J|A|C|S
ARTICLES
Published on Web 09/30/2005

7-*endo* Radical Cyclizations Catalyzed by Titanocene(III). Straightforward Synthesis of Terpenoids with Seven-Membered Carbocycles

José Justicia,[†] Juan L. Oller-López,[†] Araceli G. Campaña,[†] J. Enrique Oltra,*[,†] Juan M. Cuerva,*[,†] Elena Buñuel,[‡] and Diego J. Cárdenas*[,‡]

Contribution from the Department of Organic Chemistry, University of Granada, Faculty of Sciences, Campus Fuentenueva s/n, E-18071 Granada, Spain, and Departamento de Química Orgánica, C-I, Universidad Autónoma de Madrid, Cantoblanco, E-28049 Madrid, Spain

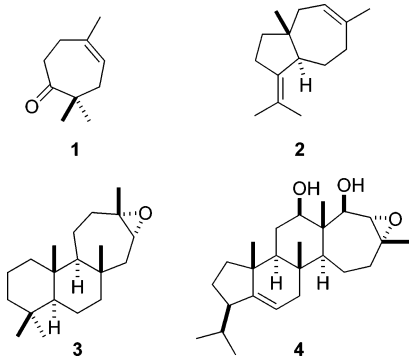
Received June 30, 2005; E-mail: jmcuerva@ugr.es; joltra@ugr.es

Abstract: We describe a novel procedure for the straightforward synthesis of seven-membered carbocycles via free-radical chemistry, based on titanocene(III)-catalyzed 7-*endo*-dig and 7-*endo*-trig cyclizations. This procedure has proved to be useful for the chemical preparation of terpenoids with different skeletons containing cycloheptane rings, including the first total syntheses of dauca-4(11),8-diene (**2**), barekoxide (**3**), authentic laukarlaol (**81**), and a valparane diterpenoid (**72**), as well as a substantially improved synthesis of karahanaenone (**1**). We also provide theoretical and experimental evidence in support of a plausible mechanism, which may rationalize the preference for the unusual 7-*endo* cyclization mode shown by radicals with substitution patterns characteristic of the linalyl, nerolidyl, and geranyl linalyl systems. In light of these chemical findings, we discuss the potential involvement of radical cyclizations in the biosynthesis of some terpenoids containing seven-membered carbocycles.

Introduction

Seven-membered carbocycles (as well as five- and six-membered ones) are often classified as "common rings" because of their relatively low ring strain.[1] It is not surprising therefore that they are quite widespread in nature, where they can be found in the carbon skeleton of different alkaloids[2] and specially numerous terpenoids, including monocyclic substances such as the monoterpenoid karahanaenone (**1**),[3] bicyclic sesquiterpenoids such as daucadiene **2**,[4] tricyclic diterpenoids such as barekoxide (**3**),[5] tetracyclic sesterterpenoids such as aspergilloxide (**4**) (Chart 1),[6] and many others.[7]

Chart 1. Chemical Structures of Terpenoids with Different Skeletons Containing a Seven-Membered Carbocycle



Nevertheless, as compared to cyclopentanes and cyclohexanes, general methods for the synthesis of cycloheptane systems are still notoriously scarce. To repair this deficit, several researchers have made considerable efforts to develop methods based mainly on metal-mediated cycloadditions, ring expansion strategies, and metathesis reactions.[8] Alternative methods based on simple or cascade cyclizations have received much less attention, however, possibly because of the general assumption

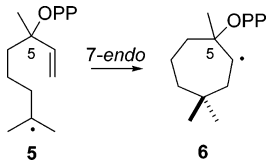
[†] University of Granada.
[‡] Universidad Autónoma de Madrid.

(1) Eliel, E. L.; Wilen, S. H.; Doyle, M. P. *Basic Organic Stereochemistry*; Wiley-Interscience: New York, 2001.
(2) Mann, J.; Davidson, R. S.; Hobbs, J. B.; Banthorpe, D. V.; Harborne, J. B. *Natural products: their chemistry and biological significance*; Longman Scientific & Technical: Harlow, U.K., 1994.
(3) Naya, Y.; Kotake, M. *Tetrahedron Lett.* **1968**, *9*, 1645−1649.
(4) (a) Warmers, U.; König, W. A. *Phytochemistry* **1999**, *52*, 99−104. (b) Cool, L. G. *Phytochemistry* **2001**, *58*, 969−972.
(5) (a) Kuniyoshi, M.; Marma, M. S.; Higa, T.; Bernardinelli, G.; Jefford, C. W. *J. Nat. Prod.* **2001**, *64*, 696−700. (b) Kuniyoshi, M.; Marma, M. S.; Higa, T.; Bernardinelli, G.; Jefford, C. W. *Chem. Commun.* **2000**, 1155−1156. (c) Rudi, A.; Kashman, Y. *J. Nat. Prod.* **1992**, *55*, 1408−1414.
(6) Cueto, M.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2002**, *4*, 1583−1585.
(7) For an exhaustive overview of natural terpenoids classified by skeleton type, including most of those containing seven-membered rings, see: Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: London, 1991.
(8) For reviews, see: (a) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3007. (b) Hoshomi, A.; Tominaga, Y. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, pp 593−615. (c) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1−19. For selected recent reports: (d) Prié, G.; Prévost, N.; Twin, H.; Fernandes, S. A.; Hayes, J.; Shipman, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6517−6519. (e) Dzwiniel, T. L.; Stryker, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9184−9185. (f) Barluenga, J.; Alonso, J.; Fañamás, F. J.; Borge, J.; García-Granda, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5510−5513. (g) López, F.; Castedo, L.; Mascareñas, J. L. *Chem.-Eur. J.* **2002**, *8*, 884−899. (h) Barluenga, J.; Alonso, J.; Rodríguez, F.; Fañamás, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2460−2462. (i) Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348−5349. For synthesis of diterpenoids with a seven-membered carbocycle by ring closing metathesis, see: (j) Pfeiffer, M. W. B.; Philips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334−5335. (k) Nakashima, K.; Inoue, K.; Sono, M.; Tori, M. *J. Org. Chem.* **2002**, *67*, 6034−6040.

that entropic factors do not favor cyclizations leading to seven-membered rings.[9] Nevertheless, it is generally believed that nature uses these types of cyclization processes to build terpenoids such as **1**−**4**.[2−7]

The homolytic opening of epoxides mediated by bis(cyclopentadienyl)titanium(III) chloride, introduced by Nugent and RajanBabu,[10] has become a formidable tool in organic synthesis.[11] The reaction proceeds under mild conditions compatible with many functional groups, and the titanocene(III) complex employed can be generated in situ by simply stirring commercial Cp_2TiCl_2 with Mn, Zn, or Al in THF to form an equilibrium mixture of the monomer Cp_2TiCl and the dimer $(Cp_2TiCl)_2$.[12] The process can also be carried out with substoichiometric proportions of the titanocene catalyst by adding either a protic titanocene-regenerating agent such as 2,4,6-collidine hydrochloride,[13] or an aprotic one such as the combination Me_3SiCl/collidine.[14] Relying on this latter catalytic version, we have recently developed a novel strategy for the synthesis of terpenoids that mimics oxidosqualene cyclase enzymes using free-radical chemistry.[15] This procedure, based on the radical cascade cyclization of suitable epoxypolyprenes, has provided satisfactory yields of relatively complex substances such as malabaricane triterpenoids, which contain *trans*-fused five- and six-membered rings in their carbon skeleton, among others. At first glance, however, the possibility of adapting this method to the synthesis of seven-membered carbocycles seemed unlikely because of the general tendency of 6-heptenyl radicals to undergo 6-*exo* instead of 7-*endo* cyclizations.[16] Nevertheless, a careful inspection of the literature revealed that 5,5-dioxygenated 6-heptenoyl radicals inverted their cyclization tendency in favor of the 7-*endo* mode.[17] In light of this observation, we realized that a 5,5-disubstituted alkyl radical such as **5**, hypothetically derived from the known terpenoid precursor linalyl pyrophosphate, should be prone to 7-*endo* cyclization processes (Scheme 1).

Scheme 1. Hypothetical 7-*endo* Cyclization of Radical **5** Derived from Linalyl Pyrophosphate



As preliminary experiments carried out in our laboratory supported this hypothesis,[18] we decided to try to develop a bioinspired strategy that was generally valid for the synthesis of terpenoids with different skeletons containing seven-membered carbocycles. Thus, our aim in this paper is to describe the titanocene(III)-catalyzed cyclization of epoxides derived from simpler analogues (acetates) of linalyl, nerolidyl, and geranyl linalyl pyrophosphates (putative biogenetic precursors of terpenoids)[2] and prove the synthetic usefulness of this procedure in the preparation of mono- (such as **1**), bi- (such as **2**), and tricyclic (such as **3**) terpenoids containing cycloheptane systems.

Results and Discussion

Titanocene(III)-Catalyzed 7-*endo*-trig Cyclizations. In preliminary assays made in our laboratory, a considerable excess (2.2 equiv) of the transition-metal complex was needed to complete the cyclization of 6,7-epoxylinalyl (**9**) and 10,11-epoxynerolidyl (**10**) acetates.[18] Moreover, dilution levels to the order of 10^{-3} M were required to reduce formation of byproducts derived from the premature trapping of intermediate radicals by the excess of titanocene(III).[19] To avoid these drawbacks, we decided to use the catalytic version based on the aprotic combination Me_3SiCl/2,4,6-collidine, which is compatible with oxiranes and capable of regenerating Cp_2TiCl_2 from both $Cp_2Ti(Cl)H$ and oxygen-bound titanium derivatives including $Cp_2Ti(Cl)OAc$.[15] Thus, we prepared a set of epoxyalkenes (**7**−**13**) by regioselective epoxidation of commercially available raw materials, and treated them with a substoichiometric quantity of Cp_2TiCl_2 (0.2 equiv), Mn dust, and the Me_3SiCl and 2,4,6-collidine mixture in dry THF (10^{-1} M substrate concentration). The results are summarized in Table 1.

Titanocene(III)-catalyzed cyclization of epoxyalkenes **7** and **8** gave cyclohexanols **14** and **15**, respectively, but, as hoped, cyclization of the allylically disubstituted substrates **9**−**13** mainly provided products (**16**, **18**, and **20**) containing the desired seven-membered ring in acceptable yields.[20] Physical and spectroscopic data of both the synthetic aroma chemical karahanaenol[21] (**16**) and the widdrol-related[22] sesquiterpenoid **18**[18] matched those previously reported. The HRMS of **20** indicated a $C_{20}H_{34}O$ molecular formula corresponding to four

(9) For a review about the Perkin ring-closure reaction, see: (a) Byrne, L. A.; Gilheany, D. G. *Synlett* **2004**, 933−943. For a review on unusual radical cyclizations, including 7-*endo*, see: (b) Srikrishna, A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 151−187. There are only a few reports dealing with the application of simple or cascade cyclizations for the synthesis of terpenoids containing seven-membered carbocycles. For a seminal work on the synthesis of serratenediol via cationic 7-*endo* cyclization, see: (c) Prestwich, G. D.; Labovitz, J. N. *J. Am. Chem. Soc.* **1974**, *96*, 7103−7105. For an improved synthesis of serratenediol, see: (d) Zhang, J.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3215−3216. For the synthesis of two sesquiterpene guaianolides via tandem 5-*exo*/7-*endo* radical cyclization, see: (e) Lee, E.; Lim, J. W.; Yoon, C. H.; Sung, Y.; Kim, Y. K.; Yun, M.; Kim, S. *J. Am. Chem. Soc.* **1997**, *119*, 8391−8392.

(10) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986−997.

(11) For recent reviews covering this subject, see: (a) Gansäuer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5556−5573. (b) Gansäuer, A.; Rinker, B. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 435−450. (c) Gansäuer, A.; Narayan, S. *Adv. Synth. Catal.* **2002**, *344*, 465−475. (d) Gansäuer, A.; Rinker, B. *Tetrahedron* **2002**, *58*, 7017−7026. (e) Gansäuer, A.; Pierobon, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 207−220 (f) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771−2788.

(12) Enemærke, R. J.; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. *J. Am. Chem. Soc.* **2004**, *126*, 7853−7864.

(13) (a) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849−12859. (b) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 101−103. (c) Gansäuer, A.; Bluhm, H. *Chem. Commun.* **1998**, 2143−2144.

(14) Barrero, A. F.; Rosales, A.; Cuerva, J. M.; Oltra, J. E. *Org. Lett.* **2003**, 5, 1935−1938.

(15) Justicia, J.; Rosales, A.; Buñuel, E.; Oller-López, J. L.; Valdivia, M.; Haïdour, A.; Oltra, J. E.; Barrero, A. F.; Cárdenas, D. J.; Cuerva, J. M. *Chem.-Eur. J.* **2004**, *10*, 1778−1788.

(16) (a) Bailey, W. F.; Longstaff, S. C. *Org. Lett.* **2001**, *3*, 2217−2219. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, Germany, 1996; pp 77−82.

(17) Crich, D.; Fortt, S. M. *Tetrahedron* **1989**, *45*, 6581−6589.

(18) Barrero, A. F.; Cuerva, J. M.; Herrador, M. M.; Valdivia, M. V. *J. Org. Chem.* **2001**, *66*, 4074−4078.

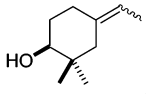
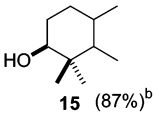
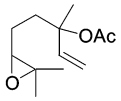
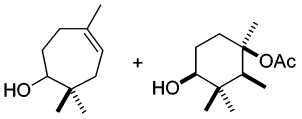
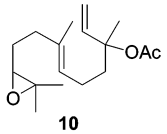
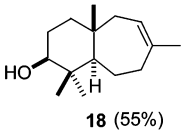
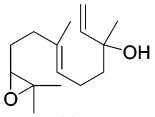
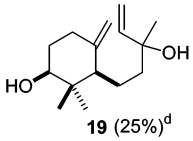
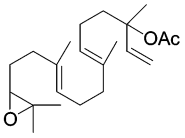
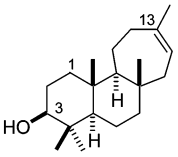
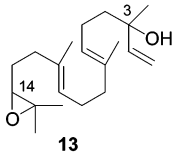
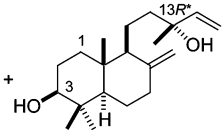
(19) There is theoretical and experimental evidence to suggest that free-radical cyclizations take place in a stepwise manner via discrete carbon-centered radicals; see the corresponding discussion in ref 15.

(20) Even the lowest yield of 39% obtained in the preparation of **20** from **12** can be regarded as satisfactory if we bear in mind that in just one step the reaction selectively provided a product containing three fused (trans/anti/trans) six-/six-/seven-membered rings, an endocyclic double bond, and five stereogenic centers, among 96 potential regio- and stereoisomers.

(21) Wang, D.; Chan, T. H. *Chem. Commun.* **1984**, 1273.

(22) Widdrol, a unique sesquiterpenoid found in plants of the genus *Widdringtonia*, has the same carbon skeleton as **18**, see: Uyehara, T.; Yamada, J.; Furuta, T.; Kato, T.; Yamamoto, Y. *Tetrahedron* **1987**, *43*, 5605−5620 and references therein.

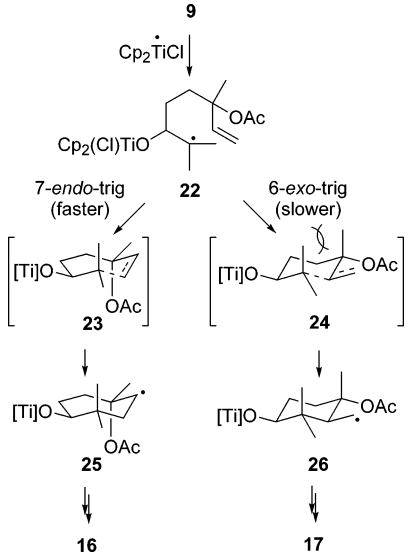
Table 1. Titanocene(III)-Catalyzed Cyclization of Epoxyalkenes **7**−**13**

Substrate	Cyclization products (yield)
 **7**	 **14** (54%)[a]
 **8**	 **15** (87%)[b]
 **9**	 **16** (55%) + **17** (34%)[c]
 **10**	 **18** (55%)
 **11**	**18** (35%) +  **19** (25%)[d]
 **12**	 **20** (39%)
 **13**	**20** (30%) +  **21** (10%)[e]

[a] Mixture of *E*/*Z* isomers (9:1 ratio). [b] Three-stereoisomer mixture (5.5:4:1 ratio). [c] This yield refers to a mixture of **17** and two minor stereoisomers. [d] Epimeric mixture (1:1 ratio) of products described in ref 15. [e] Only the 3*S**,13*R** diastereomer[15] was detected.

degrees of unsaturation, whereas its ^{13}C NMR spectrum showed only two signals of sp^2 carbons (δ 122.7 and 141.4) assignable to a trisubstituted double bond, thus revealing the tricyclic nature of the product. In the IR spectrum, a hydroxyl absorption band appeared at 3415 cm^{-1}, and in the ^{1}H NMR spectrum the chemical shift, multiplicity, and coupling constant values of H-3 (δ 3.22, dd, J = 11.5, 4.8 Hz) indicated that the OH group was attached at C-3 in an equatorial position. Apart from the differences derived form this hydroxyl group and the double bond at Δ^{13}, the NMR data of **20** agreed well with those reported for the tricyclic trans/anti/trans-fused six-/six-/seven-membered terpenoid **3**.[5] We therefore tentatively assigned to it structure **20**, depicted in Table 1. This structure was subsequently confirmed by the chemical correlation established during the synthesis of barekoxide (see below).

Scheme 2. Hanessian's Transition-State Model Adapted to the 7-*endo*-trig Cyclization of Radical **22**



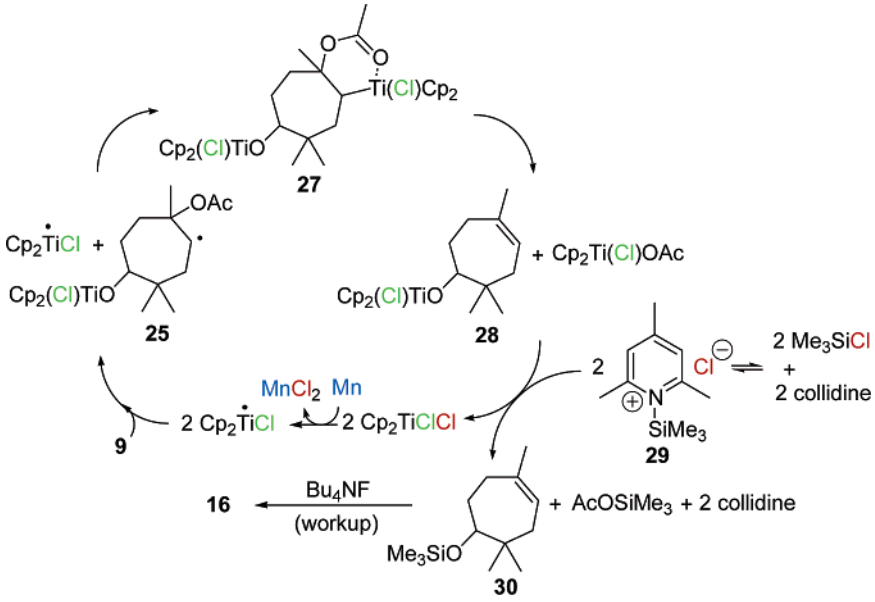
The results summarized in Table 1 merit some comments. First, the titanocene(III)-catalyzed cyclizations of **9** and **10** provided yields similar to those obtained under stoichiometric conditions[18] but required lesser quantities of Cp_2TiCl_2 and dilution levels lower by 1 and 2 orders of magnitude, respectively. Second, the allylic disubstitution pattern characteristic of linalyl, nerolidyl, and geranyl linalyl derivatives such as **9**−**13** clearly favored 7-*endo* cyclizations versus 6-*exo* ones, and, in this sense, an allylic ester group seemed to be more effective than a hydroxyl one. The following mechanistic discussion may rationalize these observations.

In cyclization processes where either nonsubstituted[23] or monosubstituted[16a] 6-heptenyl radicals are involved, the relative proportions of 6-*exo* and 7-*endo* cyclization products are a consequence of the K_{exo}/K_{endo} ratios, which are always higher than 1.[16a] Moreover, the stereochemistry of the six-membered carbocycles obtained can be rationalized by the chairlike transition-state model reported by Hanessian et al.[24] In our case, however, the results of Table 1 suggest that in a 6-heptenyl radical such as **22**, with a 1,1,5,5-tetrasubstitution pattern, the value of the K_{exo}/K_{endo} ratio is lower than 1 and consequently the 7-*endo* cyclization product predominates. Hanessian's model can be adapted to explain this phenomenon (see Scheme 2).

In a chairlike transition state such as **24**, its particular substitution pattern inevitably creates a 1,3-diaxial interaction, which presumably will increase the activation energy and should consequently reduce the reaction rate of the 6-*exo* cyclization process. In contrast, a seven-membered ring can adopt conformations such as **23** in which this diaxial interaction is released.[25] Therefore, the 7-*endo* cyclization rate should not be altered (as compared to that of nonsubstituted or monosubstituted radicals) and the K_{exo}/K_{endo} ratio will be inverted toward values lesser than 1, thus giving proportions of the secondary radical (**25**) which are higher than those of the primary one (**26**). There is strong evidence to support the fact that primary alkyl radicals

(23) Beckwith, A. L. J.; Moad, G. *Chem. Commun.* **1974**, 472−473.
(24) Hanessian, S.; Dhanoa, D. S.; Beaulieu, P. L. *Can. J. Chem.* **1987**, *65*, 1859−1866.
(25) For conformational analysis of seven-membered rings, see: Eliel, E. L.; Wilen, S. H.; Doyle, M. P. *Basic Organic Stereochemistry*; Wiley-Interscience: New York, 2001; pp 485−487.

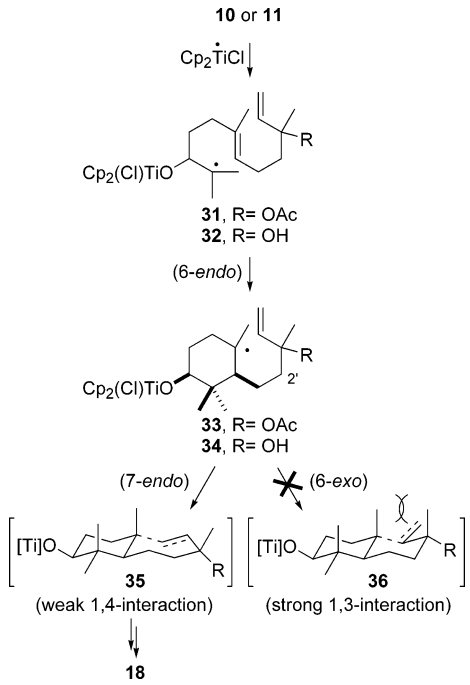
Scheme 3. Catalytic Cycle for the Radical Cyclization of **9** to **16** Mediated by Titanocene(III)



formed after titanocene-mediated 5-*exo*-trig cyclizations are trapped by a second titanocene(III) species to give an alkyl−Ti^{IV} complex, the C−Ti bond of which finally undergoes hydrolysis during the aqueous workup to give the corresponding alkane.[10] In a similar way, the secondary radical **25** could be trapped by another Cp_2TiCl species in a process facilitated by titanium coordination with the acetate group, which would lead to the bicyclic Ti^{IV} complex **27** (Scheme 3). This complex obeys the 18-electron rule[26] and might quickly evolve toward alkene **28** by $Cp_2Ti(Cl)OAc$ elimination, thus avoiding further hydrolysis of the C−Ti bond.[27] The formation of a supposedly strong Ti−O bond[28] might act as the driving force for this elimination process.

Finally, $Cp_2Ti^{IV}Cl_2$ would be regenerated from **28** and $Cp_2Ti(Cl)OAc$, by reaction with **29** (presumably derived from the Me_3SiCl/collidine couple) and subsequently reduced to $Cp_2Ti^{III}Cl$ by the Mn dust present in the medium. In this way, the catalytic cycle depicted in Scheme 3 would be complete. Thus, the two electrons needed for each turnover would be provided by the oxidation of Mn^0 to Mn^{II} with a concomitant transference of two chlorine atoms from the reactive Me_3SiCl to the relatively weak Lewis acid $MnCl_2$. This process, highlighted in Scheme 3, might be the driving force for the cycle.

Scheme 4. Titanocene(III)-Mediated Radical Cascade Cyclization of **10** and **11** into **18**



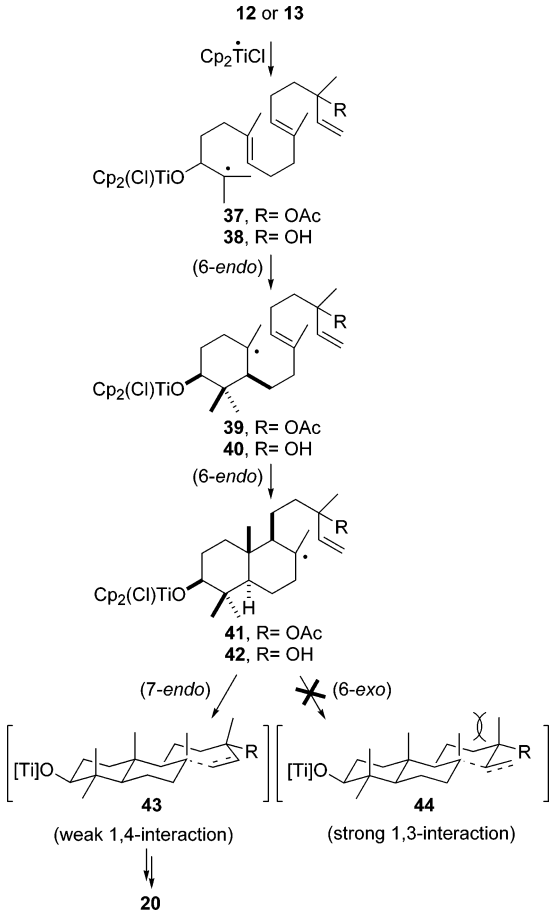
The above discussion suggests that the preference for a seven-membered carbocycle observed in the titanocene-catalyzed rearrangement of **9** derives not from an increased 7-*endo* cyclization rate but rather from a restricted 6-*exo* cyclization. This restraint should be even more acute with radicals **33**, **34** (Scheme 4), **41**, and **42** (Scheme 5) because of the enhanced 1,3-diaxial interaction caused by the higher rigidity introduced into the potential transition states **36** and **44** by the preexisting cyclohexane rings.[29] In fact, in the titanocene(III)-catalyzed cyclizations of **10**−**13**, we detected no product that might have been derived from these transition states (see Table 1).

(26) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Sausalito, CA, 1999; pp 2−4.

(27) There is strong evidence to support the idea that, in the presence of water, the C−Ti bond of an alkyl−Ti^{IV} complex easily undergoes hydrolysis to give the corresponding alkane, see: Barrero, A. F.; Oltra, J. E.; Cuerva, J. M.; Rosales, A. *J. Org. Chem.* **2002**, *67*, 2566−2571 and ref 10. Nevertheless, when we repeated the titanocene(III)-catalyzed cyclization of **9** in the presence of water, apart from **16** and **17**, we only detected a trace of 5-hydroxy-1,4,4-trimethylcycloheptyl acetate, the expected hydrolysis product. This result supported the intermediacy of complex **27** and confirmed that the rearrangement of β-acetoxyalkyl−Ti^{IV} complexes (such as **27**) toward alkenes (such as **28**) is a relatively fast process, as we had previously suggested (cf., ref 14).

(28) With some exceptions, such as those derived from stable nitroxyl radicals, Ti−O bonds are generally quite strong. For relevant discussions on this subject, see: (a) Huang, K.-W.; Han, J. H.; Cole, A. P.; Musgrave, C. B.; Waymouth, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 3807−3816. (b) Gansäuer, A.; Rinker, B.; Ndene-Schiffer, N.; Pierobon, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C. *Eur. J. Org. Chem.* **2004**, 2337−2351. (c) Gansäuer, A.; Rinker, B.; Pierobon, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3687−3690. (d) Huang, K.-W.; Waymouth, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 8200−8201. (e) Calhorda, M. J.; Carrondo, M. A. A. F. C. T.; Dias, A. R.; Domingos, A. M. T. S.; Simoes, J. A. M.; Teixeira, C. *Organometallics* **1986**, *5*, 660−667.

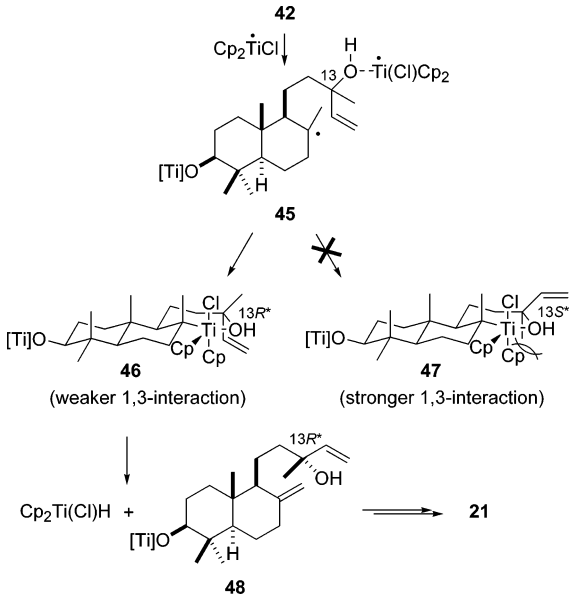
Scheme 5. Titanocene(III)-Mediated Radical Cascade Cyclization of **12** and **13** into **20**



Moreover, from the titanocene(III)-catalyzed cyclizations of alcohols **11** and **13**, we isolated considerable proportions of the partially cyclized products **19** and **21** (Table 1). Partially cyclized byproducts closely related to these compounds have been obtained before from the radical cascade cyclizations of other epoxypolyenes and presumably derive from the premature trapping of radical intermediates (such as **34** or **42**) by a second titanocene(III) species (cf., ref 15). It should be noted, however, that in the latter case we started from a stereoisomeric mixture of **13** (3*S**,14*S**/3*R**,14*S** in a ratio of roughly 1:1) but only detected the 3*S**,13*R** diastereomer of the bicyclic product **21** (see Table 1). This result suggests that the stereogenic C-13 center (labdane numbering system) bearing the OH group is possibly involved in the process through an alkyl−Ti^{IV} cyclic intermediate (**46**), facilitated by Ti−O coordination, which only admits the 13*R** relative configuration for steric reasons (see Scheme 6).

Theoretical Calculations. We performed calculations at DFT level on model compounds to determine the activation and reaction energies for 6-*exo*-trig and 7-*endo*-trig radical cyclizations.[30] Given that titanium lies far away from the reaction centers involved in the cyclization process, it was removed from the model structures to facilitate our calculations. Results

Scheme 6. Titanocene(III)-Trapping of Radical **42** Facilitated by Ti−O Coordination



obtained are summarized in Figures 1 and 2. Reaction and activation energies are referred to the most stable conformer of the corresponding substrate.[31] Computational results are in agreement with experimental observations and support our hypothesis about the effect of the disubstitution pattern at C-5 and related positions on the cyclization mode.

Thus, 7-*endo* cyclization of **I** (the model for the 2*S**,5*S** stereoisomer of radical **22**) is more favorable than the 6-*exo* process due to both kinetic and thermodynamic reasons. Both reactions are exothermic and show relatively low activation energies (11.3 versus 13.5 kcal mol^{-1}). The energy difference between transition states $\mathbf{TS}_{I-II}$ and $\mathbf{TS}_{I-III}$ is 2.2 kcal mol^{-1}, and the seven-membered ring **III** is 8.0 kcal mol^{-1} more stable than the six-membered ring **II**. These values suggest that the 2*S**,5*S** stereoisomer of **22** should preferentially evolve to give **16**. In the cyclization of the 2*S**,5*R** diastereomer **IV**, however, the energy difference between $\mathbf{TS}_{IV-V}$ and $\mathbf{TS}_{IV-VI}$ is favorable for the formation of the six-membered ring **V** by only 0.5 kcal mol^{-1}. This low value suggests that the cyclization of the 2*S**,5*R** stereoisomer of radical **22** should give **17** accompanied by a considerable proportion of **16**. As in our experiments, we employed an isomeric mixture of **9** in a 1:1 ratio;[18] our theoretical calculations predict the formation of a mixture containing the 7-*endo* cyclization product, as the major component, and a lesser amount of the 6-*exo* cyclization derivative (coming from the 2*S**,5*R** stereoisomer), as it was experimentally observed in the formation of **16** and **17** from **9** (see Table 1). The different behavior we have found for **I** and **IV** is related to the different 1,3 repulsive interactions mentioned above (shown for the 2*S**,5*S** stereoisomer **24** in Scheme 2). The 1,3-diaxial arrangement of two methyl groups in $\mathbf{TS}_{I-II}$ disfavors the 6-*exo* cyclization from **I**, whereas lower repulsions are exerted by the axial acetate in $\mathbf{TS}_{IV-V}$. Natural bonding orbital analysis (NBO) of transition states did not show any significant interaction between the acetate group and the incipient radical,

(29) The stereochemistry and nonconcerted character of 6-*endo*-trig cyclizations leading to intermediate radicals closely related to **33**, **34**, **41**, and **42** have been discussed elsewhere; see ref 15.

(30) For a recent theoretical and experimental study of titanocene-catalyzed 3-*exo* cyclizations, see: Friedrich, J.; Dolg, M.; Gansäuer, A.; Geich-Gimbel, D.; Lauterbach, T. *J. Am. Chem. Soc.* **2005**, *127*, 7071−7077.

(31) Although IRC studies afforded different conformers, they all can be easily interconverted. For the sake of simplicity, we have only depicted the energy of the most stable conformer. Full details can be found in the Supporting Information.

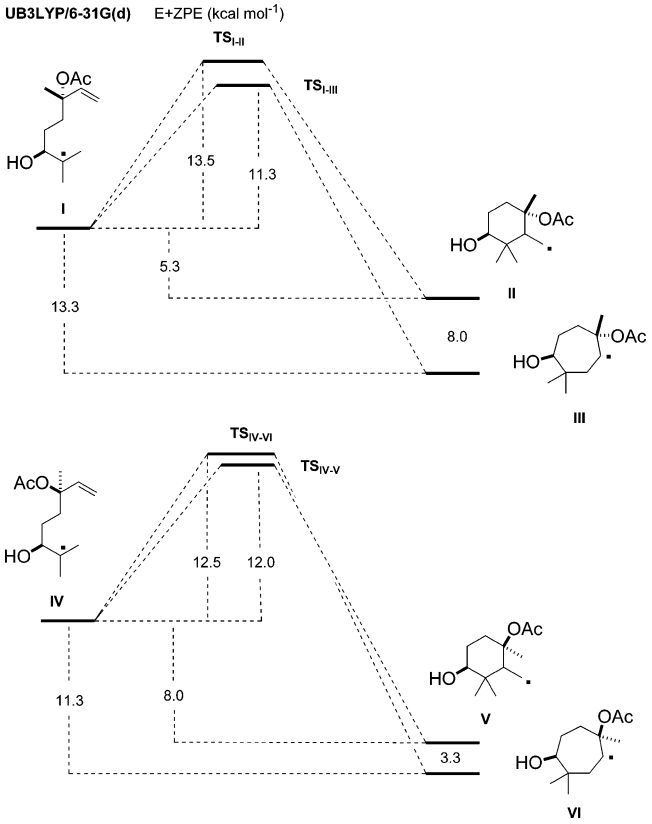


Figure 1. Activation and reaction energies calculated for the formation of monocyclic derivatives from the diastereomers **I** and **IV**.

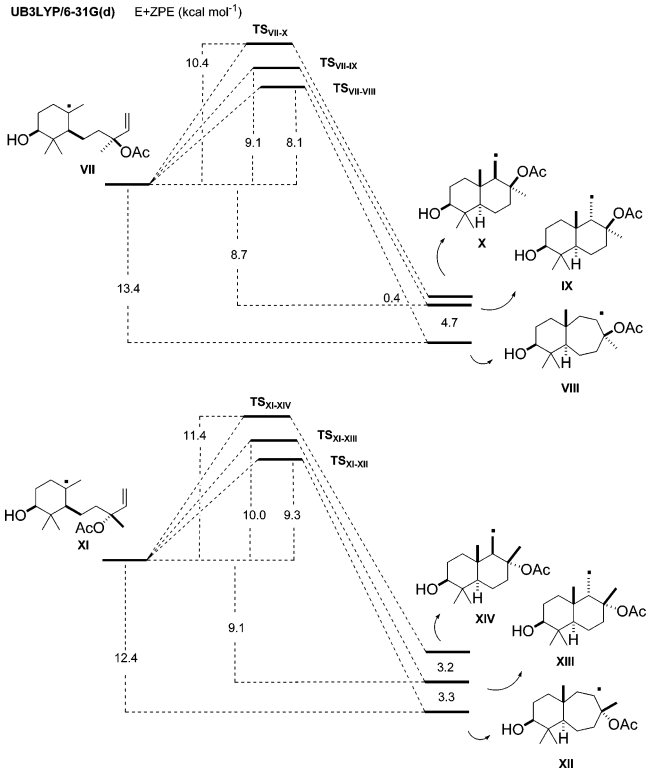


Figure 2. Activation and reaction energies for the formation of bicyclic derivatives from **VII** and **XI**.

which further supported that axial repulsion was the main reason for the observed selectivity.

We have also computed the reaction pathways for the second ring formation in the radical cyclization of diastereomers **VII** (model for the 3′*S** stereoisomer of **33**) and **XI** (model for the 3′*R** isomer of **33**) (Figure 2).

More possibilities have to be considered in these cases because of the formation of two new stereogenic centers in the hypothetical 6-*exo* cyclizations. Nevertheless, 7-*endo* cyclization is the preferred pathway regardless of the starting diastereoisomer and the relative configuration of the new centers. Formation of the two possible six-member rings derivatives shows higher activation energies in all cases. In addition, seven-membered ring derivatives **VIII** and **XII** are the most stable isomers in each case. Experimental results paralleled calculated relative energies because in the titanocene-catalyzed cyclization of **10**, only the seven-membered ring **18** was observed (Table 1). The same stereochemical reasons as for the case of **9** lie behind these data.

Results presented in this section support that radicals such as **22** and **33**, with a substitution pattern characteristic of linalyl, and nerolidyl pyrophosphate systems,[2] have an intrinsic tendency to undergo 7-*endo*-trig cyclizations. Moreover, it is presumable that radical **41** should have the same cyclization tendency. As we will see later, these observations might have not only synthetic but also biogenetic relevance.

Titanocene(III)-Catalyzed 7-*endo*-dig Cyclizations. Despite the fact that 7-*endo*-dig cyclizations are considered to be favored by Baldwin's rules,[32] methods to achieve 7-*endo*-dig carbocyclizations are few and far between and the only one we have found to offer any synthetic usefulness is the $HfCl_4$-catalyzed intramolecular allylsilylation of alkynes developed by Yamamoto's group, a process which takes place via carbocationic intermediates.[33] From a synthetic point of view, therefore, novel alternative methods using free-radical chemistry seemed desirable. In this context, and bearing in mind the mechanisms discussed above, we anticipated that the cyclization of 5,5-disubstituted 6-heptynyl radicals might preferably take place in a 7-*endo*-dig manner to give seven-membered cycloalkenes. To check the feasibility and scope of this radical cyclization, we prepared epoxyalkyne **55** and epoxyalkenynes **56** and **57**, via a simple sequence starting from the commercially available ketones **49**−**51** (Scheme 7), and treated them with a substoichiometric quantity of Cp_2TiCl_2 (20 mol %), Mn dust, and the Me_3SiCl/2,4,6-collidine couple in dry THF.[34] The results are summarized in Table 2.

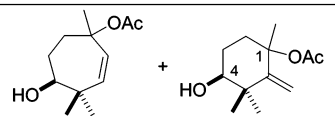
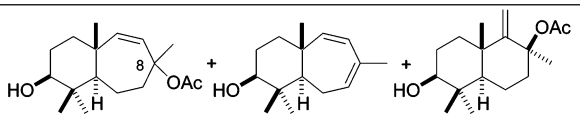
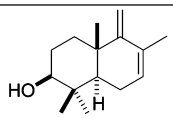
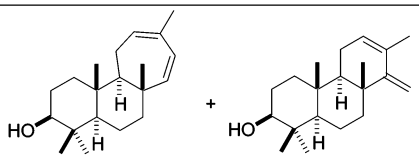
After 4 h of reaction, the titanocene(III)-catalyzed cyclization of epoxyalkyne **55** provided the seven-membered cycloalkene **58** (38% isolated yield), together with a lower proportion of **59**. Under the same conditions, epoxyalkenyne **56** gave a mixture containing acetate **60** and conjugated diene **61**, which became the main reaction product after a longer reaction time (16 h). A conjugated cycloheptadiene (**64**) was also the main cyclization product after 16 h of treatment of **57**. There is solid

(32) (a) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: Oxford, 2001; pp 1140−1144. (b) Baldwin, J. E.; Lusch, M. J. *Tetrahedron* **1982**, *38*, 2939−2947. (c) Baldwin, J. E. *Chem. Commun.* **1976**, 734−736. (d) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *Chem. Commun.* **1976**, 736−738.

(33) Imamura, K.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 5339−5340.

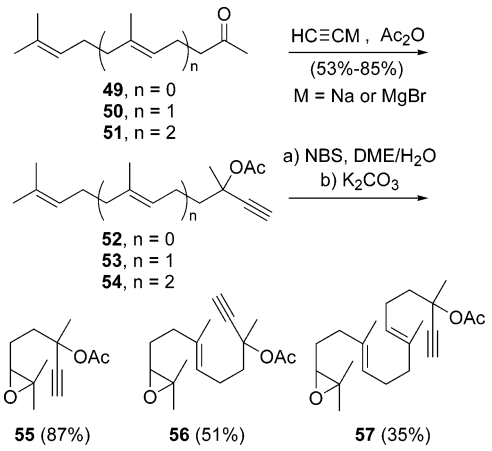
(34) It should be noted that when epoxyalkynes **55** and **56** were treated with stoichiometric quantities of titanocene(III), no seven-membered ring products were detected. These results, probably due to an increased premature trapping of intermediate radicals by the high concentration of titanocene species, reinforce the synthetic value of the catalytic procedure.

Table 2. Titanocene(III)-Catalyzed Cyclization of Epoxyalk(en)ynes **55**−**57**

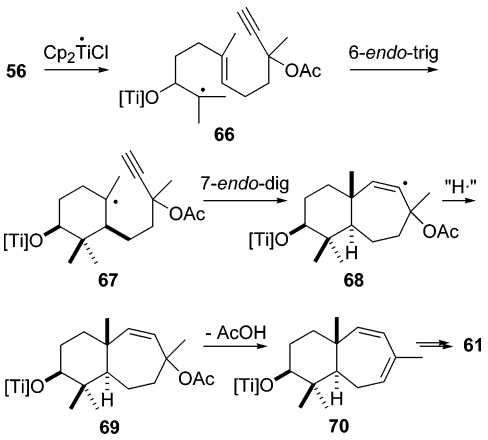
Epoxide	Cyclization Products	Reaction Time
55	 **58** (38%)[a] **59** (34%)[b]	4 h
56	 **60** (17%)[c] **61** (19%) **62** (21%)	4 h
56	**61** (31%) +  **63** (16%)	16 h
57	 **64** (11%) **65** (6%)	16 h

[a] Diastereomer mixture (2:1 ratio). [b] Mixture of 1*R**,4*S** and 1*S**,4*S** diastereomers (2:1 ratio). [c] Only one isolated diastereomer (8*R** probable configuration).

Scheme 7. Synthesis of Epoxyalk(en)ynes **55**−**57**



Scheme 8. Titanocene(III)-Mediated Cyclization of **56** into **61**



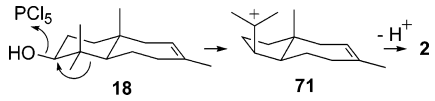
evidence to indicate that terminal vinyl radicals formed in titanocene-mediated 5-*exo*-dig cyclizations are reduced to the corresponding exocyclic alkenes by hydrogen abstraction from the THF used as solvent.[10] The results shown in Table 2 suggest that internal vinyl radicals (such as **68**) derived from 7-*endo*-dig cyclizations might also be reduced by hydrogen abstraction from THF or collidine present in the medium to give the corresponding endocyclic alkenes (such as **69**) (see Scheme 8). Subsequently, the allylic tertiary acetate **69** would evolve toward the conjugated diene **70** by AcOH elimination. It should be noted that when we treated acetate **60** under similar conditions but in the absence of Cp_2TiCl_2, we recovered unchanged starting material and no diene **61** was detected, thus revealing the crucial role played by titanocene species in the elimination process. Moreover, the formation of a single stereoisomer of **60** and **62** showed the high sensitivity of the 6-*exo*-dig and 7-*endo*-dig radical cyclizations against stereochemical factors, as occurred with the 6-*exo*-trig and 7-*endo*-trig processes.

To the best of our knowledge, the results presented in this section represent the first examples of 7-*endo*-dig carbocyclizations using free-radical chemistry reported to date.

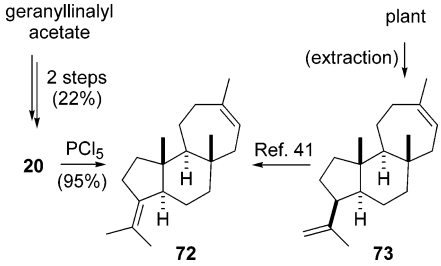
Synthesis of Terpenoids Containing Seven-Membered Carbocycles. With the valuable intermediates **16**, **18**, and **20** in our hands, the synthesis of natural products **1**−**3** and related terpenoids containing seven-membered carbocycles seemed relatively easy. In fact, simple Dess−Martin oxidation (DMO) of **16** gave karahanaenone (**1**).[35] Thus, we completed the total synthesis of this aroma chemical from commercial linalyl acetate in only three steps (*m*-CPBA epoxidation,[36] titanocene-catalyzed

(35) Justicia, J.; Oltra, J. E.; Cuerva, J. M. *J. Org. Chem.*, in press.
(36) Kametani, T.; Kurobe, H.; Nemoto, H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 756−760.

Scheme 9. Synthesis of **2** from **18** via Carbocation **71**



Scheme 10. Total Synthesis of **72** and Its Chemical Correlation[41] with Natural Valparane **73**

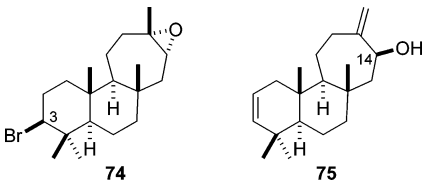


cyclization, and DMO) with a 38% overall yield, substantially improving previously described procedures.[37]

Among the sesquiterpenoids with a daucane skeleton[7] reported, one can find some confusing structural assignments.[38] Thus, the daucadiene structure **2** was originally assigned to a metabolite from the liverwort *Bazzania trilobata*,[4a] but, two years later, its mirror image was proposed for another metabolite with different NMR data found in the hybrid cypress species ×*Cupressocyparis leylandii*.[4b] In this context, we deemed that the chemical synthesis of **2** from **18** might help to resolve this discrepancy and establish an unambiguous synthetic reference for facilitating further elucidation of the structure of related natural products. For this purpose, we chose the well-established six- to five-membered ring contraction procedure employed by Ourisson and others.[39] Thus, we treated **18** with PCl_5 obtaining a 75% yield of **2**, presumably via tertiary carbocation **71** (Scheme 9). As this rearrangement does not affect the interannular junction,[39] the trans stereochemistry of **2** was guaranteed. NMR data of this synthetic product matched those reported for the metabolite found in the cypress species, thus confirming the structure and relative stereochemistry proposed by Cool for this natural product.[4b] To the best of our knowledge, this is the first synthesis reported for dauca-4(11),8-diene (**2**) (three steps and 19% overall yield from nerolidyl acetate).

In 1990, Urones et al.[40] discovered a new type of diterpenoids with a novel trans/anti/trans-fused five-/six-/seven-membered tricyclic skeleton called valparane, which has eluded chemical synthesis until now. The success obtained in the preparation of **2** prompted us to choose valaparane **72** as a synthetic target to check the usefulness of our method to build this type of terpenoid. Thus, we treated **20** with PCl_5 obtaining an excellent 95% yield of the expected product **72** (Scheme 10). Spectroscopic data of this product matched those of the semisynthetic derivative (**72**) prepared from natural valparane **73** by Urones' group,[41] thus confirming the structure proposed for the natural product. To the best of our knowledge, this is the first total synthesis of a valparane terpenoid described to date. It was achieved in only three steps from geranyl-linalyl acetate with a 21% overall yield (Scheme 10).

Chart 2. Structures Proposed for Natural 3-Bromo-barekoxide (**74**)[5a,b] and Laukarlaol (**75**)[43]



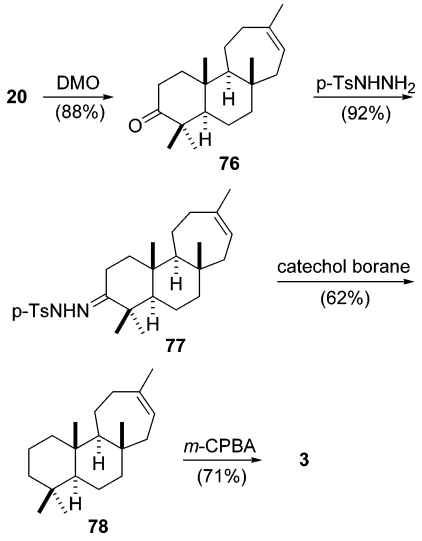
Marine natural products constitute one of the most exciting examples of chemical diversity. Many of them are biosynthesized by metabolic pathways exclusive to marine organisms and have shown an astonishing array of biological properties.[42] In 1992, while studying pharmacologically active metabolites from sponges, Rudi and Kashman isolated barekoxide (**3**),[5c] a marine diterpenoid with an unprecedented carbon skeleton, the structure of which was established with the aid of X-ray analysis of its 3-bromo-derivative **74**.[5a,b] Three years later, Su et al. isolated the closely related terpenoid laukarlaol from the red alga *Laurencia karlae* and proposed the structure **75** on the basis of spectral data (Chart 2).[43]

Barekoxide and laukarlaol attracted our attention not only because of the synthetic challenge they posed but also because of their intriguing biogenesis.[5a,b] Therefore, we decided to attempt their chemical synthesis from **20** trying to corroborate structures **3** and **75**, provide chemical evidence concerning their biogenesis, and facilitate further biological analysis.[44] Dess−Martin oxidation of **20** gave ketone **76**, which, after treatment with *p*-toluenesulfonyl hydrazide, furnished tosylhydrazone **77** (Scheme 11). Catecholborane reduction[45] of **77** gave hydrocarbon **78**, and, finally, *m*-CPBA epoxidation of **78** took place selectively at the α-face of the molecule, providing a 71% yield of **3**. The spectroscopic data of synthetic **3** were in accordance with those reported for natural barekoxide,[5] and thus we achieved the first chemical synthesis of this marine product in only six steps from geranyl linalyl acetate at an 8% overall yield.

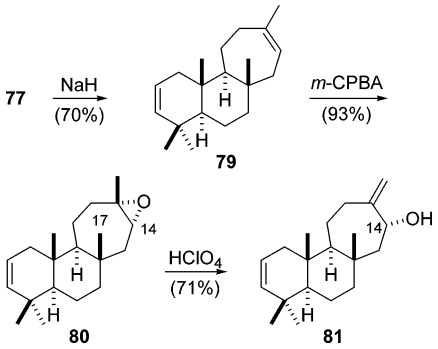
Tosylhydrazone **77** also served as a branch point to start a divergent route toward authentic laukarlaol (Scheme 12). Thus, the treatment of **77** with sodium hydride gave diene **79**, which, as occurred with the closely related alkene **78**, underwent selective epoxidation at the α-face of the Δ^{13} double bond. NOE observed between H-14 and H_3-17 confirmed the α-disposition of the oxirane ring of **80** (see Figure 3).[46] Finally, the perchloric acid opening of epoxide **80** completed the total synthesis of alcohol **81** (seven steps with more than 8% overall yield), which

(37) (a) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Palomino, P. L. *Tetrahedron* **1994**, *50*, 13239−13250. (b) Uneyama, K.; Date, T.; Torii, S. *J. Org. Chem.* **1985**, *50*, 3160−3163.
(38) See, for example, the discussion concerning the relative stereochemistry of dauca-7,11-diene: (a) Cassidy, M. P.; Ghisalberti, E. L. *J. Nat. Prod.* **1993**, *56*, 1190−1193. (b) Bohlmann, F.; Zdero, C. *Phytochemistry* **1982**, *21*, 2263−2267.
(39) (a) Harayama, T.; Shinkai, Y.; Hashimoto, Y.; Fukushi, H.; Inubushi, Y. *Tetrahedron Lett.* **1983**, *24*, 5241−5244. (b) Biellmann, J. F.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1962**, 331−336.
(40) Urones, J. G.; Marcos, I. S.; Basabe, P.; Alonso, C. A.; Diez, D.; Garrido, N. M.; Oliva, I. M.; Rodilla, J. S.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron Lett.* **1990**, *31*, 4501−4504.
(41) Urones, J. G.; Marcos, I. S.; Basabe, P.; Alonso, C.; Oliva, I. M.; Garrido, N. M.; Martín, D. D.; Lithgow, A. M. *Tetrahedron* **1993**, *49*, 4051−4062.
(42) (a) Salomon, C. E.; Magarvey, N. A.; Sherman, D. V. *Nat. Prod. Rep.* **2004**, *21*, 105−121. (b) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2004**, *21*, 1−49 and previous issues in this series.
(43) Su, J. Y.; Zhong, Y. L.; Zeng, L. M.; Wu, H. M.; Ma, K. *Phytochemistry* **1995**, *40*, 195−197.
(44) Barekoxide was isolated from the sponge *Chelonaplysilla erecta*, the extract of which showed antitumoral activity (cf., ref 5c).
(45) Yee, N. K. N.; Coates, R. M. *J. Org. Chem.* **1992**, *57*, 4598−4608.
(46) The interatomic distance between H-14 and H-17 of **80** is 2.757 Å in the minimized energy conformation shown in Figure 3 (CS ChemBats3D Pro, MOPAC).

Scheme 11. Synthesis of Barekoxide (**3**) from **20**



Scheme 12. Synthesis of Authentic Laukarlaol (**81**) from **20**



showed spectroscopic data matching those reported for natural laukarlaol.[47] Therefore, the relative 14*S** stereochemistry (**75**) originally proposed for this natural product[43] should be revised to the 14*R** one depicted in **81**.

The results shown in this section confirm the utility of titanocene(III)-catalyzed radical cyclizations for the straightforward synthesis of mono (**1**), sesqui (**2**), and diterpenoids (**3**, **72**, and **81**) with different carbon skeletons containing a seven-membered carbocyle.

Biogenetic Discussion. The new findings concerning the intrinsic tendency shown by radicals **22**, **33**, **34**, **41**, and **42** (with a substitution pattern characteristic of the linalyl, nerolidyl, and geranyl linalyl systems) to undergo 7-*endo* cyclizations led us to consider the possible implications of this phenomenon in the biosynthesis of **1**−**3**. Linalyl, nerolidyl, and geranyl linalyl pyrophosphate esters and the corresponding alcohols are recognized among the acyclic biogenetic parents of mono-, sesqui-, and diterpenoids, together with their allylic isomers, the geranyl, farnesyl, and geranyl geranyl systems, respectively.[2,48] Furthermore, it is generally assumed that the enzyme-catalyzed cyclization of these precursors toward the different terpenoid skeletons takes place via hypothetical carbocation intermediates.[2,48] Nevertheless, apart from the currently well-studied enzymatic cyclization of squalene and oxidosqualene to sterols

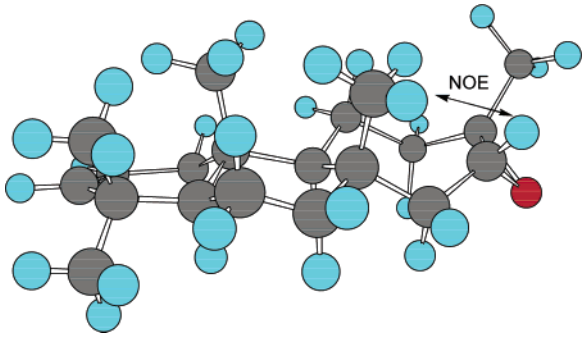


Figure 3. Minimized energy conformation of **80**. NOE between H-14 and H-17. Red = O, gray = C, blue = H.

and triterpenes,[49] there is no conclusive evidence proving the true nature of the cyclization mechanisms involved in the biogenesis of many other terpenoids. In this context, it has been proposed that the biosynthesis of daucane sesquiterpenoids (such as **2**) and the diterpenoid barekoxide (**3**) occurs via conventional carbocationic cyclization of the corresponding nerolidyl and geranyl linalyl precursors.[5a,b,50] On subjecting linalyl, nerolidyl, and geranyl linalyl derivatives to carbocationic-type cyclizations, however, different researchers have obtained six-membered cyclic ethers (presumably via intramolecular oxygen trapping of the corresponding carbocation intermediates), but seven-membered carbocycles have never been reported.[51] These results suggest that the behavior shown by **22**, **33**, **34**, **41**, and **42** only applies to free-radical intermediates and not to their carbocationic counterparts. Obviously, these observations do not constitute a conclusive argument in favor of radical metabolite intermediates but suggest that the possibility that radical cyclizations are involved in the biosynthesis of some terpenoids with seven-membered carbocycles cannot be completely ruled out. In this sense, the biogenesis of marine barekane diterpenoids is especially interesting.[52] Thus, the co-occurrence of the bromo-derivative **74** together with barekoxide (**3**) in the red alga *Laurencia luzonensis*[5a,b] might well point to a biogenetic cyclization initiated by bromine radical addition, a well-known chemical process.[53] In light of recent findings, the alternative bromonium-ion-initiated cationic cyclization proposed by Kuniyoshi et al.[5a,b] seems quite unlikely because Carter-Franklin and Butler have shown how enzymes such as vanadium bromoperoxidase, which catalyzes this type of cationic process, produce tetrahydropiranyl ethers and snyderol derivatives but not seven-membered carbocycles.[54]

(47) A copy of the ^{1}H NMR spectrum of synthetic **81** and a table with ^{13}C NMR data of **81** and natural laukarlaol[43] are given for comparison as Supporting Information.

(48) For a review on the biosynthesis of C_5-C_{25} terpenoids, see: Dewick, P. M. *Nat. Prod. Rep.* **2002**, *19*, 181−222 and previous issues in this series.

(49) For excellent reviews on this subject, see: (a) Hohino, T.; Sato, T. *Chem. Commun.* **2002**, 291−301. (b) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812−2833. (c) Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189−2206. For more recent reports, see: (d) Nishizawa, M.; Yadav, A.; Iwamoto, Y.; Imagawa, H. *Tetrahedron* **2004**, *60*, 9223−9234. (e) Hess, B. A., Jr. *Org. Lett.* **2003**, *5*, 165−167. (f) Hess, B. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 10286−10287.

(50) Ghisalberti, E. L. *Phytochemistry* **1994**, *37*, 597−623.

(51) (a) Uyanic, M.; Ishibashi, H.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 1601−1604. (b) Khomenko, T. M.; Tatarova, L. E.; Korchagina, D. V.; Barkhash, V. A. *Russ. J. Org. Chem.* **2002**, *38*, 498−506. (c) Polovinca, M. P.; Korchagina, D. V.; Gatilov, Y. V.; Bagrianskaya, I. Y.; Barkhash, V. A.; Shcherbukhin, V. V.; Zefirov, N. S.; Perutskii, V. B.; Ungur, N. D.; Vlad, P. F. *J. Org. Chem.* **1994**, *59*, 1509−1517. (d) Kametani, T.; Fukumoto, K.; Kurobe, H.; Nemoto, H. *Tetrahedron Lett.* **1981**, *22*, 3653−3656.

(52) We propose the name "barekane" for the diterpenoid skeleton shared by **3**, **74**, and **81**.

(53) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York, 1990; Part A, pp 695−701.

(54) Carter-Franklin, J. N.; Butler, A. *J. Am. Chem. Soc.* **2004**, *126*, 15060−15066.

Conclusions

We have developed a new strategy for the straightforward synthesis of seven-membered carbocycles, based on titanocene(III)-catalyzed 7-*endo*-dig and 7-*endo*-trig cyclizations via free-radical chemistry. This procedure has proved to be useful for the preparation of several natural products including mono-, sesqui-, and diterpenoids with different skeletons containing cycloheptane rings. We have also provided theoretical and experimental evidence in support of a plausible mechanism to rationalize the preference for the unusual 7-*endo* cyclization mode shown by radicals with substitution patterns characteristic of the linalyl, nerolidyl, and geranyl linalyl systems. In light of these chemical findings, we discuss the potential involvement of radical cyclizations in the biosynthesis of some terpenoids with seven-membered carbocycles. We are currently engaged in the total synthesis of aspergilloxide (**4**) in the hope of extending the scope of our method to the chemical preparation of bioactive sesterterpenoids found in marine organisms.

Computational Methods

Calculations were performed with the Gaussian 03 series of programs.[55] The geometries of all intermediates were optimized at the DFT level using the B3LYP hybrid functional,[56] using the standard 6-31G(d) basis set for C, H, and O. Transition states were graphically located. Harmonic frequencies were calculated at the same level of theory to characterize the stationary points and to determine the zero-point energies (ZPE). Final energies include ZPE correction without scaling. Intrinsic reaction coordinate (IRC) studies were performed to ensure connection between reagents and products. The bonding characteristics of the different stationary points were analyzed by means of the Natural Bond Orbital (NBO) analysis of Weinhold et al.[57]

Experimental Section

General. For the reactions with titanocene, all solvents and additives were thoroughly deoxygenated prior to use. Although all structures are drawn as one enantiomers, the synthesized compounds are racemic. Substances **7**,[58] **8**,[59] **9**,[18] and **10**[18] were prepared according to published procedures. The following known compounds were isolated as pure samples and their NMR spectra were identical to the reported compounds: **1**,[3] **2**,[4b] **3**,[5] **11**,[60] **16**,[18] **17**,[18] **18**,[18] **19**,[15] **21**,[15] **52**,[61] **53**,[62] **55**,[63] and **72**.[41] Preparation procedures for substrates **11**−**13** and **52**−**57** as well as physical and spectroscopic data for **12**−**15**, **20**, **56**−**65**, **76**−**80**, and 5-hydroxy-1,4,4-trimethylcycloheptyl acetate are given as Supporting Information.

Model Procedure for Titanocene(III)-Catalyzed Cyclizations. Thoroughly deoxygenated THF (20 mL) was added to a mixture of Cp_2TiCl_2 (0.5 mmol) and Mn dust (20 mmol) under an Ar atmosphere, and the suspension was stirred at room temperature until it turned lime green (after about 15 min). A solution of epoxide (2.5 mmol), 2,4,6-collidine (20 mmol), and Me_3SiCl (10 mmol) in THF (2 mL) was then added, and the mixture was stirred for 16 h. The reaction was quenched with 2 N HCl and extracted with *t*-BuOMe. The organic layer was washed with brine, dried with anhyd Na_2SO_4, and the solvent was removed. The residue was dissolved in THF (20 mL) and stirred with Bu_4NF (10 mmol) for 2 h.[64] The mixture was then diluted with *t*-BuOMe, washed with brine, dried with anhyd Na_2SO_4, and the solvent was removed. The products were isolated by flash chromatography of the residue to give the corresponding carbocycles at the yields referred to in Tables 1 and 2.

Synthesis of Daucadiene 2. A solution of **18** (70 mg, 0.31 mmol) and PCl_5 (72 mg, 0.34 mmol) in a benzene:toluene mixture (15 mL, 2:1) was stirred for 1 h at 0 °C. The reaction was quenched with 5% aqueous K_2CO_3, extracted with *t*-BuOMe, washed with water, dried with anhydrous Na_2SO_4, and the solvent was removed. The residue was submitted to flash chromatography (hexane) to give **2**[4b] (47 mg, 75%) as a colorless oil.

Synthesis of Valparane 72. A solution of **20** (17 mg, 0.06 mmol) and PCl_5 (15 mg, 0.07 mmol) in a benzene:toluene mixture (15 mL, 2:1) was stirred for 1 h at 0 °C. The reaction was quenched with 5% aqueous K_2CO_3, extracted with *t*-BuOMe, washed with water, dried with anhydrous Na_2SO_4, and the solvent removed. The residue was chromatographed (hexane) to give **72**[41] (15 mg, 95%) as a colorless oil.

Preparation of Ketone 76. A solution of **20** (290 mg, 1.06 mmol) and Dess−Martin periodinane (1.50 g, 2.84 mmol) in wet CH_2Cl_2 (33 mL) was stirred for 45 h at room temperature. The reaction was diluted with *t*-BuOMe, washed with a 1:1 mixture of 10% aqueous $Na_2S_2O_3$ and saturated $NaHCO_3$ solutions, washed with brine, dried with anhydrous Na_2SO_4, and the solvent was removed. The residue was submitted to flash chromatogrphy (4:1 hexane:*t*-BuOMe) to give **76** (253 mg, 88%).

Preparation of Tosylhydrazone 77. A solution of **76** (231 mg, 0.80 mmol) and $TsNHNH_2$ (223 mg, 1.20 mmol) in absolute EtOH (10 mL) was refluxed for 2 h. The solvent was removed, and the residue was submitted to flash chrmotagraphy (4:1 hexane:*t*-BuOMe) to give **77** (334 mg, 92%).

Preparation of Tricyclic Alkene 78. Catecholborane (0.21 mL of 1 M in THF, 0.21 mmol) was added to a solution of **77** (32 mg, 0.07 mmol) in CH_2Cl_2 at 0 °C. The mixture was stirred for 30 min at 0 °C and then for 1 h at room temperature. MeOH (1 mL) and NaOAc (44 mg, 0.42 mmol) were then added. This mixture was stirred at room temperature for another 16 h, diluted with *t*-BuOMe, washed with water, dried with anhydrous Na_2SO_4, and the solvent was removed. The residue was chromatographed (hexane) to give **78** (12 mg, 62%).

Synthesis of Barekoxide (3). A mixture of **78** (8 mg, 0.03 mmol) and *m*-CPBA (18 mg, 0.07 mmol) in CH_2Cl_2 (5 mL) was stirred for 1 h at room temperature. The reaction was diluted with CH_2Cl_2, washed with water, dried with anhydrous Na_2SO_4, and the solvent removed. The residue was submitted to flash chromatography (95:5 hexane:*t*-BuOMe) to give barekoxide[5] (**3**) (6 mg, 71%) as a white solid, mp 86−90 °C (lit.[5a,b] mp 140 °C).

Preparation of Tricyclic Diene 79. A mixture of **77** (290 mg, 0.64 mmol) and NaH (763 mg, 31.7 mmol) in toluene (10 mL) was boiled under reflux for 1 h. The reaction was diluted with *t*-BuOMe, washed with water, dried with anhydrous Na_2SO_4, and the solvent removed. The residue was chromatographed (hexane) to give **79** (121 mg, 70%).

Preparation of Epoxide 80. A solution of **79** (70 mg, 0.26 mmol) and *m*-CPBA (44 mg, 0.26 mmol) in CH_2Cl_2 (5 mL) was stirred for 30 min at 0 °C. The reaction was diluted with CH_2Cl_2, washed with water, dried with anhydrous Na_2SO_4, and the solvent removed. The residue was submitted to flash chromatography (95:5 hexane:*t*-BuOMe) to give **80** (69 mg, 93%).

Synthesis of Authentic Laukarlaol (81). Two drops of 60% $HClO_4$ were added to a solution of **80** (17 mg, 0.06 mmol) in DMF (2 mL) at

(55) Frisch, M. J.; et al. *Gaussian 03*, revision B.03; Gaussian, Inc.: Pittsburgh, PA, 2003.
(56) (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098−3100. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.
(57) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899−926.
(58) Rodriguez, J.; Dulcore, J. P. *J. Org. Chem.* **1991**, *56*, 469−471.
(59) Cernigliaro, C. J.; Kocienski, P. J. *J. Org. Chem.* **1977**, *42*, 3622−3624
(60) Miyase, T.; Ueno, A.; Takizawa, N.; Kobayashi, H.; Karasawa, H. *Chem. Pharm. Bull.* **1987**, *35*, 1109−11017.
(61) Anjum, S.; Marco-Contellés, J. *Tetrahedron* **2005**, *61*, 4793−4803.
(62) Fürstner, A.; Hammen, P. *Chem. Commun.* **2004**, 2546−2547. See also ref 60.
(63) Torii, S.; Uneyama, K.; Tanaka, H.; Yamanaka, T.; Yasuda, T.; Ono, M.; Kohmoto, Y. *J. Org. Chem.* **1981**, *46*, 3312−3315.

(64) In some experiments, acidic quenching was enough to promote the desilylation reaction.

room temperature. The reaction was stirred for 16 h and then diluted with *t*-BuOMe, washed with water, dried with anhydrous Na_2SO_4, and the solvent was removed. The residue was submitted to flash chromatography (4:1 hexane:*t*-BuOMe) to give **81** (12 mg, 71%) as a white solid, mp 105−106 °C (lit.[43] mp 128−129) with NMR and mass spectra matching those reported for natural laukarlaol.[43] EIHRMS calcd for $C_{20}H_{32}O$ *m*/*z* 288.2453, found *m*/*z* 288.2453.

Acknowledgment. We thank the Spanish "Junta de Andalucía" for financial support (research group FQM339), Dr. A. F. Barrero for his collaboration in the early stage of this work, and our English colleague Dr. J. Trout for revising our text. J.J. and J.L.O.-L. thank the Spanish Ministry of Education and Science for grants enabling them to pursue these studies. D.J.C. and E.B. thank the Spanish Ministry of Education and Science for Project CTQ2004-02040/BQU and the "Centro de Computación Científica (UAM)" for computation time.

Supporting Information Available: Preparation procedures for substrates **11**−**13** and **52**−**57** as well as physical and spectroscopic data for **12**−**15**, **20**, **56**−**65**, **76**−**80**, and 5-hydroxy-1,4,4-trimethylcycloheptyl acetate. A comparison between ^{13}C NMR data reported for natural laukarlaol[43] and those from synthetic **81**. Complete ref 55 with the full authors list. Copies of the ^{1}H or ^{13}C NMR spectra for all of the new compounds. Atomic coordinates and energies for stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

JA054316O