epoxide[b]		Cyclization products		Yield [%][c]
1		(*E*,*Z*)-**35**[d]		**41**	44
2		(*Z*)-**36**		**42**	37
3		(*E*)-**37**		**43**	33
4		**38**		**44**	45[d]
5		**39**		**45**	54
6		**40**		**46**	77
7		(*E*,*Z*)-**34**[d]		**47**	21

[a] See the Experimental Section for the conditions; [b] 1:1 mixture of diastereoisomers; [c] yields refer to the starting diastereoisomeric mixture; [d] 1:1 mixture of *E*/*Z* isomers.

The results obtained in the cyclization of epoxides **34**–**40** showed the same trends than those observed in Table 1. Again, the chemical compatibility with the different substituents allowed us an easy access to interesting polycyclic building blocks in terpene synthesis in few steps. In fact, alcohol derived from the saponification of acetate group in compound **41** (Table 2, entry 1) is an advanced intermediate in the synthesis of 8-*epi*-myrrhanol A, an epimer of the natural polypodane triterpene isolated from guggul-gum resin with anti-inflammatory activity.[4f,26] Remarkably, only one stereoisomer undergoes the cyclization in Table 2 (entries 1–3), thus obtaining exclusively the 3*S**,8*S**,9*R** diastereoisomer. They present a *cis* relationship between the oxygenated function at C8 and the side chain at C9. The same stereoselection is observed in tricyclic product **47**. This stereochemical outcome is attributable to the steric restrictions imposed by the first cyclization. The success of the last cyclization is only possible if the oxygenated function presents an axial arrangement. The flexibility of monocyclic precursors, allowing other energetically acceptable transition states, is the responsible for the observation of both diastereoisomers in some monocyclization reactions. Again, a 6-*exo*-dig cyclization took place when compound **38** was used as starting material. Substrate (3*S**,8*S**)-**44** is an interesting building block for the synthesis of diterpenes and norditerpenes due to its functionality. Although the yields of these polycyclizations might seem modest, they

are referred to the original diastereoisomeric mixture. Taking into account the inability to cyclize of one of the diastereoisomers present in the starting mixture, the reported yields are more than acceptable for this kind of transformation. As it was previously observed in Table 1, mixtures of cyclization products with different ring sizes were not obtained, confirming the excellent control over the regioselectivity of this reaction. In the case of 7-*endo*-trig cyclizations (Table 2, entries 5 and 6), both epimers in C8 are apparently able to cyclize, thus giving better yields.

Computational study of the 6-*exo* versus 7-*endo* regioselectivity: To understand the origins of the observed selectivity, we studied mono- and bicyclization processes with the aid of computational methods. To this end, DFT calculations (Gaussian 09)[27] using a B3LYP functional were carried out.[16g,28] We will first discuss the influence of the position of a methyl substituent in the monocyclization reaction (Schemes 5–7). From Scheme 5 we can observe that for α-substituted 3*S**,6*S** diastereoisomers **I** with *Z* configuration in the alkene, the 7-*endo*-trig cyclization process is dis-



Scheme 5. Activation and reaction energies and Gibbs free energies calculated for cyclization reactions of model radicals: a) **I** and b) **III**. The TS for **Ia** to **Ic** could not be found.

favored both kinetically ($E_a = 11.8$ and 12.9 vs. 17.2 kcal mol^{-1}) and thermodynamically ($\Delta E = -9.0$ and -7.1 vs. -4.6 and -0.8 kcal mol^{-1}) for both axial–axial (**Ia**) and equatorial–equatorial (**Ib**) precyclization conformers (Scheme 5a). As a reference, we used the unfolded state because the prefolding energy significantly changes from one conformer to another. Similar results were obtained with α-substituted 3*S**,6*R** diastereoisomer. In this case, the thermodynamics of the process is again favorable to 6-*exo*-trig cyclization ($\Delta E = -13.3$ and -8.2 vs. -4.6 and -3.0 kcal mol^{-1}) as well as the kinetics ($E_a = 8.0$ and 11.1 vs. 13.4 and 17.6 kcal mol^{-1}). These theoretical data are therefore in complete agreement with experimental results, in which we only observe six-membered carbocycles despite the relative configuration of the starting epoxides. The reason of these remarkable regioselectivity could be explain based on the transition state structure. Thus, for example, in the seven-membered transition state $\mathbf{TS_{Ib–IId}}$ the 1,2-interactions between methyl groups presumably rises up the activation energy if we compared with the observed 1,3-diaxial interaction in chair-like transition states $\mathbf{TS_{Ia–IIa}}$ and $\mathbf{TS_{Ib–IIb}}$ (Figure 3). Similar trends are also observed when 6-*exo*-trig cyclizations are favored.

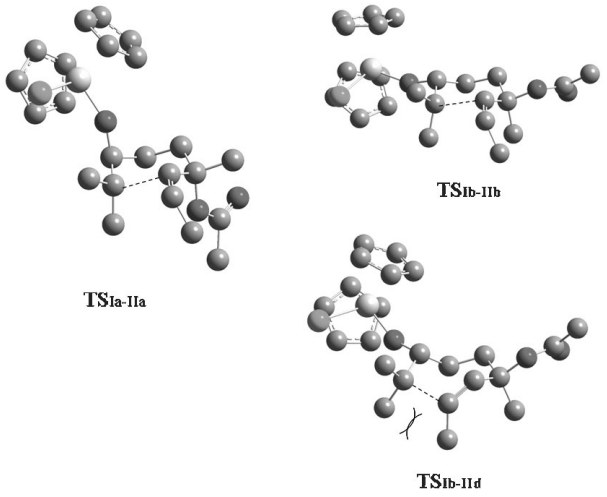


Figure 3. Transition states for the cyclization of compound (*Z*)-**6**.

We also calculated the same processes with the corresponding α-substituted diastereoisomers **V** and **VII**, presenting an alkene with *E* configuration (Scheme 6). In this case, we can observe that the reaction profile is more complex, but with both diastereoisomers the reaction yielding the six-membered carbocycle is preferred, as we observed in the corresponding reactions. Nevertheless, the kinetics and thermodynamics is less favorable than in structures presenting a double bond with a *Z* configuration.

β-Methyl substituted diastereoisomers **IX** and **XI** were also studied (Scheme 7). In agreement with the experimental results, only 7-*endo*-trig cyclizations were energetically favored for both diastereoisomers. Moreover, 7-*endo*-trig cyclizations are also kinetically favored by 5–6 kcal mol^{-1}. A simple examination of the corresponding transition states clarifies the observed regioselectivity. For example, the existence of a substitution in the β position increases the activation energy of chair-like transition states $\mathbf{TS_{IXa–Xa}}$ and $\mathbf{TS_{IXb–Xb}}$ owing to the presence of four methyl groups in consecutive positions (Figure 4). On the other hand, such unfavorable 1,2 interactions do not exist in transition states $\mathbf{TS_{IXa–Xc}}$ and $\mathbf{TS_{IXb–Xd}}$. Moreover, the seven-membered rings can adopt conformations in which the 1,3-diaxial interaction is also released.

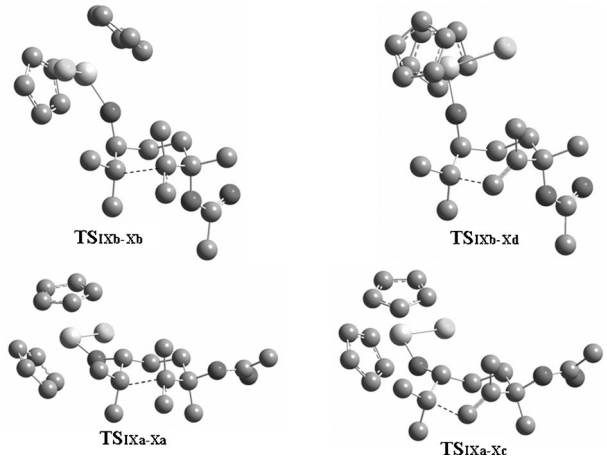
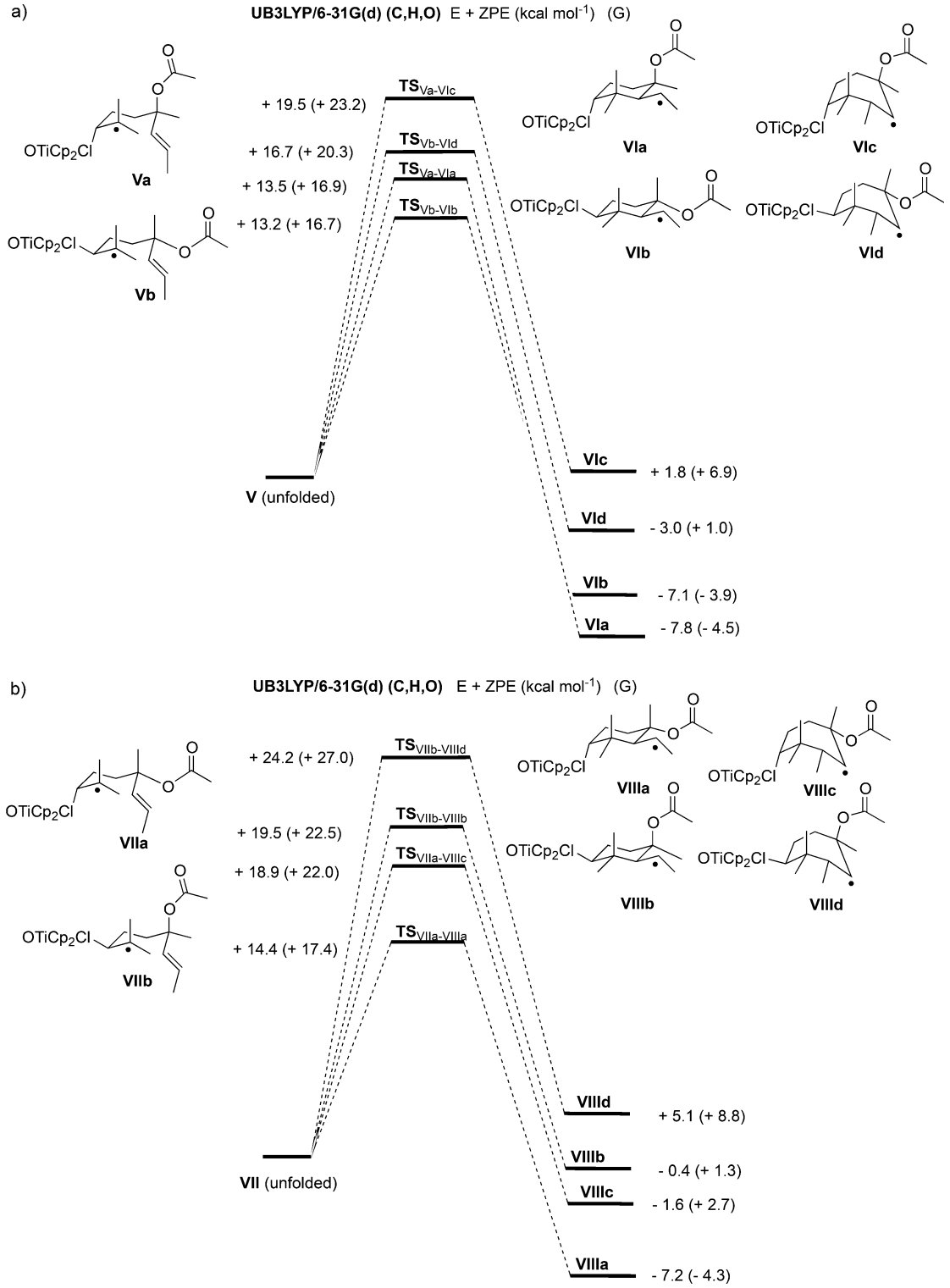


Figure 4. Transition states for the cyclization of compound **15**.

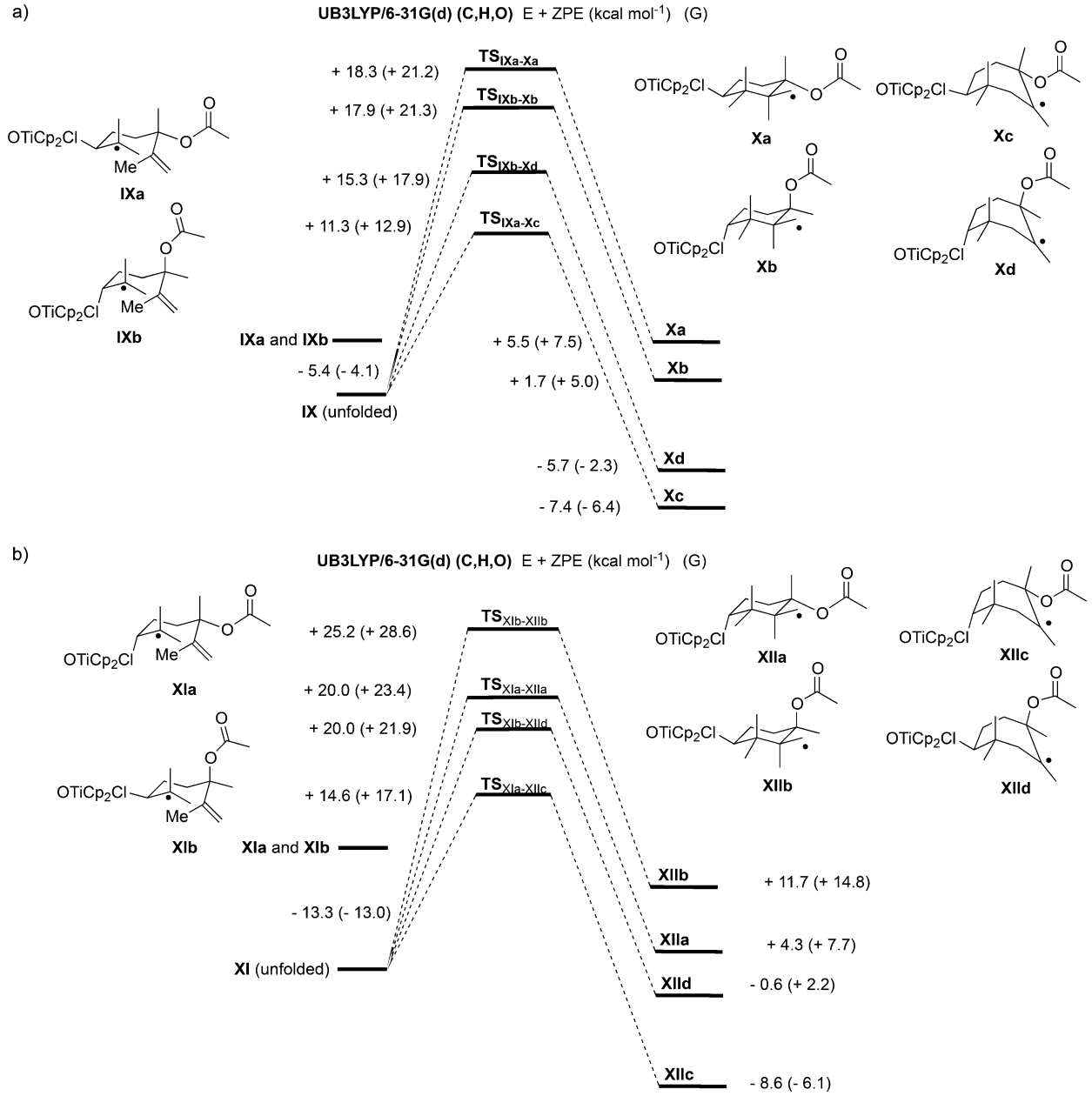
For simplicity, we restricted our study of bicyclization processes to model radicals **XIII**, **XV**, **XVII**, and **XIX** (Scheme 8). In this case, all the final products derive from intermediate monocyclic radicals presenting a *cis* relationship between the C3 hydroxyl group and the C5 alkyl side chain. For the study of the second cyclization, a methyl group was included as substituent in the α and β positions. In the former case, we focused our attention on the *Z* stereoisomer owing to the similar results observed in the monocyclization reaction. Also for simplicity, the titanocene(IV) alkoxide at C3 has been replaced in this study for a simple hydroxyl group. Again, α-methyl substituted radicals **XIII** and **XV** prefer to undergo a 6-*exo*-trig radical cyclization, which is kinetically ($E_a = 7.9$ and 11.0 vs. 14.4 and 15.5 kcal mol^{-1}) and energetically favored ($\Delta E = -10.7$ and -7.5 vs. -3.5 and 0.6 kcal mol^{-1}). According to the experimental results, we could observe that the energetic profile for the radical cyclization of 3*S**,8*S** diastereoisomer **XIII** is more favorable than the corresponding to the 3*S**,8*R** diastereoisomer **XV**, thus justifying the stereodiscrimination observed. The disfavored stereoisomer **XV** is then consumed by secondary reactions before the required second cyclization. Both β-methyl substituted 3*S**,8*S** and 3*S**,8*R** diastereoisomeric monocyclic radicals **XVII** and **XIX** presented low activation barriers for the observed 7-*endo*-trig radical cyclization. This theoretical result justifies the better yield observed in the corresponding cyclizations, due to both diastereoisomers being productive in the reaction.



Scheme 6. Activation and reaction energies and Gibbs free energies calculated for cyclization reactions of model radicals: a) **V** and b) **VII**.

Conclusion

In this article we have presented an efficient methodology for the preparation of versatile building blocks for terpene synthesis, based on the highly efficient control over the type of desired cyclization. This control is completely determined by the position of different substituents in the starting acyclic polyprenic chain, which drives the reaction exclusively to form six- or seven-membered carbocycles. Remarkably, the synthesized 6-membered carbocycles have a trisubstitut-



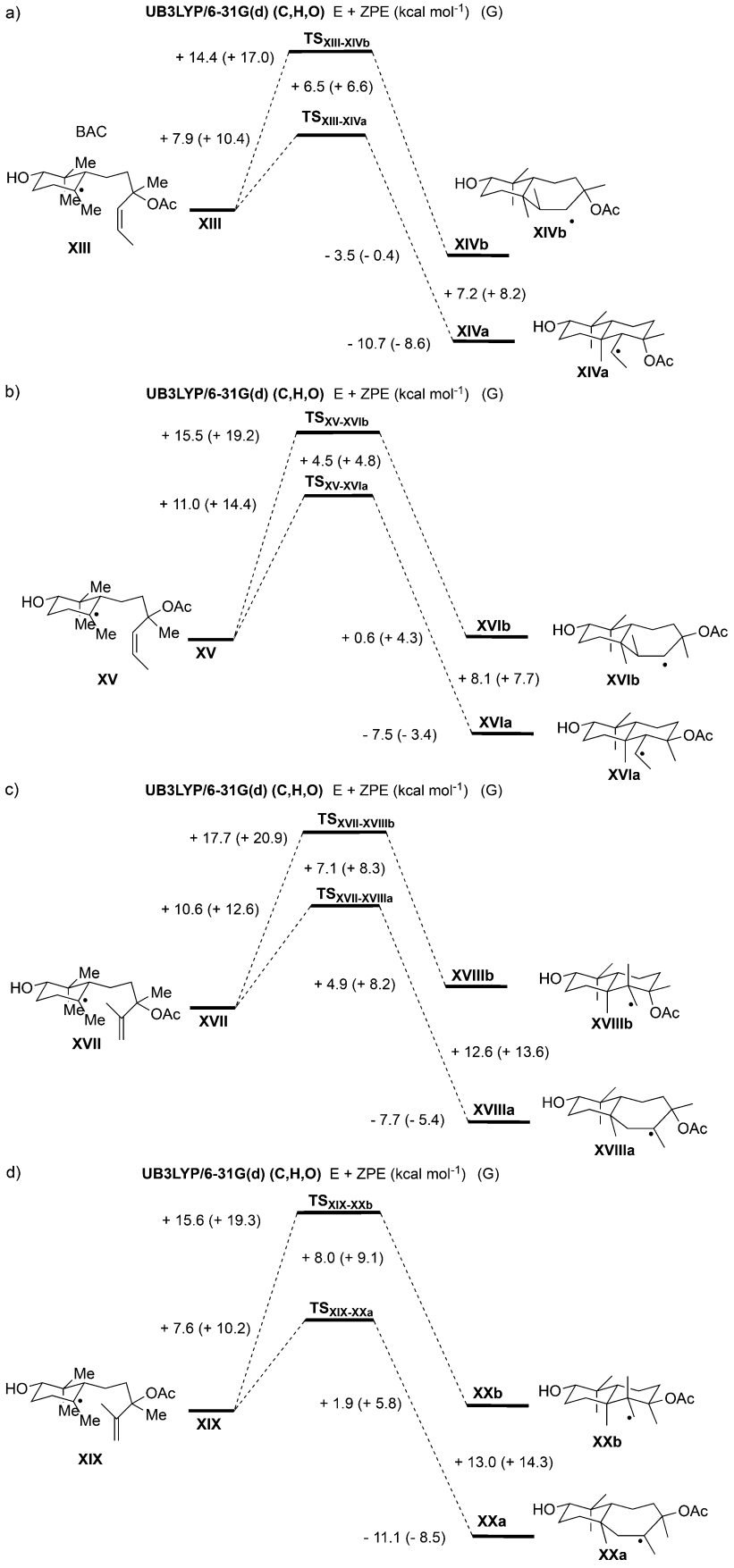
Scheme 7. Activation and reaction energies and Gibbs free energies calculated for cyclization reactions of model radicals: a) **IX** and b) **XI**.

ed oxygenated function, which is present in numerous natural terpenes, and bothersome to prepare by using other methodologies. The excellent control found in these reactions has been also confirmed using extensive theoretical calculations. Currently, we are performing additional studies to extend our method for the cyclization of higher size rings, and its application in the synthesis of complex natural products.

Experimental Section

General details: Deoxygenated solvents and reagents were used for all reactions involving [$TiClCp_2$]. 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 by using NMR (300, 400 and 500 MHz) spectrometers. ^1H and ^{13}C NMR spectra of compounds **32**,[29] and **33**[30] matched with those previously described.

General procedure for Ti^{III}-catalyzed bioinspired cyclizations: Strictly deoxygenated THF (20 mL) was added to a mixture of [$TiCl_2Cp_2$] (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 epoxide (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 2N HCl and extracted with EtOAc. The organic layer was washed with brine, dried (anhydrous Na_2SO_4) and the solvent removed. Products **18–29** and **41–47** were isolated by flash chromatography of the residue (hexane/EtOAc) and characterized by spectroscopic techniques. Results



Scheme 8. Activation and reaction energies and Gibbs free energies calculated for cyclization reactions of model radicals: a) **XIII**, b) **XV**, c) **XVII**, and d) **XIX**.

are depicted in Tables 1 and 2. Compound **47** was purified by using 15% $AgNO_3$/silica gel.

Acknowledgements

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