DOI: 10.1002/ejoc.200500849

Titanocene-Mediated Radical Cyclization: An Emergent Method Towards the Synthesis of Natural Products

Alejandro F. Barrero,*[a] José F. Quílez del Moral,[a] Elena M. Sánchez,[a] and Jesús F. Arteaga[a]

Keywords: Radical reactions / Titanium / Cyclization / Domino reactions / Natural products

The reaction of the Cp_2TiCl complex with oxiranes leads to homolytic opening of the heterocycle with high regioselectivity. Although the resulting β-titanoxyl radical can evolve in different ways, when the epoxide reacting with Cp_2TiCl possesses suitable unsaturated moieties such as olefins, triple bonds, carbonyls or nitriles in its structure, intramolecular addition of this β-titanoxyl radical to these unsaturated groups can take place, leading to a cyclization process. Structures containing from three- to seven-membered rings have been synthesized using either stoichiometric or catalytic quantities of titanocene. Although a number of applications for these titanium-mediated cyclization reactions have been reported in the synthesis of natural products and bioactive compounds such as antibiotic γ-lactones, lignans and β-lactams, we consider that the strategy involving the opening and ensuing cyclization of the monoepoxides of polyprenes, which resulted in the preparation of C_{10}, C_{15}, C_{20} and C_{30} terpenoids, including mono-, bi- and tricyclic natural products, deserves special mention. Attractive aspects of this reaction are good stereochemical control and the oxidative termination of the process, which leads regioselectively to exocyclic olefins.

1. Introduction

Free-radical cyclization reactions are recognized as having a powerful effect on carbon–carbon bond-forming reactions, including the construction of mono- and polycyclic compounds. These processes usually occur with regio- and stereoselective control and can be modulated to form different-sized rings.[1] They have been applied to the synthesis of a number of natural products, including terpenoids and steroids,[2] lignans and other oxygenated heterocycles,[3] and β-lactams.[4]

Among the different types of free-radical cyclization reactions available, special attention should be paid to annulation and related cascade sequences because of their great potential in synthetic reactions, allowing as they do multiple ring-closures in just one step.[5] These reactions are of special interest in the synthesis of terpenoids and sterols because the enzymatic systems acting in the biosynthesis of these compounds are mimicked.[6]

[a] Department of Organic Chemistry, Institute of Biotechnology, University of Granada,
Avenida Fuentenueva, 18071 Granada, Spain
Fax: + 34-958-243318
E-mail: afbarre@ugr.es

The first descriptions of free-radical-based polycyclization reactions in polyprenes were published by Breslow and Julia and their co-workers.[7] Since then a number of impressive reports of cascade radical cyclization reactions have appeared, amongst which are Curran and Rakiewicz's total synthesis of hirsutene[8] and the development of different methods leading to triquinane frameworks.[9]

β-Keto esters have been used as substrates to generate carbon-centered radicals after exposure to $Mn(OAc)_3$. The radicals thus generated have been reported to trigger a number of cyclization reactions,[10] including tandem processes, that lead to the synthesis of ambrox,[11] isosteviol,[12] (–)-triptolide[13] and wentilactone B.[14]

Acyl radicals generated by the reduction of acylselenides have been reported to initiate polycyclization reactions and in some cases up to seven cycles have been formed simultaneously.[15] In addition, photoinduced electronic transfer (PET) processes in polyprenes have led to the synthesis of polycyclic terpenes hydroxylated at the C-3 position by nucleophilic trapping of the initial radical carbocation with water and subsequent radical polycyclization.[16]

The Cp_2TiCl complex can easily be prepared from commercial Cp_2TiCl_2 (Figure 1) by using reductants such as

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

Figure 1. Preparation of the Cp_2TiCl complex from commercial Cp_2TiCl_2. Cp_2TiCl exists as an equilibrium between a monomer and a dimer species.

Al,[17] Zn[18] or Mn.[19] The nature of this reducing agent in solution was studied by Skrydstrup et al., who proved its existence as an equilibrium between a monomer and a dimer species.[20] The reaction of these Ti^{III} species with oxiranes leads to the homolytic opening of the heterocycle, thus forming the β-titanoxyl radical **I**,[21] which in turn can react with a second molecule of Cp_2TiCl, leading to the alkyltitanium complex **II** (Scheme 1). Starting from both species, a number of interesting organic transformations have been developed. Thus **II** has been used to generate olefins by the elimination of $(Cp_2TiCl)_2O$[22] and to prepare allylic alcohols by β-elimination of $Cp_2Ti(Cl)H$.[23]

Radical **I** can also be reduced with hydrogen donors to alcohols.[22,24] This reduction has been applied to the formation of both 1,2- and 1,3-diols from Sharpless epoxides[24,25] and β-hydroxyketones from α,β-epoxyketones.[26] Catalytic Ti^{III}-mediated reduction reactions have been developed using hydrochlorides of substituted pyridines (collidine hydrochloride, for example).[27] The catalytic reduction of α,β-epoxyketones has led to good yields of β-hydroxyketones.[26] The use of chiral titanocene complexes has been reported to reduce *meso*-epoxides enantioselectively.[27b,27e]

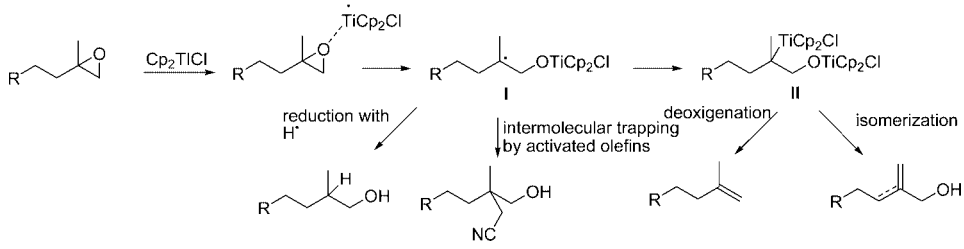
The β-titanoxyl radical **I** can also react with olefins activated with unsaturated groups such as nitriles or esters to create new carbon–carbon bonds by using Ti^{III} in either equimolar[24,28] or catalytic quantities.[19a,27e,29] In conceptually similar reactions, epoxide-derived radicals have proved to add to α,β-unsaturated carbene complexes.[30]

Alejandro Fernández Barrerro was born in Orense (Spain) in 1949. He obtained his Ph.D. degree in 1975 at the University of Salamanca under the guidance of Professors Joaquín Pascual de Teresa, Arturo San Feliciano and Inés Sánchez Bellido. After working as a research scientist at the Compañía Española de Petróleos Research Center in San Fernando de Henares (Spain), he returned to the University of Salamanca as a Lecturer. He moved to the Universidad of Granada as Full Professor in 1983, where he has been Head of the Organic Chemistry Department for five years. His formative labour includes the direction of more than 40 doctoral theses. His current interests are the chemistry of terpenoids and the application of both radical cyclization reactions and new couplings catalyzed by transition metals to the synthesis of natural bioactive products.

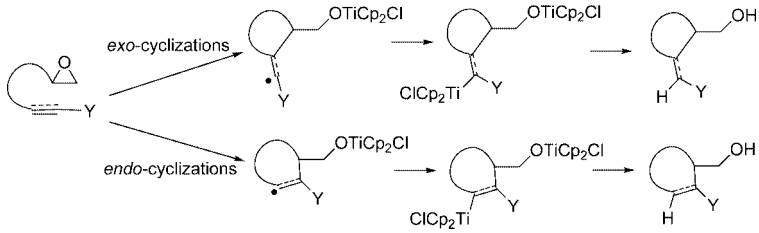
José Francisco Quílez del Moral was born in Linares (Spain) in 1967 and studied Chemistry at the University of Granada, where he graduated in 1990. He received his Ph.D. degree in 1996 under the supervision of Prof. A. F. Barrero. In 1997, he started a 20 month post-doctotal fellowship with Prof. S. Arseniyadis at the Institut de Chimie des Substances Naturelles at Gif-sur Yvette (France) working on the total synthesis of taxol. He returned to Granada as assistant professor and joined Prof. A. F Barrero's group in 1998. He is currently a senior lecturer and his research interests are directed towards the development of new methods for the synthesis of molecules having biological activity.

Elena M. Sánchez Fernández was born in Barcelona (Spain) in 1978 and she graduated in Chemistry in 2001 at the University of Granada. She is currently a Ph.D. student at the same University under the supervision of Prof. Alejandro F. Barrero. Her main interest is the application of radical chemistry to the synthesis of terpenoids.

Jesús F. Arteaga was born in 1979 and he graduated in Chemistry in 2002 at the University of Granada. He is currently a Ph.D. student under the supervision of Prof. Alejandro F. Barrero at the same university. He was visiting Ph.D. Student in 2004 at the Institut de Chimie des Substances Naturelles (CNRS, Gif-sur-Yvette, France) with Prof. Simeon Arseniyadis. His research interests are mainly focused on the development of new applications of free-radical chemistry in the synthesis of natural products.



Scheme 1.



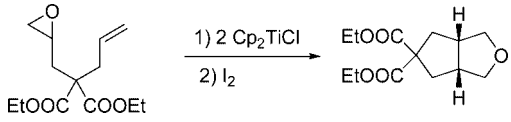
Scheme 2.

When the epoxide reacting with Cp_2TiCl contains suitable unsaturated groups such as olefins, triple bonds, carbonyls or nitriles in its structure, the addition of radical **I** to these moieties can take place, leading to a cyclization process. Within this context, the aim of this review is to look at the different cyclization reactions mediated by Cp_2TiCl and to examine its use as a versatile tool in the construction of natural products (Scheme 2).

2. Cp_2TiCl-Mediated Cyclization with Unsaturated Epoxides

The reaction of epoxyolefins of type **1** or epoxyalkynes with 2 mol of Cp_2TiCl has led to highly efficient 5-*exo* cyclization reactions (Scheme 3).[21,24]

The proposed mechanism for this reaction involves the alkyltitanium **III** species, formed by trapping the carbon-centered radical resulting from the cyclization step by a second molecule of Cp_2TiCl. The existence of **III** has been proven by trapping with D_2O/D^+ or by reaction with I_2 to give the corresponding primary halide. The synthesis of tetrahydrofurans (Scheme 4) represents a straightforward application of this reaction.

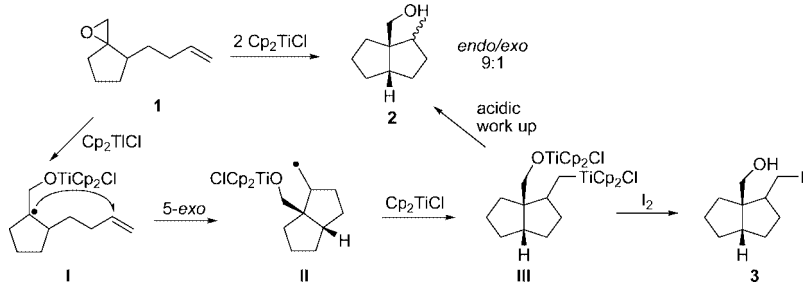


Scheme 4.

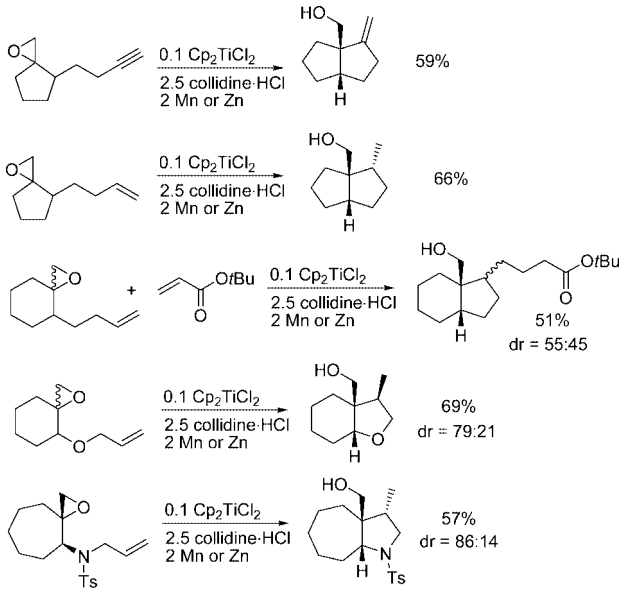
A catalytic version of this process developed by Gansäuer et al.[19,31] has given excellent results with 5-*exo* carbo- or heterocyclization reactions, leading to cyclopentanes, tetrahydrofurans and pyrrolidines (Scheme 5).[32,19b] An extension of this idea was the intermolecular trapping of the radical formed in the cyclization step by α,β-unsaturated carbonyl compounds.[33]

The capacity of collidine hydrochloride to protonate either a Ti–O or a Ti–C bond is shown in the proposed mechanism (Scheme 6).[27f]. The control of the observed diastereoselectivity can be explained on the basis of the most favored conformations of type **I** radical intermediates.[19b]

Fernández-Mateos et al. analyzed the effect of chain length on the Ti^{III}-induced cyclization of epoxyalkenes.[34] Only 5- and 6-*exo* cyclization reactions took place. The product obtained is the result of a final reduction of the



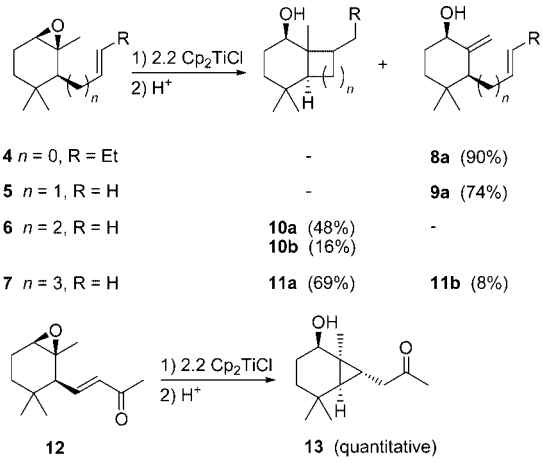
Scheme 3.



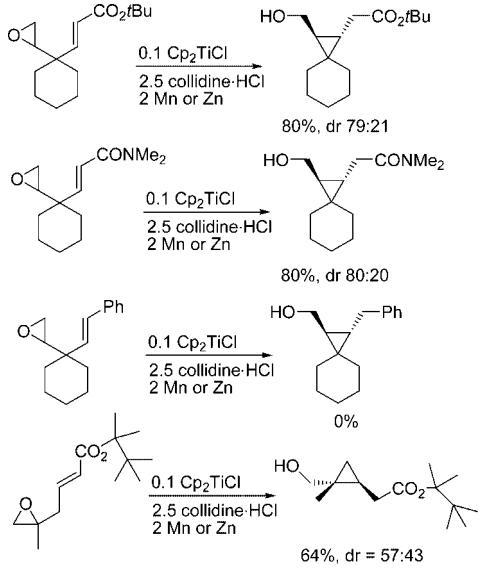
Scheme 5.

alkyltitanium species generated. Remarkably, the presence of a carbonyl group conjugated to the double bond exerts an accelerating effect on the cyclization reaction. Thus, when **12** is used as the substrate the 3-*exo* process occurs quantitatively (Scheme 7). In relation to this, Gansäuer and co-workers established, through a combined theoretical and experimental study of titanocene-mediated 3-*exo* cyclization reactions (Scheme 8), that these reactions are thermodynamically favorable and that the efficiency of the process depends on the ease with which the cyclopropyl radicals are trapped by a second molecule of Cp_2TiCl.[35]

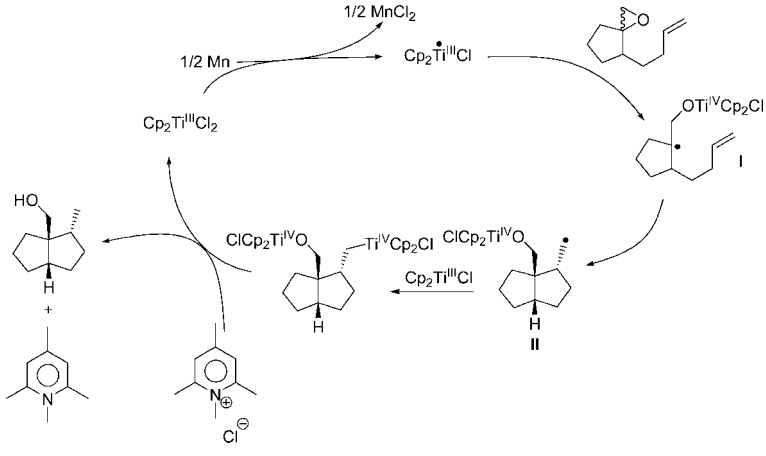
Epoxyaldehydes, epoxyketones and epoxynitriles have also been used as substrates in Ti^{III}-mediated cyclization reactions.[36] Cycloalkanols were obtained with the epoxycarbonyl substrates, while cycloalkanones were the result of the radical cyclization of epoxynitriles. As far as experiments performed with epoxycarbonyl derivatives are concerned, good yields of reaction products ranging from cy-



Scheme 7.

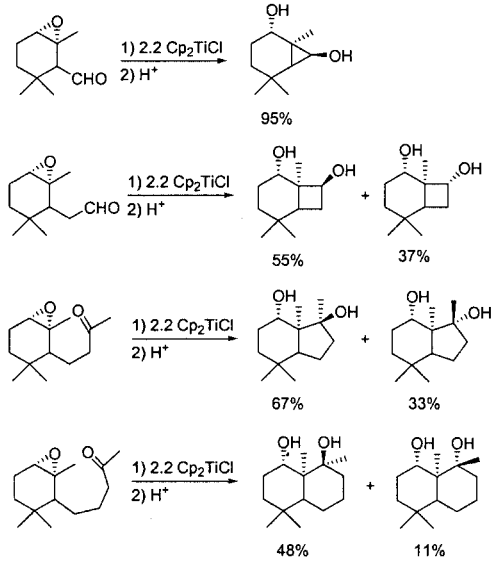


Scheme 8.



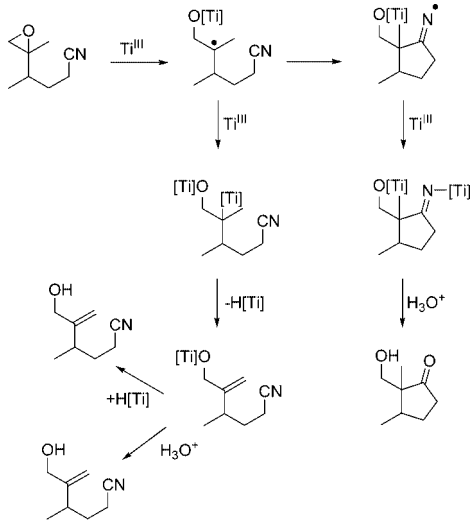
Scheme 6.

clopropanols to cyclohexanols have been obtained, with a particularly high yield of the corresponding cyclopropanol (Scheme 9).



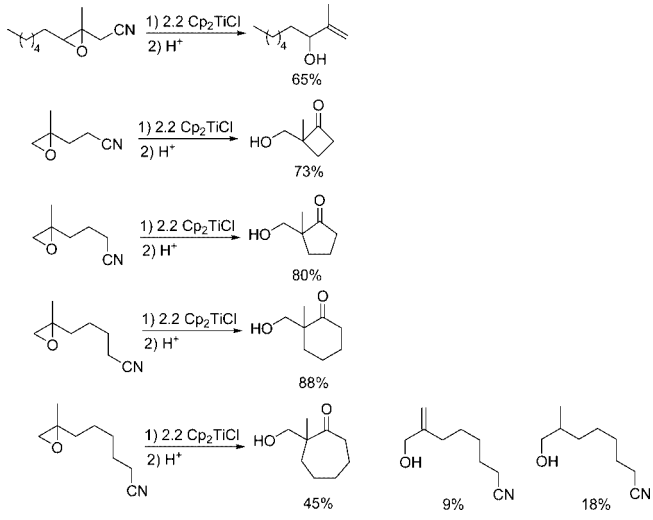
Scheme 9.

The loss of efficiency detected in the 6-*exo* processes is due to a competitive β-hydrogen elimination from the carbon-centered radical resulting from the initial opening of the epoxide.[36a]



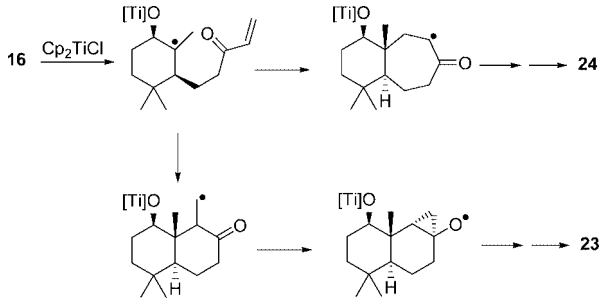
Scheme 10.

As far as the behavior of epoxynitriles is concerned, the method affords good yields of 4-, 5- and 6-*exo*-dig products.[36b] The mechanism proposed requires the addition of a β-titanoxyl radical to the nitrile to cause the imine radical thus generated to evolve into the corresponding ketone (Scheme 10). Note that with α-epoxynitriles a loss of the nitrile group is also observed. Finally, in the case of ε-epoxynitriles, elimination of the β-titanoxyl radical intermediate competes with the 7-*exo*-dig cyclization reaction (Scheme 11).

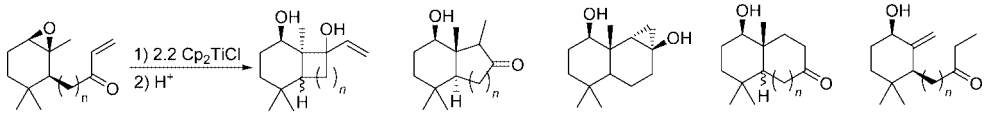


Scheme 11.

Studies carried out on a series of epoxyketones conjugated to a monosubstituted double bond revealed that good



Scheme 13.



14 $n = 0$	**18** (68%)	-	-	-	**19** (13%)
15 $n = 1$	**20** (40%)	**21** (17%)	-	**22** (21%)	-
16 $n = 2$	-	-	**23** (51%)	**24** (26%)	-
17 $n = 3$	-	**25** (22%)	-	**26** (8%)	-

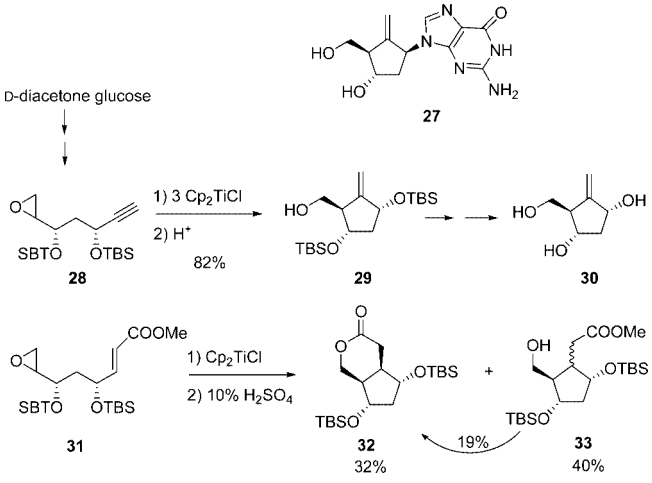
Scheme 12.

chemoselective cyclization to the cyclopropyl derivative was only observed when β-ketones were used as the starting material (Scheme 12).[34] In the rest of the series, mixtures of cyclization reactions occurred to form either carbon–carbon or carbon–oxygen bonds.

The formation of **23** may be put down to a tandem process, the first step being a 6-*exo* cyclization followed by a rapid 3-*exo* cyclization (Scheme 13).

3. Application of Titanium-Catalyzed Cyclization Reactions to the Synthesis of Natural Products and Bioactive Compounds

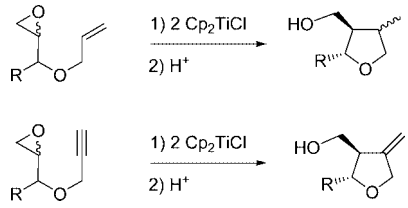
Entecavir (**27**) is a synthetic carbocyclic nucleoside which combats the hepatitis B virus. Ziegler has reported two approaches to the synthesis of the carbocyclic core of this molecule starting from D-diacetone glucose.[37] The key step of these synthetic routes involves the titanocene-induced cyclization of epoxyalkyne **28** or epoxyalkene **31**. Thus, starting from **28**, an 82% yield of carbocycle **29** is obtained whilst the cyclization of **31** affords a 32% yield of lactone **32** together with a 40% yield of diastereomers **33**, which after lactonization give an additional 19% of **32** (Scheme 14).



Scheme 14.

3.1 Synthesis of Tetrahydrofuran Derivatives: Antibiotic γ-Lactones and Lignans

Titanocene-mediated 5-*exo*-dig and 5-*exo*-trig cyclization reactions have been extensively used in the synthesis of both lignans and natural products presenting tetrahydrofuran precursors of γ-lactones (Scheme 15).

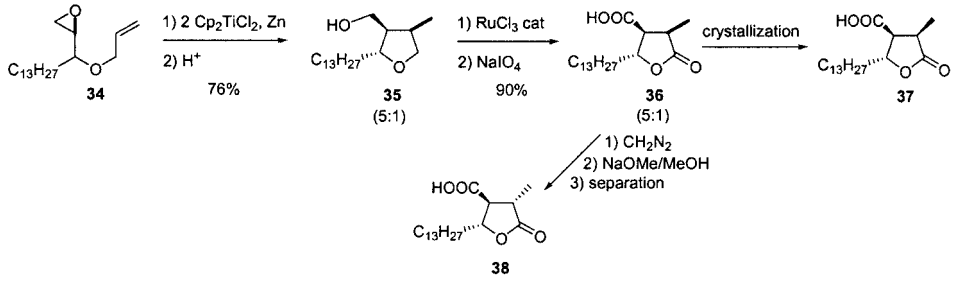


Scheme 15.

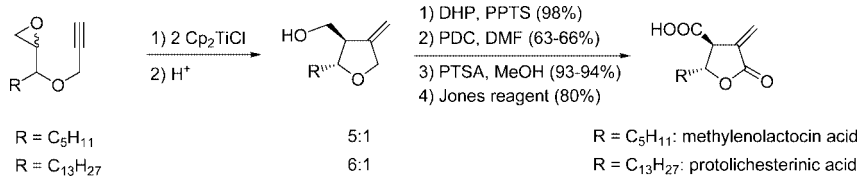
(±)-Dihydroprotolichesterinic acid (**37**) and (±)-roccellaric acid (**38**), two potent antibacterial compounds,[38] have been efficiently synthesized using epoxyalkene **34** (1:1 mixture of diastereomers) as the starting substrate (Scheme 16).[39] This cyclization reaction afforded a 76% yield of a 5:1 mixture of diastereomers (β-methyl/α-methyl).

A further application of this protocol was reported by Roy and co-workers with a series of 5-*exo*-dig cyclization reactions in their synthesis of (±)-methylenolactocin, isolated from *Penicillium sp.*,[40a] and (±)-protolichesterinic acid, isolated from different species of the moss *Cetraria*[40b] (Scheme 17).[41] The good diastereoselectivities found could be due to steric hindrances in the chair-like transition state of the β-titanoxyl radical in the cyclization step. In the last step of these syntheses, oxidation with Jones' reagent causes epimerization at the C-4 position, which causes the mixture of diastereomers obtained in the previous step to converge towards the desired thermodynamically most stable isomer.

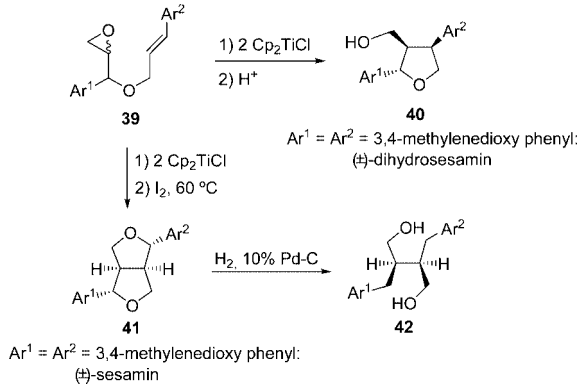
The same authors extended this protocol to the synthesis of three types of lignans: furanolignans such as (±)-laricireisiniol dimethyl ether, furofuranolignans such as (±)-sesamin and (±)-pinoresinol and acyclic lignans (Scheme 18).[42] The exposure of epoxyalkenes **39** to an excess of titanocene followed by acidic quenching leads to a 5:1 mixture of diastereomers, the main one possessing structure **40**. Following this protocol, (±)-dihydrosesamin and other natural lignans were easily synthesized. When the β-titanoxyl radical generated after cyclization was treated in situ with iodine for 1 h at 60 °C, good yields of furofuranolignans **41** were obtained [in the case of (±)-sesamin, 93%]. Extensive hydrogenation of these furofuranolignans also leads very efficiently to acyclic lignans **42**.



Scheme 16.



Scheme 17.

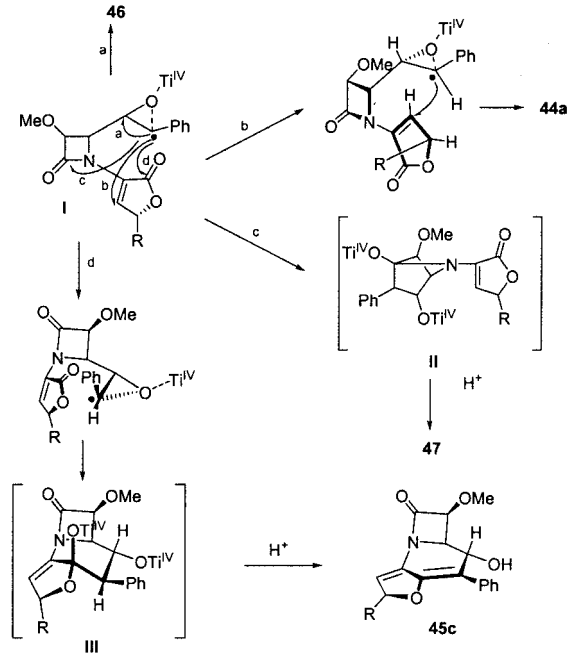


Scheme 18.

3.2 Synthesis of β-Lactam Antibiotics

Different β-lactam monoepoxides have been made to react with Cp_2TiCl to afford new β-lactam antibiotics possessing cabapenem-, carbacephen- or tribactam-type skeletons. When the series of epoxymonobactams **43a**–**d** were subjected to Ti^{III}-induced cyclization conditions, it was found that the desired tribactam **44** was only obtained when the starting epoxide possessed an α configuration at the C-5 position (Scheme 19).[43]

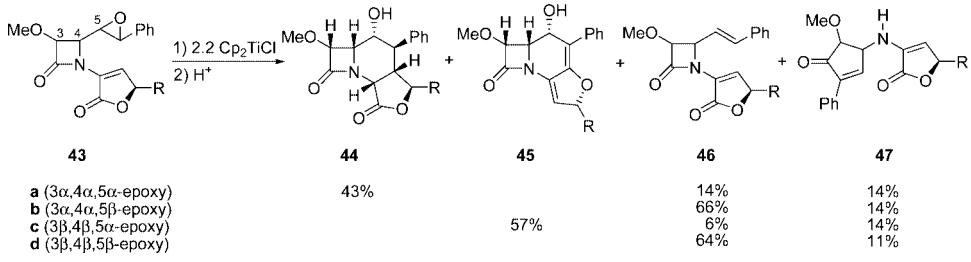
Thus, Michael addition of the β-titanoxyl radical derived from **43a** to the α,β-unsaturated γ-lactone led, by a 6-*endo*-trig process, to a 43% yield of **44a**. On the other hand, diastereomer **43c** led, under the same conditions, to a 57% yield of tribactam **45c**. In this case the radical formed after the reductive opening of the epoxide attacked the lactone carbonyl group, thus leading to the corresponding β-titanoxy derivative, which was subsequently eliminated during work up. No cyclized products were obtained when epoxides **43b**,**d** were used as substrates, but olefins, resulting from deoxygenation of the starting material, were found. The absence of cyclization products in these cases may well be put down to the fact that the (C6–O)σ* orbital of the initial radical cannot align correctly with the enone π orbital. Surprisingly, all the epoxy β-lactams studied afforded amines **47** as minor products. The formation of these compounds can be explained by 4-*exo*-trig addition of the β-titanoxyl radical to the carbonyl of the lactam followed by an acid-promoted rearrangement (Scheme 20).



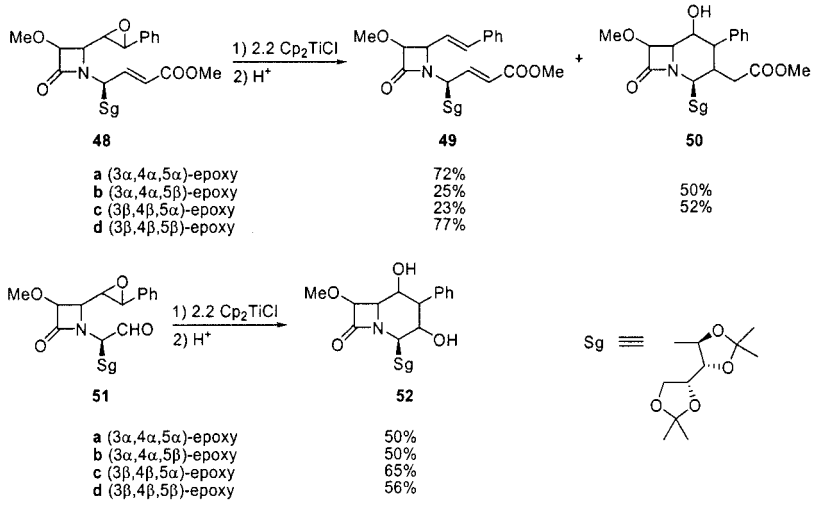
Scheme 20.

The application of this method has been further extended by the same authors using α,β-unsaturated esters **48** and aldehydes **51** as radical acceptors (Scheme 21).[44]

The reaction of epoxides **48b**,**c** with titanocene(III) chloride led stereospecifically to carbacephams **50b**,**c**. With isomers **48a** and **48d** as substrates, only the corresponding deoxygenated products **49a** and **49d** were obtained. The explanation for these results was reached after analyzing the steric hindrances associated with the most stable conforma-



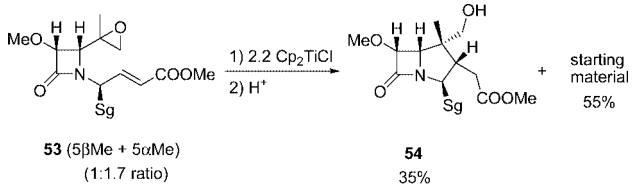
Scheme 19.



Scheme 21.

tions of the starting substrates **48a** and **48d**. In the case of monobactams possessing an aldehyde, such as **51**, the reaction proceeded to give exclusively the cyclization products. The smaller size of the aldehyde allowed the intermediate benzyl radical to approach the radical acceptor to afford the desired carbacephams.

Variations on the carbonated structure of the starting epoxide also led to Ti^{III}-mediated 5-*exo*-trig cyclization reactions (Scheme 22).[45] Thus, a satisfactory yield of carbacepham **54** was obtained from the mixture of epoxides **53** when the level of conversion was low. When epoxides **53** were allowed to react for 16 h to increase the degree of conversion, mixtures of unknown compounds were formed.



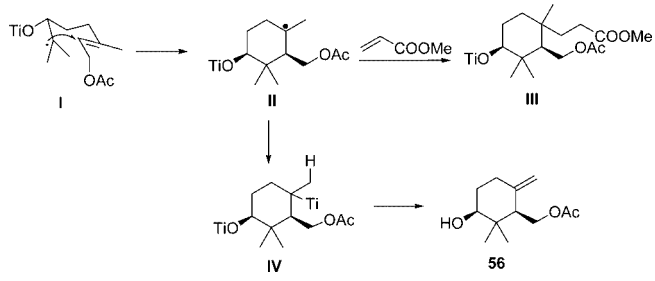
Scheme 22.

3.3. Synthesis of Terpenoids

Monocyclization reactions of monoepoxides of acyclic polyprenes led to the formation of five-, six- and seven-membered rings.

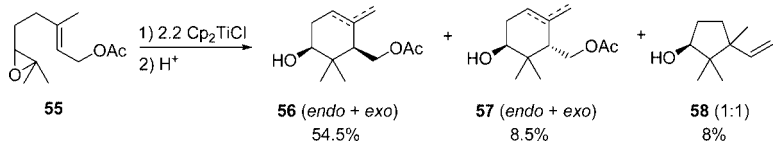
A Ti^{III}-mediated strategy to synthesize cyclic six- and seven-membered-ring terpenoids consisting of the opening and ensuing cyclization of monoepoxides of acyclic mono- and sesquiterpenes has been reported.[46] Good stereochemical control together with the oxidative termination of the process, which leads regioselectively to exocyclic olefins, are attractive aspects of this method. Apart from satisfactory yields, this kind of termination improves not only the ionic processes but also other radical cyclization reactions that afford reduction products.[15b,16b]

6,7-Epoxygeranyl acetate (**55**) was the first substrate to react with an excess of Cp_2TiCl in THF (Scheme 23). Under these conditions a 63% yield of the 6-*endo* cyclization products was obtained, the *exo* isomers being the major compounds formed. The *cis* relationship between the hydroxy and the acetoxymethyl groups is a consequence of the chair-like transition state of the cyclization step. The formation of **III** when the reaction was carried out in the presence of methyl acrylate strongly supports a stepwise mechanism for this transformation (Scheme 24). The ease of $Cp_2Ti(Cl)H$ β-elimination from the cyclic alkyltitanium intermediate would account for the observed regioselective exocyclic elimination.



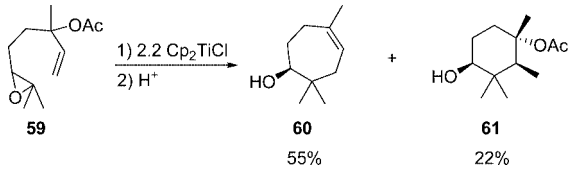
Scheme 24.

Surprisingly, a remarkable 55% yield of the 7-*endo*-trig cyclized product **60** was obtained from 6,7-epoxylinalyl ace-



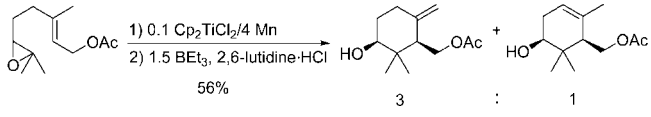
Scheme 23.

tate as substrate (Scheme 25). This transformation constitutes a rapid and efficient synthesis of the monoterpene (±)-karahanahenol. Together with **60**, **61** was obtained as a minor component as a result of a 6-*exo* cyclization process. Protonolysis of the alkyltitanium radical intermediate explains its formation. Although the preference of nucleophilic radicals to cyclize by a 6-*exo*-trig process rather than by the 7-*endo* mode has been reported,[47] the predominance of the latter form of cyclization in the case of **59** has been attributed to a Thorpe–Ingold effect induced by the methyl and acetate groups on the C-3 atom.[46]



Scheme 25.

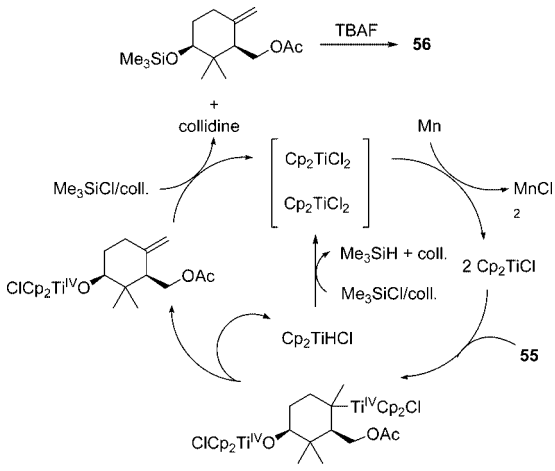
Two titanium-catalyzed versions of this homolytic epoxide-opening reaction have recently emerged, solving the tediousness of the work up required when stoichiometric amounts of titanium are used. Takahashi and co-workers combined 2,6-lutidine·HCl and Et_3B as mediators to regenerate the Ti^{IV} species.[48] Thus, using this system, the best result for the reductive cyclization of 6,7-epoxygeranyl acetate was achieved with the proportions shown in Scheme 26.



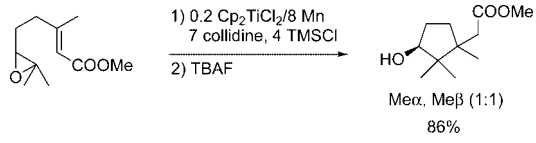
Scheme 26.

Bearing in mind the mechanism of the catalytic system, 2,6-lutidine·HCl is thought to produce Cp_2TiCl_2 from the titanium alkoxide, whilst Et_3B promotes the conversion of $Cp_2Ti(Cl)H$ to give Cp_2TiCl. The proposed catalytic system is shown in Scheme 27.

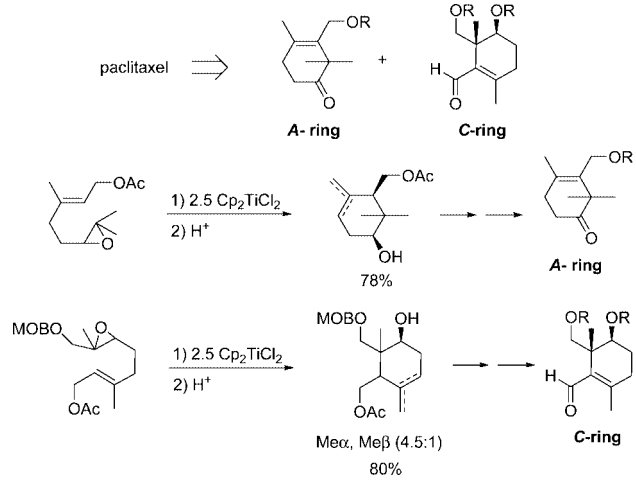
A second catalytic cycle was developed in our laboratory.[49] Thus, a series of acyclic monoepoxyterpenoids were cyclized using 0.2 equiv. of Cp_2TiCl_2, 8 equiv. of Mn, 4 equiv. of TMSCl and 7 equiv. of 2,4,6-collidine. The catalytic cycle is shown in Scheme 28. With 6,7-epoxygeranyl acetate a 51% yield of *exo*-**56** was obtained after purification by column chromatography.



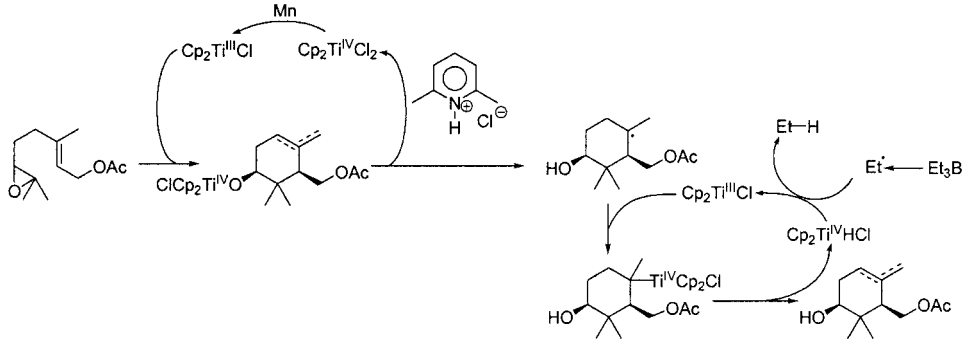
Scheme 28.



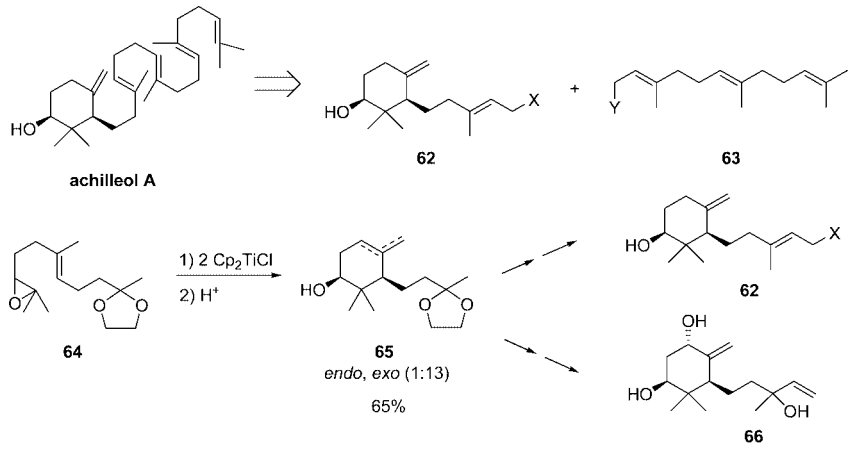
Scheme 29.



Scheme 30.



Scheme 27.



Scheme 31.

A remarkable increase in the yield of cyclization was observed when methyl 6,7-epoxygeranate was subjected to this Ti^{III}-catalytic protocol (an 86% yield of the 5-*exo*-trig cyclization products was isolated, Scheme 29).[50]

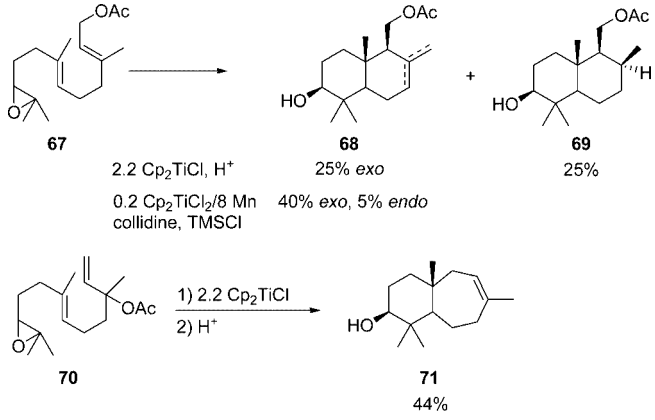
Ti^{III}-mediated 6-*endo* cyclization reactions have been used in a number of synthetic endeavors. In their studies on the synthesis of paclitaxel, Takahashi and co-workers prepared the A and C ring synthons of this compound starting from geraniol (Scheme 30).[51]

Another interesting example of the application of this method was the first synthesis of the monocyclic triterpene achilleol A by Barrero et al.[52] In this convergent approach the monocyclic synthon **62** was prepared from epoxide **64**, obtained from commercial geranyl ketone (Scheme 31).

The same starting epoxide was used by Cárdenas and Cuerva and their co-workers in their synthesis of sesquiterpene **66**.[49] A Ti^{III} catalytic protocol was used in this work.

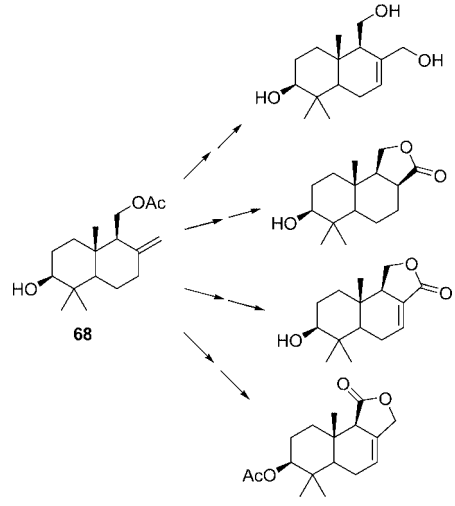
Domino Cyclization Reactions

Cp_2TiCl-mediated cascade radical cyclization reactions aimed at synthesizing polycyclic terpenoids were achieved when 10,11-epoxyfarnesyl acetate (**67**) and 10,11-epoxynerolidyl acetate (**70**) were exposed to an excess of Cp_2TiCl_2/Mn (Scheme 32).[46] Both the drimane derivatives **68** and **69** and the 6+7 bicyclic system **71** were obtained by 6-*endo*/6-*endo* and 6-*endo*/7-*endo* processes, respectively. Compound **71** proved to be a valuable intermediate in the synthesis of daucanes by A-ring construction.



Scheme 32.

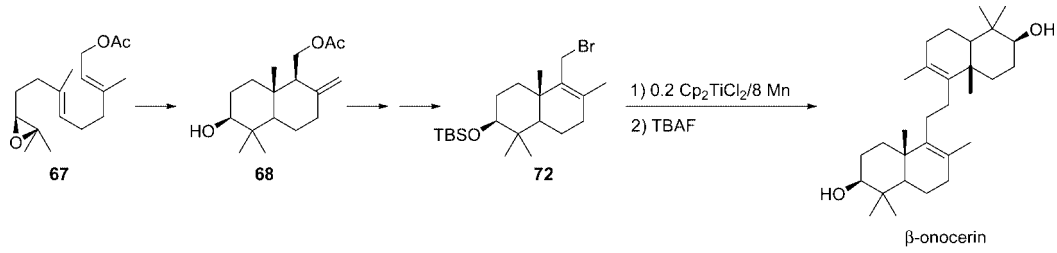
Catalysis of this reaction improves its efficiency considerably. Thus, an extra 15% of **68** was obtained compared with the stoichiometric version of the reaction. Under these catalytic conditions different natural drimanes presenting antifeedant activity have been synthesized (Scheme 33).[53]



Scheme 33.

The titanocene-catalyzed cyclization of (10*S*)-10,11-epoxyfarnesyl acetate (**67**), obtained by Sharpless asymmetric *cis*-hydroxylation using AD-mixβ [contains chiral ligand $(DHQD)_2PHAL$ (hydroquinidine 1,4-phthalazinediyl diether), $K_3Fe(CN)_6$, K_2CO_3 and $K_2OsO_4{\cdot}2H_2O$], led to the formation of a 97% yield of the optically active derivative of **68** in 97% *ee*. This bicyclic compound has been used in the asymmetric synthesis of β-onocerin (Scheme 34).[54]

The versatility of this strategy for the rapid preparation of different bicyclic terpenoids is shown once more by the synthesis of 3β-hydroxymanool (**76**),[49] a labdane isolated from *Gleichemia japonica*.[55] Thus the opening and cyclization of the epoxyketal derived from farnesyl ketone gave 42% of bicyclic **75**, which after a straightforward transfor-



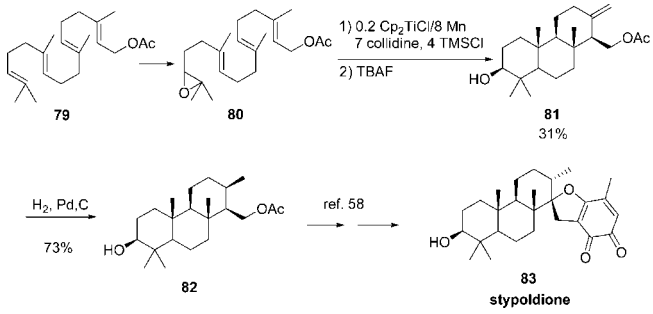
Scheme 34.

mation was converted into the natural product **76** (Scheme 35).

Bicyclic **75** has also been used as an intermediate in a new synthesis of the labdane rostranone (**78**) (Scheme 36), isolated from *Nolana rostrata*.[56] In this approach, the protocol for the titanocene-mediated cyclization of monoepoxides, used for the construction of **75**, was combined with a palladium-mediated functionalization of the equatorial methyl group on the C-4 atom of the A ring of cyclic terpenoids.[57]

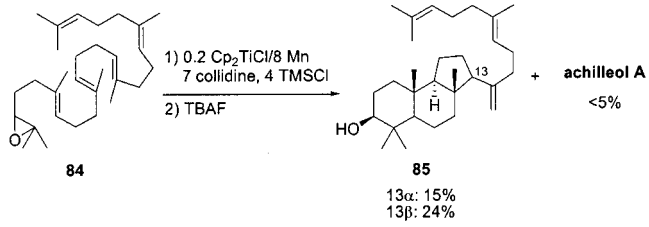
A formal synthesis of the marine metabolite stypoldione (**83**),[58] which shows interesting antitumoral activity, was accomplished starting from geranylgeranyl acetate (**79**) (Scheme 37).[49] Thus, subjection of this polyprenoid to the protocol for van Tamelen selective epoxidation, followed by Ti^{III}-mediated homolytic opening of the corresponding epoxide and the ensuing cyclization and finally a triple 6-*endo* cyclization process afforded a 31% yield of anticopalane (**81**). Note the total stereochemical control of the cyclization to the *trans*/*anti*-*trans* tricycle. Catalytic hydrogenation of **81** led to **82**, whose conversion into stypoldione has been reported elsewhere.[58]

The opening and cyclization of 2,3-oxidosqualene (**84**) gave a 39% yield of malabaricanes (**85**)[59] together with a minor quantity of achilleol A in a process that mimics the action of the enzymes involved in the biosynthesis of triterpenes (Scheme 38). The malabaricanes are formed by a tandem 6-*endo*/6-*endo*/5-*exo* process as a consequence of the substitution pattern of the double bonds in squalene. The isolation of achilleol A demonstrates once again that these cyclization reactions take place in a nonconcerted

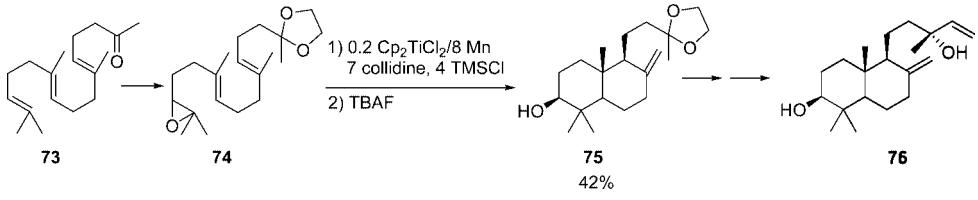


Scheme 37.

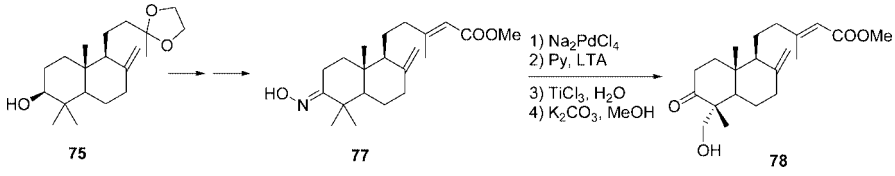
fashion via discrete mono-, bi- and tricyclic carbon-centered radicals. Theoretical calculations have been made to gain more information about the nature of the process. Thus, both concerted and stepwise mechanisms were considered and calculations were carried out at the DFT level of theory to find the energy minimum of each intermediate radical.[49]



Scheme 38.



Scheme 35.

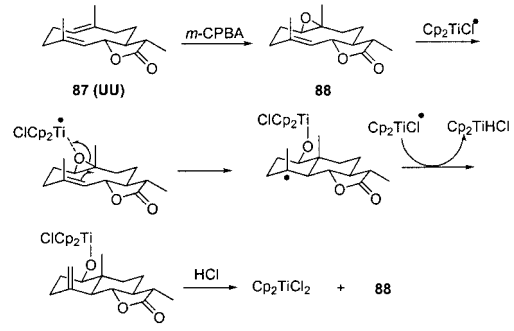


Scheme 36.

Transannular Cyclization Reactions

Germacranolides such as (+)-costunolide (**86**), stenophyllolide (**91**) and salonitenolide (**95**) can be obtained in multigram quantities from different *Asteraceae* and are thus excellent chiral starting materials for the synthesis of eudesmanolides or elemanolides such as vernolepine and other derivatives.[60] In this context the exposure of epoxygermacranolide (**87**), obtained in high yields from costunolide, to an excess of Ti^{III} led to a 91% yield of dihydroreynosin (**88**), a natural product isolated from *Michelia compesa*[61] (Scheme 39). Analogously 1,10-epoxycostunolide (**89**) was transformed efficiently into (+)-reynosin (**90**),[60d] a natural eudesmanolide isolated from *Ambrosia contertiflora*.[62] The Ti^{III}-catalyzed cyclization protocol that uses TMSCl/collidine as a Ti^{III} regenerator proved to mediate this skeletal interconversion. Thus, exposure of **87** to these catalytic conditions led to a 74% yield of **88** whilst the stenophyllolide derivative **92** afforded a 50% yield of natural eudesmanolide **93**. Restoration of the conjugated double bond permitted the transformation of **93** into the also naturally occurring (+)-9β-hydroxyreynosin (**94**). These molecules have been isolated from *Inula heterolepis* and *Artemisia herbaalba*, respectively.[63] The versatility of this transformation was once again proven by obtaining a 47% yield of (+)-β-cyclopyrethrosin (**97**) by the titanocene-mediated cyclization of 8,12-lactone **96**, which was obtained easily from salonitenolide.[64]

The known UU preferred conformation in solution has been proposed for germacranolides such as **87**[65] to explain not only the good-to-excellent yields of these transannular cyclization reactions but also the high regio- and stereoselectivity of the process (Scheme 40). Thus, this conformation allows for the overlap between the π orbital of the C-4–C-5 double bond and the incipient p orbital that develops at the C-10 atom, leading to a 6-*endo* cyclization product via a *trans*-fused chair/chair-like transition state which is responsible for the control of the regio- and stereochemistries of the product.[60d]



Scheme 40.

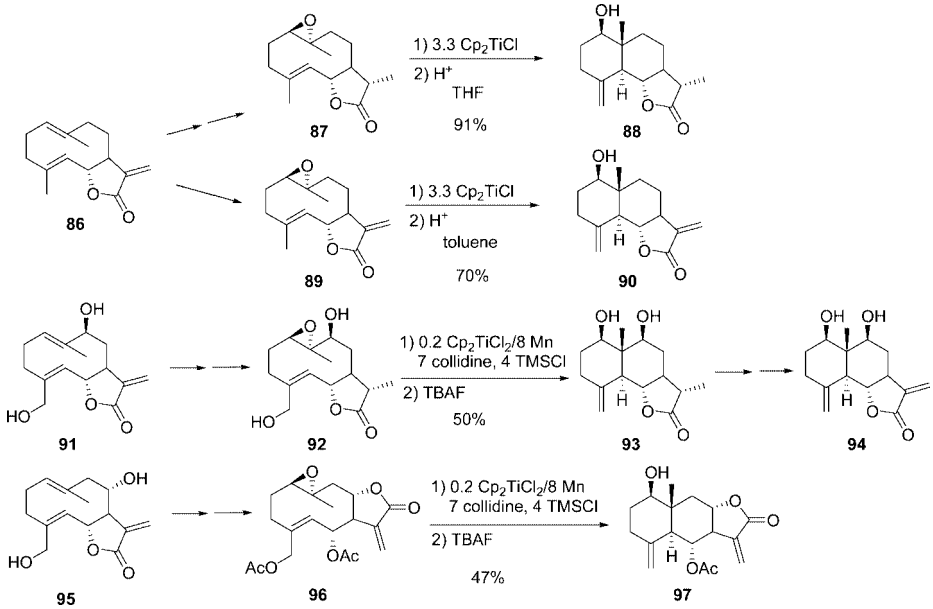
Cyclization Reactions to Other Kinds of Terpenoids

Synthesis of (±)-Ceratopicanol

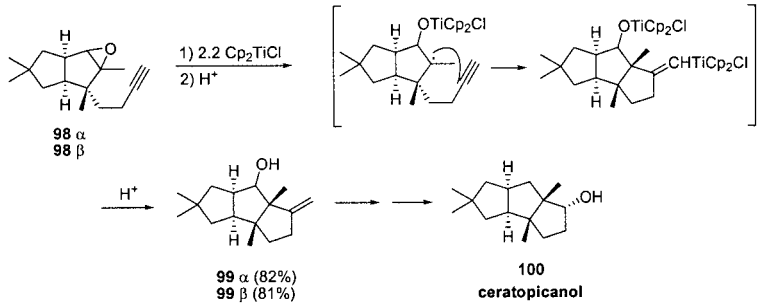
One of the first examples of polycyclic synthesis using this Ti^{III}-based methodology was that of ceratopicanol (**100**). In their synthesis of this natural compound,[66] Clive et al. performed the cyclization of epoxyalkynes **98** with 2.2 equivalents of Cp_2TiCl_2 and an excess of Mn to give, by a 5-*exo*-dig process, 82 and 81% of the tricyclic compounds **99**, which were further transformed into (±)-ceratopicanol in five steps (Scheme 41).[67]

Synthesis of Meroterpenoids

Ti^{III}-catalyzed cyclization reactions of the aryl epoxypolyprenoids **101**–**105**, obtained by Stille coupling of the corresponding aryl stannanes and epoxypolyprenes, led to



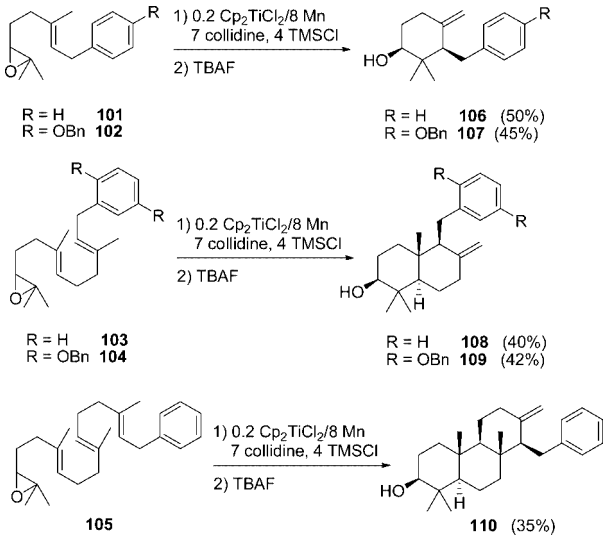
Scheme 39.



Scheme 41.

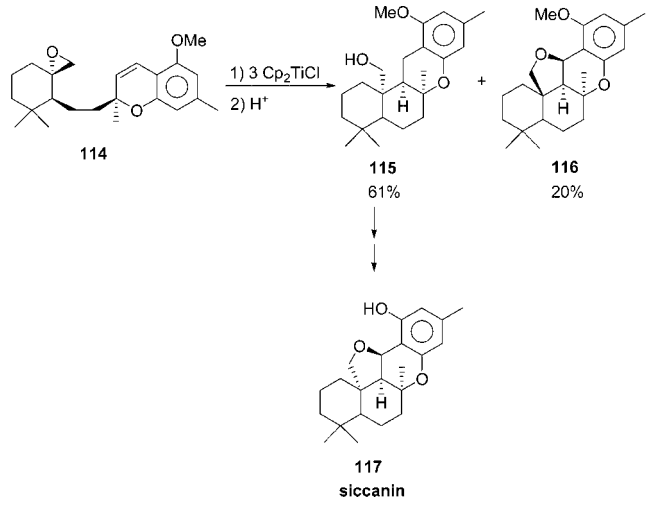
the cyclic meroterpenoids **106**–**110** (Scheme 42).[68] These reactions are in accord with the cyclization and termination models previously established for the corresponding acetoxypolyprenes.[46,49]

Merosesquiterpene (+)-smenospondiol (**113**), which exhibits interesting biological properties, has been synthesized by employing a protocol involving a Ti^{III}-mediated cascade cyclization of epoxide **111** as the key step (Scheme 43).[69] Optimization of the cyclization conditions led to the use of a mixture of benzene and THF (5:1) at reflux to afford a 72% yield of bicyclic **112**. From **112** the synthesis of (+)-smenospondiol was accomplished in 11 steps.



Scheme 42.

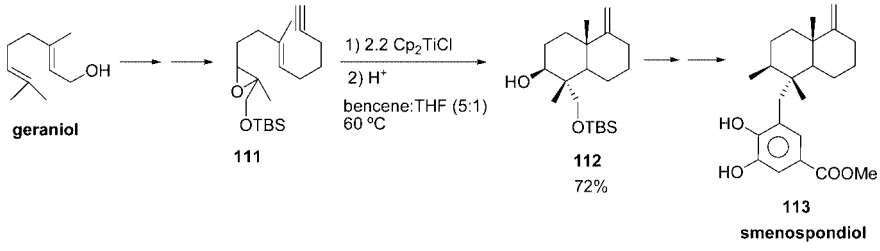
Siccanin (**117**) is a mould metabolite isolated from *Helminthosporium siccans*[70] with potent antifungal activity.[71] Its biological interest has attracted the attention of a number of chemists. Among them, Trost et al. have developed a synthetic route to this compound that involves the radical cyclization of epoxide **114** and uses an excess of Cp_2TiCl_2 (Scheme 44).[72] The tetracyclic alcohol thus obtained is converted into siccanin after two further chemical transformations.



Scheme 44.

4. Summary and Outlook

As has been shown in this review, the Cp_2TiCl-mediated opening and ensuing cyclization of oxiranes has received a great deal of attention in recent years. The regio- and



Scheme 43.

stereochemical control of the reaction, together with the mildness of the experimental conditions, which include the use of catalytic quantities of titanium, are among the reasons that explain the interest shown by many researchers in this reaction. Thus, Ti^{III}-mediated mono- or domino polycyclization reactions have been reported to be the key step in a number of synthetic endeavors, which in turn corroborates the versatility of this protocol. Bearing in mind all these considerations, further applications of this strategy are likely to appear in the near future and work in the field is in progress.

Acknowledgments

We acknowledge the Spanish Ministry of Science and Technology, Project BQU 2002-03211, for partial support of this research. The authors thank the Spanish Ministry of Education and Science and the Regional Andalucian Government for grants to J. F. A. and E. M. S. Thanks also go to our colleague Dr. J. Trout for revising our English text.

[1] a) B. Giese, *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon Press, Oxford, **1986**; b) D. P. Curran in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, vol. 4, pp. 779–831; c) D. P. Curran, N. A. Porter, B. G. Fiese, *Stereochemistry of Radical Reactions*, VCH, Weinheim, **1996**; d) A. F. Parsons, *An Introduction to Free Racical Chemistry*, Blackwell Science, Oxford, **2000**, ch. 7, pp. 139–159; e) P. Renaud, M. P. Sibi (Eds.), *Radicals in Organic Synthesis*, Wiley-VCH, Weinheim, **2001**, vol. 2.

[2] A. L. Dhimane, L. Fensterbank, M. Malacria in *Radicals in Organic Synthesis* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, vol. 2, pp. 350–382.

[3] E. Lee in *Radicals in Organic Synthesis* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, vol. 2, pp. 303–333.

[4] A. Srikrishna in *Radicals in Organic Synthesis* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, vol. 2, pp. 151–187.

[5] a) C. P. Jasperse, D. P. Curran, T. L. Fevig, *Chem. Rev.* **1991**, *91*, 1237–1286; b) R. A. Bunce, *Tetrahedron* **1995**, *51*, 13103–13159; c) A. J. McCarroll, J. Walton, *Angew. Chem. Int. Ed.* **2001**, *40*, 2224–2248; d) A. J. McCarroll, J. Walton, *J. Chem. Soc., Perkin Trans. 1* **2001**, 3215–3229.

[6] a) K. W. Wendt, G. E. Schulz, E. J. Corey, D. R. Liu, *Angew. Chem. Int. Ed.* **2000**, *39*, 2812–2833; b) M. C. de la Torre, M. A. Sierra, *Angew. Chem. Int. Ed.* **2004**, *43*, 160–181.

[7] a) R. Breslow, E. Barret, E. Mohacsi, *Tetrahedron Lett.* **1962**, *3*, 1207–1211; b) R. Breslow, J. T. Groves, S. S. Olin, *Tetrahedron Lett.* **1966**, *7*, 4717–4719; c) J. Y. Lallemand, M. Julia, D. Mansuy, *Tetrahedron Lett.* **1973**, *14*, 4461–4464.

[8] D. P. Curran, D. M. Rakiewicz, *Tetrahedron* **1985**, *41*, 3943–3958.

[9] a) A. L. J. Beckwith, C. H. Schiesser, *Tetrahedron* **1985**, *41*, 3925–3941; b) M. A. Dombrowski, S. A. Kates, B. B. Snider, *J. Am. Chem. Soc.* **1990**, *112*, 2759–2767; c) M. Journet, M. Malacria, *J. Org. Chem.* **1992**, *57*, 3085–3093; d) M. Journet, M. Malacria, *J. Org. Chem.* **1994**, *59*, 718–719; e) P. Devin, L. Festerbank, M. Malacria, *J. Org. Chem.* **1998**, *63*, 6764–6765.

[10] B. B. Snider, *Chem. Rev.* **1996**, *96*, 339–363.

[11] P. A. Zoretic, H. Fang, A. A. Ribeiro, *J. Org. Chem.* **1998**, *63*, 4779–4785.

[12] B. B. Snider, J. Y. Kiselgof, B. M. Foxman, *J. Org. Chem.* **1998**, *63*, 7945–7952.

[13] a) D. Yang, X.-Y. Ye, S. Gu, M. Xu, *J. Am. Chem. Soc.* **1999**, *121*, 5579–5580; b) D. Yang, X.-Y. Ye, S. Gu, M. Xu, *J. Org. Chem.* **2000**, *65*, 2208–2217.

[14] A. F. Barrero, M. M. Herrador, J. F. Quílez del Moral, M. V. Valdivia, *Org. Lett.* **2002**, *4*, 1379–1382.

[15] a) A. Batsanov, L. Chen, G. Bryon Gill, G. Pattenden, *J. Chem. Soc., Perkin Trans. 1* **1996**, 45–55; b) G. Pattenden, L. Roberts, A. J. Blake, *J. Chem. Soc., Perkin Trans. 1* **1998**, 863–868.

[16] a) K. D. Warzecha, X. Xing, M. Demuth, *Pure Appl. Chem.* **1997**, *69*, 109–112; b) U. Hoffmann, Y. Gao, B. Pandey, S. Klinge, K. D. Warzecha, C. Kruger, H. D. Roth, M. Demuth, *J. Am. Chem. Soc.* **1993**, *115*, 10358–10359; c) X. Xing, M. Demuth, *Synlett* **1999**, 987–990; d) X. Xing, M. Demuth, *Eur. J. Org. Chem.* **2001**, 537–544.

[17] R. S. P. Coutts, P. C. Wailes, R. L. Martin, *J. Organomet. Chem.* **1973**, *50*, 145–151.

[18] M. L. H. Green, C. R. Lucas, *J. Chem. Soc., Dalton Trans.* **1972**, 1000–1003.

[19] a) A. Gansäuer, H. Bluhm, M. Pierobon, *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859; b) A. Gansäuer, M. Pierobon, H. Bluhm, *Synthesis* **2001**, 2500–2520.

[20] R. J. Enemærke, G. H. Hjøllund, K. Daasbjerg, T. Skrydstrup, *C. R. Acad. Sci. Ser. IIc* **2001**, *4*, 435–438.

[21] W. A. Nugent, T. V. RajanBabu, *J. Am. Chem. Soc.* **1988**, *110*, 8561–8562.

[22] W. A. Nugent, T. V. RajanBabu, M. S. Beattie, *J. Am. Chem. Soc.* **1990**, *112*, 6408–6409.

[23] F. Bermejo, C. Sandoval, *J. Org. Chem.* **2004**, *69*, 5275–5280.

[24] T. V. RajanBabu, W. A. Nugent, *J. Am. Chem. Soc.* **1994**, *116*, 986–997.

[25] a) S. Weigand, R. Brückner, *Synlett* **1997**, 225–228; b) J. S. Yadav, D. Srinivas, *Chem. Lett.* **1997**, 905–906; c) K. B. Jørgensen, T. Suenaga, T. Nakata, *Tetrahedron Lett.* **1999**, *40*, 8855–8858; d) T. K. Chakraborty, S. Das, *Tetrahedron Lett.* **2003**, *43*, 2313–2315; e) T. K. Chakraborty, R. J. Goswami, *Tetrahedron Lett.* **2004**, *45*, 7637–7639.

[26] C. Hardouin, F. Chevallier, B. Rousseau, E. Doris, *J. Org. Chem.* **2001**, *66*, 1046–1048.

[27] a) A. Gansäuer, *Synlett* **1998**, 801–809; b) A. Gansäuer, T. Lauterbach, H. Bluhm, M. Noltemeyer, *Angew. Chem. Int. Ed.* **1999**, *38*, 2909–2910; c) A. Gansäuer, H. Bluhm, *Chem. Rev.* **2000**, *100*, 2771–2788; d) A. Gansäuer, S. Narayan, *Adv. Synth. Catal.* **2002**, *344*, 465–475; e) A. Gansäuer, H. Bluhm, B. Rinker, S. Narayan, M. Schick, T. Lauterbach, M. Pierobon, *Chem. Eur. J.* **2003**, *9*, 531–542; f) A. Gansäuer, T. Lauterbach, S. Narayan, *Angew. Chem. Int. Ed.* **2003**, *42*, 5556–5573; g) A. Gansäuer, A. Barchuk, D. Fielenbach, *Synthesis* **2004**, 2567–2573.

[28] T. V. RajanBabu, W. A. Nugent, *J. Am. Chem. Soc.* **1989**, *111*, 4525–4527.

[29] A. Gansäuer, H. Bluhm, *Chem. Commun.* **1998**, 2143–2144.

[30] a) C. A. Merlic, D. Xu, *J. Am. Chem. Soc.* **1991**, *113*, 9855–9856; b) C. A. Merlic, D. Xu, M. C. Nguyen, *Tetrahedron Lett.* **1993**, *34*, 227–230; c) K. H. Dötz, E. Gomes da Silva, *Tetrahedron* **2000**, *56*, 8291–8299.

[31] A. Gansäuer, M. Pierobon, H. Bluhm, *Angew. Chem. Int. Ed.* **1998**, *37*, 101–103.

[32] A. Gansäuer, M. Pierobon, *Synlett* **2000**, 1357–1359.

[33] A. Gansäuer, M. Pierobon, H. Bluhm, *Angew. Chem. Int. Ed.* **2002**, *41*, 3206–3208.

[34] A. Fernández-Mateos, L. Mateos Burón, E. Martín de la Nava, R. Rabanedo Clemente, R. Rubio González, F. Sanz Gonzalez, *Synlett* **2004**, 2553–2557.

[35] J. Friedrich, M. Dolg, A. Gansäuer, D. Geich-Gimbel, T. Lauterbach, *J. Am. Chem. Soc.* **2005**, *127*, 7071–7077.

[36] a) A. Fernández-Mateos, E. Martín de la Nava, G. Pascual Coca, A. Ramos Silvo, R. Rubio González, *Org. Lett.* **1999**, *1*, 607–609; b) A. Fernández-Mateos, L. Mateos Burón, R. Rabanedo Clemente, A. I. Ramos Silvo, R. Rubio González, *Synlett* **2004**, 1011–1014.

[37] F. E. Ziegler, M. A. Sarpong, *Tetrahedron Lett.* **2003**, *59*, 9013–9018.

[38] C. J. Cavallito, D. M. Freuhauf, J. H. Bailey, *J. Am. Chem. Soc.* **1948**, *70*, 3724–3726.
[39] P. K. Mandal, S. C. Roy, *Tetrahedron* **1999**, *55*, 11395–11398.
[40] a) B. K. Park, M. Nakagawa, A. Hirota, M. Nakayama, *J. Antibiot.* **1988**, *41*, 751–758; b) W. Zopf, *Justus Liebigs Ann. Chem.* **1902**, *324*, 39–78.
[41] P. K. Mandal, G. M. Maiti, S. C. Roy, *J. Org. Chem.* **1998**, *63*, 2829–2834.
[42] a) K. K. Rana, C. Guin, S. C. Roy, *Tetrahedron Lett.* **2000**, *41*, 9337–9338; b) S. C. Roy, K. K. Rana, C. Guin, *J. Org. Chem.* **2002**, *67*, 3242–3248.
[43] G. Ruano, M. Grande, J. Anaya, *J. Org. Chem.* **2002**, *67*, 8243–8246.
[44] G. Ruano, J. Matiánez, M. Grande, J. Anaya, *J. Org. Chem.* **2003**, *68*, 2024–2027.
[45] J. Anaya, A. Fernández-Mateos, M. Grande, J. Matiánez, G. Ruano, M. R. Rubio González, *Tetrahedron* **2003**, *59*, 241–248.
[46] A. F. Barrero, J. M. Cuerva, M. M. Herrador, M. V. Valdivia, *J. Org. Chem.* **2001**, *66*, 4074–4078.
[47] A. L. J. Beckwith, G. Moad, *J. Chem. Soc., Chem. Commun.* **1974**, 472–473.
[48] S. Fuse, M. Hanochi, T. Doi, T. Takahashi, *Tetrahedron Lett.* **2004**, *45*, 1961–1963.
[49] J. Justicia, A. Rosales, E. Buñuel, J. L. Oller-López, M. Valdivia, A. Haïdour, J. E. Oltra, A. F. Barrero, D. J. Cárdenas, J. M. Cuerva, *Chem. Eur. J.* **2004**, *10*, 1778–1788.
[50] A. F. Barrero, J. F. Quílez del Moral, M. M. Herrador, I. Loayza, E. M. Sánchez, J. F. Arteaga, unpublished results.
[51] K. Nakai, M. Kamoshita, T. Doi, H. Yamada, T. Takahashi, *Tetrahedron Lett.* **2001**, *42*, 7855–7857.
[52] A. F. Barrero, J. M. Cuerva, E. J. Alvarez-Manzaneda, J. E. Oltra, R. Chahboun, *Tetrahedron Lett.* **2002**, *43*, 2793–2796.
[53] J. Justicia, J. E. Oltra, A. F. Barrero, A. Guadaño, A. González-Coloma, J. M. Cuerva, *Eur. J. Org. Chem.* **2005**, 712–718.
[54] A. F. Barrero, M. M. Herrador, J. F. Quílez del Moral, P. Arteaga, J. F. Arteaga, M. Piedra, E. Sánchez, *Org. Lett.* **2005**, *7*, 2301–2304.
[55] K. Munesada, H. L. Siddiqui, T. Suga, *Phytochemistry* **1992**, *31*, 1533–1536.
[56] J. A. Garbarino, M. C. Chamy, V. Gambaro, *Phytochemistry* **1986**, *25*, 2833–2836.
[57] a) J. Justicia, J. E. Oltra, J. M. Cuerva, *Tetrahedron Lett.* **2004**, *45*, 4293–4296; b) J. Justicia, J. E. Oltra, J. M. Cuerva, *J. Org. Chem.* **2005**, *70*, 8265–8272.
[58] a) S. J. White, R. S. Jacobs, *Mol. Pharmacol.* **1983**, *24*, 500–508; b) E. T. O'Brien, D. J. Asai, R. S. Jacobs, L. Wilson, *Mol. Pharmacol.* **1989**, *35*, 635–642; c) X. Xing, M. Demuth, *Eur. J. Org. Chem.* **2001**, 537–544.
[59] a) J. Jakupovic, F. Eid, F. Bohlmann, S. El-Dahmy, *Phytochemistry* **1987**, *26*, 1536–1538; b) F. J. Marner, A. Freyer, J. Lex, *Phytochemistry* **1991**, *30*, 3709–3712.
[60] a) A. F. Barrero, J. E. Oltra, V. Morales, M. Álvarez, *J. Nat. Prod.* **1997**, *60*, 1034–1035; b) A. F. Barrero, J. E. Oltra, M. Álvarez, *Tetrahedron Lett.* **1998**, *39*, 1401–1404; c) A. F. Barrero, J. E. Oltra, A. Barragán, M. Álvarez, *J. Chem. Soc., Perkin Trans. 1* **1998**, 4107–4113; d) A. F. Barrero, J. E. Oltra, J. M. Cuerva, A. Rosales, *J. Org. Chem.* **2002**, *67*, 2566–2571; e) A. F. Barrero, J. E. Oltra, M. Álvarez, A. Rosales, *J. Org. Chem.* **2002**, *67*, 5461–5469; f) A. F. Barrero, J. E. Oltra, A. Barragán, M. Álvarez, *J. Chem. Soc., Perkin Trans. 1* **1998**, 4107–4113.
[61] M. Ogura, G. A. Cordell, N. R. Farnsworth, *Phytochemistry* **1978**, *17*, 957–961.
[62] H. Yoshioka, W. Renold, N. H. Fischer, A. Higo, T. J. Mabry, *Phytochemistry* **1970**, *9*, 823–832.
[63] a) F. Bohlmann, N. Ates, M. Grenz, *Phytochemistry* **1982**, *21*, 1166–1168; b) A. A. Ahmed, M. Abou-El-Ela, J. Jakupovic, A. A. Scif-El-Din, N. Sabri, *Phytochemistry* **1990**, *29*, 3361–3363.
[64] A. F. Barrero, A. Rosales, J. M. Cuerva, J. E. Oltra, *Org. Lett.* **2003**, *5*, 1935–1938.
[65] W. H. Watson, R. P. Kashyap, *J. Org. Chem.* **1986**, *51*, 2521–2524.
[66] H. P. Hanssen, W. R. Abraham, *Tetrahedron* **1988**, *44*, 2175–2180.
[67] D. L. J. Clive, S. R. Magnuson, H. W. Manning, D. L. Mayhew, *J. Org. Chem.* **1996**, *61*, 2095–2108.
[68] J. Justicia, J. E. Oltra, J. M. Cuerva, *J. Org. Chem.* **2004**, *69*, 5803–5806.
[69] Y. Haruo, T. Hasegawa, H. Tanaka, T. Takahashi, *Synlett* **2001**, 1935–1937.
[70] K. J. Ishibashi, *J. Antibiot. Ser. A* **1962**, *15*, 161–167.
[71] a) A. Endo, *Sankyo Kenkyusho Nenpo* **1970**, *22*, 25–26; b) M. G. Bellotti, L. Riviera, *Chemioterapia* **1985**, *4*, 431–433.
[72] a) B. M. Trost, H. C. Shen, J. P. Surivet, *Angew. Chem. Int. Ed.* **2003**, *42*, 3943–3947; b) B. M. Trost, H. C. Shen, J. P. Surivet, *J. Am. Chem. Soc.* **2004**, *126*, 12565–12579.

Received: October 31, 2005
Published Online: January 16, 2006

