REVIEW

Recent applications of Cp₂TiCl in natural product synthesis

Sara P. Morcillo, Delia Miguel, Araceli G. Campaña, Luis Álvarez de Cienfuegos, José Justicia and Juan M. Cuerva*

This review highlights the recent applications of titanocene(III) complexes in the field of natural product synthesis from the seminal precedents to the development of modern catalytic methods. The power of the titanocene(III)-based approaches is demonstrated by the straightforward syntheses of many natural products from readily available starting materials.

Introduction

Natural product synthesis is an exigent test for newly developed methodologies. Within this context, Rajanbabu and Nugent reported a series of seminal papers about the potential role of Cp₂TiCl as a new tool in organic synthesis.[1] Soon afterwards, Gansäuer's group published a collection of relevant papers where a substoichiometric version of this protocol was developed.[2] Those results were especially important in the development of the corresponding asymmetric reactions using chiral titanocene(III) complexes.[3] After these inspiring works, titanocene(III) complexes, essentially titanocene(III) chloride (Cp₂TiCl), have recently emerged as a powerful tool in organic synthesis. They are soft single-electron-transfer (SET) reagents capable of promoting different kinds of reactions, such as homolytic epoxide[4] and oxetane[5] openings, Barbier-type reactions,[6] Wurtz-type reactions,[7] Reformatsky-type reactions,[8] reduction reactions,[9] and pinacol coupling reactions (Scheme 1).[10]

From a practical point of view, titanocene(III) complexes can be prepared and stored. Nevertheless, they are usually highly oxygen-sensitive compounds. Interestingly, they can be easily prepared *in situ* by simply stirring the corresponding titanocene(IV) precursor and manganese or zinc dust. Another key characteristic of the titanocene(III) chemistry is that whatever the reaction in which it is involved, a catalytic cycle can be closed. In that case, a titanocene(IV) regenerating agent and an electron source, such as manganese or zinc dust, are required. Although some of them have been described in the literature, only two are commonly used: the simple combination of trimethylsilyl chloride and 2,4,6-collidine for aprotic reaction

Scheme 1 General reactivity of Cp₂TiCl.
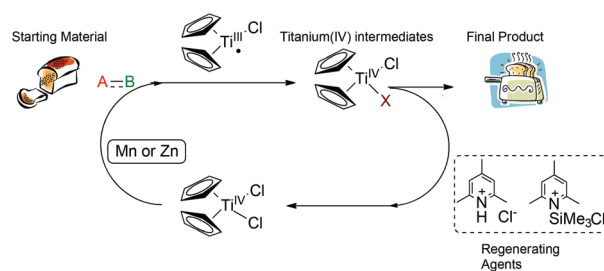
Scheme 2 Catalytic cycles in titanocene(III) chemistry.

conditions[11] and 2,4,6-collidinium hydrochloride for aqueous conditions (see Scheme 2).[2]

As far as the starting materials in titanocene(III) chemistry are concerned, they must be activated owing to the modest reduction potential of those complexes, although some exceptions have been reported.[12] Therefore, the usual titanocene(III) chemistry is restricted to three big families: epoxides, allylic and propargylic halides and α,β-unsaturated and aromatic aldehydes and ketones (see Scheme 1).

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Thus, titanocene(III) complexes can interact with epoxides to yield the corresponding carbon-centred radicals. The fate of these radicals depends upon the reaction conditions. In the presence of an excess of titanocene(III), deoxygenation reaction takes place. In the presence of a good hydrogen-atom donor, such as 1,4-cyclohexadiene, the corresponding alcohols with anti-Markovnikov regioselectivity are obtained. In the presence of an alkene, an alkyne or a carbonyl group a new C–C bond is formed, either inter- or intramolecularly. Another remarkable feature is their reactivity towards substituted carbon-centered radicals. Such radicals are usually transformed into alkenes by a mixed disproportionation process. That is, Cp$_2$TiCl is able to abstract a hydrogen atom of the α-position of a carbon-centered radical to form a C–C double bond and Cp$_2$TiClH. This transformation formally represents quite an unusual oxidation reaction of the organic substrate in radical chemistry (Scheme 3).[13]

Allylic and propargylic halides have been used in Barbier-type reactions with interesting regio- and chemoselectivities.[6] Moreover, excellent D,L-*meso* stereoselectivities have been obtained in titanocene(III)-mediated pinacol coupling reactions of α,β-unsaturated and aromatic aldehydes and ketones (Scheme 4).[10]

All these reactions have been applied in functional group interconversions in some natural product synthesis, taking advantage of their remarkable chemoselectivity. More relevant is the fact that titanocene(III)-mediated reactions have been used as the key step in the synthesis of different complex natural products such as sesterstatin 1, barekoxide, or sicannin, showing the potential of this reagent.

In this article we have summarized such contributions in the field of natural products synthesis with special emphasis in recent years.[4b,c] We have distinguished the role of titanocene(III)-complexes as a simple reagent and their use in

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José Justicia was born in Granada (Spain) in 1975. He obtained his Ph.D. degree at the University of Granada (2004) supervised by Prof. J. M. Cuerva. He performed a postdoctoral stay in the group of Prof. Andreas Gansäuer at the University of Bonn, granted by the Ministerio de Educación y Ciencia (2004–2006). From 2006 to 2011, he had contracts from the "Juan de la Cierva" Program and the "Reincorporacion de Doctores" Program from University of Granada. In 2011, he was promoted to the position of Associate Professor in the Department of Organic Chemistry at that University.

Dr Luis Álvarez de Cienfuegos Rodríguez got his Ph.D. degree in Organic Chemistry at the University of Granada in 2003, under the supervision of Prof. Rafael Robles. From 2004 to 2006, he worked as a Fundación Ramon-Areces fellow at MIT in Prof. Alexander M. Klibanov's group. From 2006 to 2007, he worked as a postdoctoral associate at Tufts University in Prof. Krishna Kumar's group. In 2008, he joined, as a researcher, Juan M. Cuerva's group at the University of Granada to work on organometallics and molecular electronics. In 2011, he was promoted to the position of Associate Professor in the Department of Organic Chemistry at that University. His research interests are free radical and transition metal chemistry.

Delia Miguel was born in Burgos (Spain) in 1981. She carried out her Ph.D. studies at the University of Burgos (2005–2009) supervised by Prof. Roberto Sanz. During this time she spent a trimester under the supervision of Prof. S. V. Ley at the University of Cambridge (United Kingdom). Her Ph.D. was focused on new strategies for the functionalization of indoles and carbonyl compounds catalyzed by Brønsted acids and gold(I) complexes. Nowadays she is performing a postdoctoral stay in the group of Juan Manuel Cuerva at the University of Granada working on different synthetic applications of multimetallic systems and on the development of organic devices for their use in molecular electronics.

Juan M. Cuerva was born in Granada, Spain. He obtained his Ph.D. in 1997 at the Universidad Autónoma de Madrid (Madrid, Spain) under the guidance of Professor Antonio M. Echavarren. In 1998, he moved to the University of Granada and since 2003 he has held the position of Associate Professor of organic chemistry in the Department of Organic Chemistry at that University. He and his research group work on the development of new synthetic methods based on radical chemistry and their applications, especially in the synthesis of natural products.
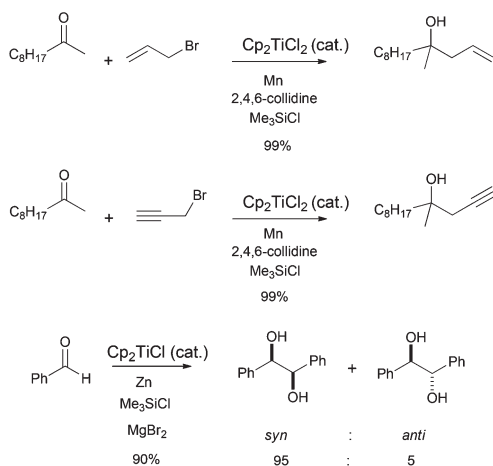
Sara P. Morcillo was born in Granada (Spain) in 1985. She studied Chemistry at Universidad of Granada where she is carrying out her Ph.D. studies on synthesis of natural products under the guidance of Dr José Justicia and Dr Juan M. Cuerva. During this time she has spent a trimester in the lab of Prof. Andreas Gansaüer at the University of Bonn (Germany).

Araceli G. Campaña obtained her Ph.D. degree at the University of Granada in 2008, guided by Prof. J. M. Cuerva. Her Ph.D. thesis dealt with the development of new synthetic methods based on multimetallic systems. Subsequently, she completed a postdoctoral stage in the lab of Prof. D. J. Cárdenas at Universidad Autónoma de Madrid (2009). From 2010 to 2012, she worked in the group of Prof. D. A. Leigh at the University of Edinburgh as a postdoctoral fellow studying small-molecule walker systems. Nowadays she is working as a 'Juan de la Cierva' postdoctoral fellow in Prof. Cuerva's group.

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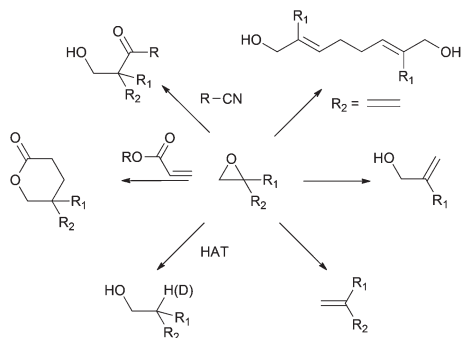
Scheme 3 Reactivity of epoxides in titanocene(III) chemistry.

Scheme 4 Examples of Cp$_2$TiCl-catalyzed Barbier-type and pinacol coupling reactions.

Scheme 5 General mechanism for epoxide deoxygenation.
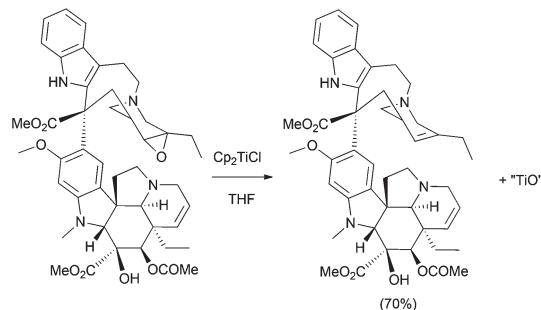
Scheme 6 Synthesis of anhydrovinblastine from leurosine.

Scheme 7 Glycal synthesis.

Scheme 8 Synthesis C-12 to C-18 fragment **1** of antibiotic rhizoxin.

building the main framework. Therefore, the article is subdivided into two sections devoted to these different applications.

Useful Cp$_2$TiCl-mediated functional group interconversions in the context of natural product synthesis

As we had commented before, the fate of carbon-centred radicals generated by Cp$_2$TiCl is determined by the reaction conditions employed. Thus, for example, such intermediates can participate in useful reduction or oxidation reactions.

Deoxygenations and dehydrogenations

In the treatment of an epoxide with Cp$_2$TiCl, as firstly presented by Rajanbabu *et al.*, the deoxygenation product appears from the reduction of the intermediate β-titanoxy radical by another molecule of Cp$_2$TiCl followed by elimination of titanocene(IV) oxides, thus yielding the corresponding olefinic product (Scheme 5).[14]
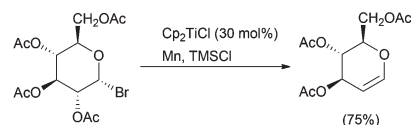
This methodology showed an interesting value and was applied to the synthesis of several cryptophycin derivatives
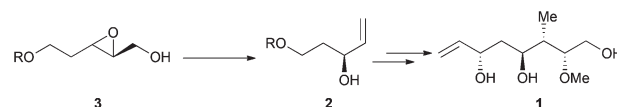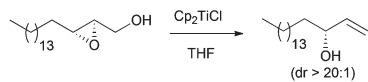
within the context of a structure–activity relationship study for their antitumor evaluation.[15] The synthesis of antitumoral alkaloid anhydrovinblastine from the selective deoxygenation of leurosine with Cp$_2$TiCl is also quite remarkable (Scheme 6).[16]

This useful transformation has also been valuable in carbohydrate chemistry for glycal synthesis from the corresponding glycosyl halides.[17] Furthermore, the amount of Cp$_2$TiCl required for glycal formation was considerably lowered to only 30 mol% by combination with a regenerating agent such as Me$_3$SiCl (Scheme 7).[18]
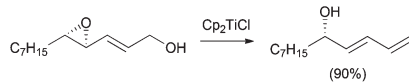
It was observed by Yavav and co-workers that treatment of 2,3-epoxy alcohols with Cp$_2$TiCl led to the corresponding allylic alcohols by a highly regioselective deoxygenation reaction.[19] Following this protocol, the stereoselective synthesis of the C-12 to C-18 segment of antibiotic rhizoxin **1** (Scheme 8) was performed from chiral carbinol **2**, prepared by a titanocene-mediated ring opening of epoxy alcohol **3**.[20]

The same protocol has also been recently applied to prepare a lipid olefin (Scheme 9), which was subsequently used in the synthesis of *C*-glycoside analogues of α-galactosylceramide.[21]
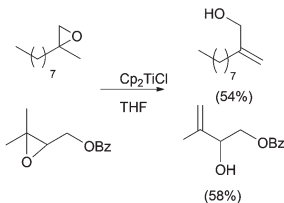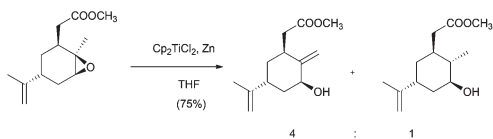
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Scheme 9 Regioselective deoxygenation of 2,3-epoxy alcohols.

Scheme 10 Synthesis of butadienyl alcohols.

**Scheme 11** Allylic alcohols obtained from tertiary radicals.

Scheme 12 Epoxide opening in carvone derivatives.

Moreover, Yavav extended the deoxygenation protocol to the treatment of epoxy allylic alcohols with Cp_2TiCl, leading to the highly regioselective synthesis of chiral butadienyl alcohols, which are valuable synthons in natural product synthesis (Scheme 10).[22]

In the presence of an excess of Cp_2TiCl, primary and secondary carbon-centred radicals undergo the previously described deoxygenation reaction to yield an alkene. Nevertheless, the formation of allylic alcohols is commonly observed in reactions involving tertiary radicals. In this case, an alternative mixed disproportionation process has been suggested to be involved.[13] Some representative examples are shown in Scheme 11.

In this sense, ring opening reactions of trisubstituted epoxides on carvone derivatives led to *exo*-methylene allylic alcohols as the major products (Scheme 12).[23] On the other hand, the treatment of α-pinene oxide derivatives with 2 equiv. of Cp_2TiCl could selectively afford a series of valuable compounds with an endocyclic double bond in their structure (Scheme 13).[24] Moreover, the radical formed after the homolytic cleavage of oxirane can evolve to other final products depending on the additives (Scheme 13).

The synthesis of one of the most biologically potent and least accessible gibberellins, GA_{32}, was achieved using another Cp_2TiCl-mediated epoxide opening reaction as the key step.[25] In this case, it was suggested that the initial 1,1-disubstituted
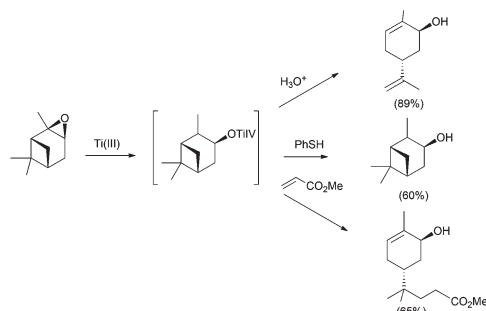
Scheme 13 Ti(III)-mediated opening of α-pinene oxide.

**Scheme 14** Cp_2TiCl in gibberellins synthesis.

epoxide was transformed into an aldehyde by reduction of the radical generated from the oxirane and Cp_2TiCl and subsequent hydride elimination to form an alkoxytitanium enolate (Scheme 14).

Reductions

Alternatively to the deoxygenation protocol, radical intermediates, mildly obtained from treatment of an epoxide with Cp_2TiCl, are reduced when they are trapped by an H-atom donor, such as 1,4-CHD or *t*-BuSH (Scheme 15).[1,2,26]
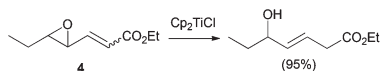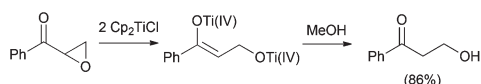
Regioselective ring opening of epoxy alcohols using *t*-BuSH as the H-atom donor was used in the stereoselective synthesis of α,β-unsaturated-δ-lactones.[27] Besides, a chiral 2-methyl-1,3-diol moiety arises from the diastereoselective opening of trisubstituted epoxy alcohols, being the key step in the synthesis of (+)-prelactone C (Scheme 16).[28] In this case, 1,4-cyclohexadiene was used as a reducing agent in combination with Cp_2TiCl. This efficient synthesis of 1,3-diols from 2,3-epoxy alcohols has been also successfully applied as the key step in the formal synthesis of (+)-antimycin A_{3b} as well as in the total synthesis of (+)-blastmycinone (Fig. 1).[29]

The regioselective reduction of vinyl epoxides has also been described. Interestingly, *E* allyl alcohols arise from both *E* and *Z* vinyl epoxides **4** (Scheme 17).[30] Nevertheless, in the treatment of terminal vinyl epoxides with Cp_2TiCl only the deoxygenated product was observed.
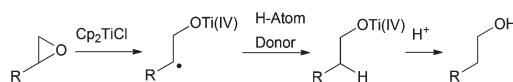
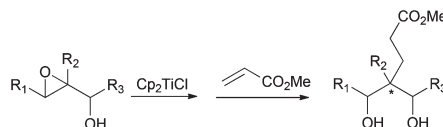**Scheme 15** General pathway towards reduced products.
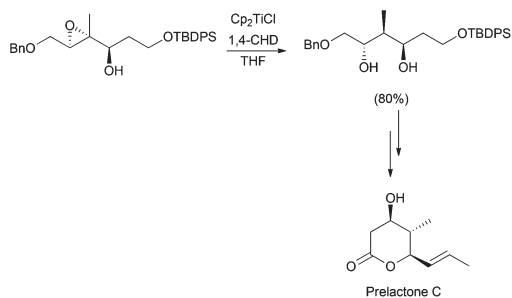
Scheme 16 Cp$_2$TiCl in the synthesis of prelactone C.
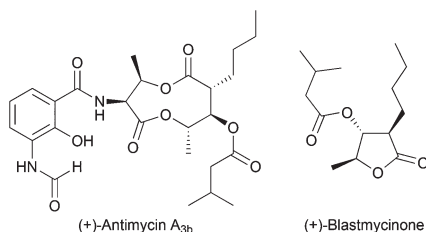
Fig. 1 (+)-Antimycin A$_{3b}$ and (+)-blastmycinone.

Scheme 17 Reduction of vinyl epoxides by Cp$_2$TiCl.

Scheme 18 Synthesis of β-hydroxy ketones.

Scheme 19 1,3-Diols from 2,3-epoxy alcohols.

Scheme 20 Preparation of α-glycosides from glycals.

Scheme 21 Cp$_2$TiCl in the synthesis of thyrsiferol.

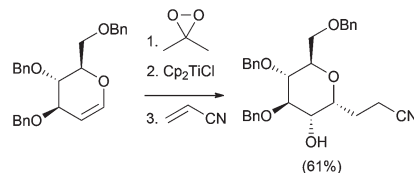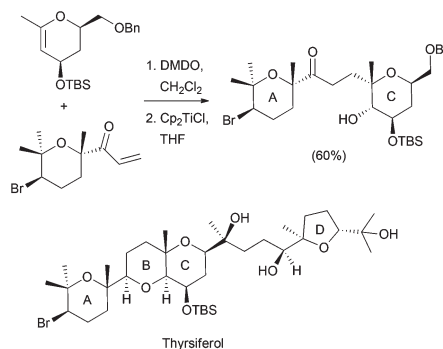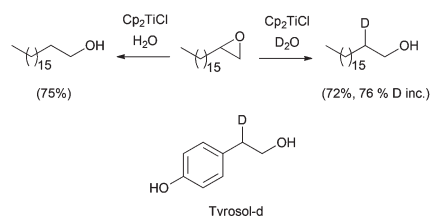**Scheme 22** Reductive epoxide opening with Cp$_2$TiCl–water.

Aldols are significant intermediates in the synthesis of many natural products. A catalytic titanocene-based system has been developed by Doris *et al.* to achieve the selective reduction of α,β-epoxy ketones to the corresponding β-hydroxy ketones (Scheme 18).[31] A year later, this group also reported the selective reduction of α,β-unsaturated ketones to the corresponding saturated ketones mediated by Cp$_2$TiCl.[32] This protocol was extended by Kosal and Ashfeld to the catalytic conjugative reduction of α,β-unsaturated aldehydes, ketones, esters and amides.[33]

If the generated radicals are trapped intramolecularly, cyclisation reactions can be easily developed. In this sense, the reductive radical cyclisations of epoxy esters have been described using titanocene chloride.[34] Thus, for example, chiral quaternary centers can be constructed.[35] In this case, the intermediate radical is intramolecularly trapped with an activated alkene (Scheme 19).[36]

Using similar reaction conditions, the stereospecific synthesis of α-glycosides has been reported from 1,2-anhydro sugars, yielding a free *C*-2 alcohol, which can be subsequently

manipulated (Scheme 20).[37] Taking also advantage of this strategy, the synthesis of the pyranopyran ring included in many natural products, such as thyrsiferol, was addressed from *C*-glycosides (Scheme 21).[38]

Reductive epoxide ring opening has also been carried out using water as a hydrogen source. Following this procedure, β-deuterated alcohols can be easily prepared in the presence of D$_2$O (Scheme 22).[39] Quite interestingly, labelled compounds prepared in this fashion can be applied as an internal standard for analysis, as was shown by using deuterated tyrosol in food analysis.

A highly regioselective epoxide reduction in the presence of water has been appropriately used in the total synthesis of microcin SF608 (Scheme 23).[40]

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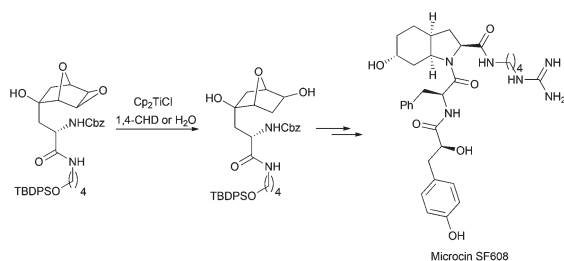
Scheme 23 Cp$_2$TiCl in the synthesis of microcin SF608.
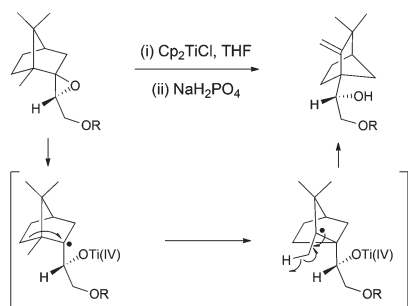
Scheme 24 Cp$_2$TiCl-promoted radical-based Wagner–Meerwein-type rearrangement.

Scheme 25 Cp$_2$TiCl-mediated allylation of aldimines.

Miscellaneous

The group of Roy observed a Cp$_2$TiCl-promoted radical-based Wagner–Meerwein-type rearrangement in camphoric systems, furnishing homoallylic alcohols with good yields (Scheme 24).[41]

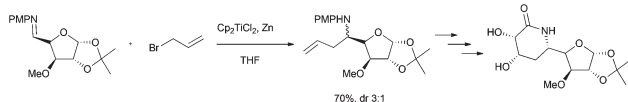Recently, this group has also reported a Cp$_2$TiCl mediated allylation of aldimines for the preparation of homoallyl amines. This methodology has been applied to the formal synthesis of aza-sugar derivatives and alkaloid skeletons (Scheme 25).[42]

Natural product synthesis based on key Cp$_2$TiCl-mediated transformations

Despite the interest of Cp$_2$TiCl in functional group interconversions, one of the remarkable characteristics of this reagent is its capability to build very efficiently different carbon skeletons. This fact has been used as a key step in many natural product syntheses, especially in lignan, terpene and meroterpene synthesis.
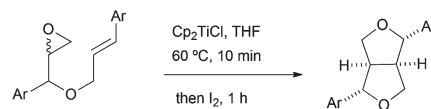
Lignans

Lignans are a broad and diverse group of compounds, which mainly derive from oxidative couplings of functionalised propyl phenols. These compounds are a major class of phytoestrogens found in plants. Due to their interesting biological properties, such as anticancer and antioxidant activities, lignans have attracted the attention of organic chemists.

The group of Roy has developed a reliable methodology for the synthesis of furano and related lignans, based on free radical chemistry mediated by *in situ* generated Cp$_2$TiCl from Cp$_2$TiCl$_2$ and zinc dust. Cp$_2$TiCl has therefore been used for the synthesis of the key tetrahydrofuran ring. The radical cascade process consists of a Cp$_2$TiCl-mediated homolytic epoxide opening (Scheme 3), an intramolecular radical cyclisation followed by an iodine-mediated etherification reaction (Scheme 26).[43]

This protocol has been used by the authors for the synthesis of the following furano lignans: dihydrosesamin **5a**,[44] lariciresinol dimethyl ether **5b**, acuminatin methyl ether **5e**, sanshodiol methyl ether **5g**, lariciresinol **5h**, acuminatin **5i**, and lariciresinol monomethyl ether **5j**. A similar approach yielded different furofuran lignans, such as sesamin **6a**, eudesmin **6b**, piperitol methyl ether **6e**, pinoresinol **6h**, piperitol **6i**, and pinoresinol monomethyl ether **6j**,[45] (Fig. 2).

Lately, the same group achieved the enantioselective synthesis of (−)-dihydrosesamin, (−)-acuminatin, (−)-sesamin and (−)-methyl piperitol starting from the corresponding chiral epoxy alcohol prepared by the Sharpless kinetic resolution method[46] (Scheme 27).

Scheme 26 Intramolecular radical cyclisation and etherification.

a, Ar$_1$ = Ar$_2$ = 3,4-methylenedioxy phenyl
b, Ar$_1$ = Ar$_2$ = 3,4-dimethoxy phenyl
c, Ar$_1$ = Ar$_2$ = 3-methoxy-4-benzyloxy phenyl
d, Ar$_1$ = 3,4-methylenedioxy phenyl
   Ar$_2$ = 3-methoxy-4-benzyloxy phenyl
e, Ar$_1$ = 3,4-methylenedioxy phenyl
   Ar$_2$ = 3,4-dimethoxy phenyl
f, Ar$_1$ = 3,4-dimethoxy phenyl
   Ar$_2$ = 3-methoxy-4-benzyloxy phenyl
g, Ar$_1$ = 3,4-dimethoxy phenyl
   Ar$_2$ = 3,4-methylenedioxy phenyl
h, Ar$_1$ = Ar$_2$ = 3-methoxy-4-hydroxy phenyl
i, Ar$_1$ = 3,4-methylenedioxy phenyl
   Ar$_2$ = 3-methoxy-4-hydroxy phenyl
j, Ar$_1$ = 3,4-dimethoxy phenyl
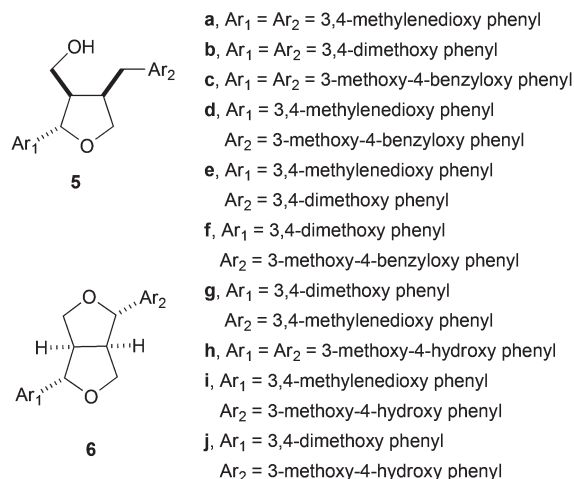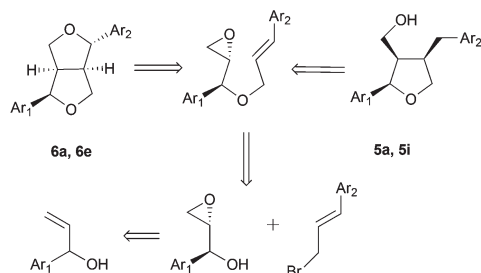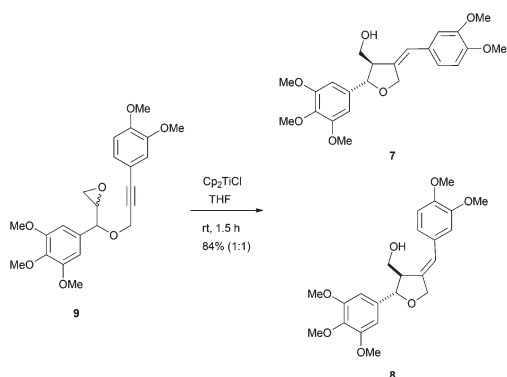   Ar$_2$ = 3-methoxy-4-hydroxy phenyl

Fig. 2 Furan- and furofuran lignans prepared using Cp$_2$TiCl.

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Scheme 27 Retrosynthetic analysis.

Scheme 28 Cp$_2$TiCl mediated the intramolecular radical cyclisation of the epoxyalkyne **9**.

Recently, the same group has reported the formal synthesis of the furano lignans magnofargesin **7** and 7′-epimagnofargesin **8** in both racemic and optically pure forms through a similar protocol.[47] In this case, the Cp$_2$TiCl-mediated radical cyclisation reaction was conducted from the epoxyalkyne **9** to give the tetrahydrofuran ring with an external alkene, which is characteristic of these compounds (Scheme 28).

Terpenes

The use of Cp$_2$TiCl-mediated cyclisations constitutes a straightforward strategy for the synthesis of natural terpenes, and therefore has been extensively used especially during the last 10 years.[48] As mentioned above, this reagent is able to promote regioselective homolytic ring opening of epoxides (Scheme 3). In the context of terpene synthesis, the radical thus generated is able to give multiple intramolecular additions to alkenes and alkynes, generating the corresponding cyclic products (see Scheme 29).[1] Remarkably, Cp$_2$TiCl can now be used in substoichiometric amounts with the aid of different Ti(III)-regenerating agents. This fact has contributed to the development of enantioselective processes and also to control the concentration of the active species in the reaction medium.[11,49] The latter fact is very important to avoid premature trapping of intermediate radicals during a (poly)cyclisation process. Moreover, in many cases, Cp$_2$TiCl is able to oxidise the final radical yielding an alkene, thus mimicking a pure cationic process. In this sense, if the global process is considered, including epoxide opening,
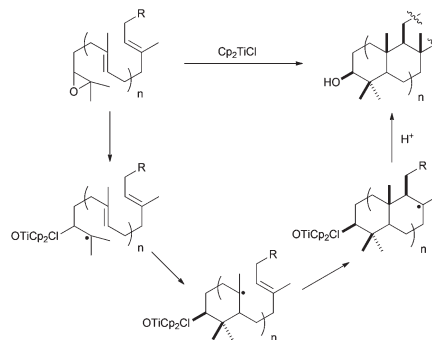

Scheme 29 Example of Cp$_2$TiCl mediated epoxypolyprene cyclisation.
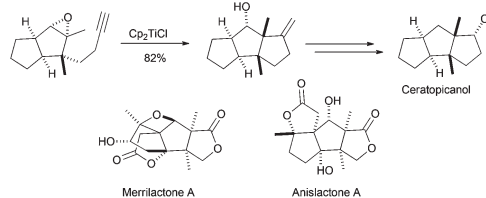
Scheme 30 Synthesis of ceratopicanol using a Cp$_2$TiCl-mediated 5-*exo*-dig cyclisation.
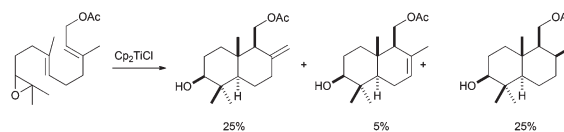
Scheme 31 First example of a Cp$_2$TiCl-mediated epoxypolyene cyclisation.

stereoselective (poly)cyclisation and the oxidative ending, this complex could be assumed to be an efficient artificial cyclase.[50]

Historically, Clive *et al.* reported in 1995 the first example of a Cp$_2$TiCl-mediated cyclisation as the key step for the synthesis of a natural sesquiterpene, ceratopicanol (Scheme 30). In this case, the last cyclopentane ring is prepared by a 5-*exo*-dig monocyclisation reaction in good yield.[51a,b] A similar strategy has been recently used in the preparation of sesquiterpenes merrilactone A and anislactone A.[51c]

The development of a more general Cp$_2$TiCl-based approach to conventional terpenic skeletons was reported by Cuerva *et al.* in 2001.[52] In that work, the authors presented the synthesis of several mono and bicyclic terpenic frameworks using stoichiometric amounts of Cp$_2$TiCl from simple epoxypolyprenes. The yields were moderate to good, with excellent stereoselectivities, mainly yielding cyclisation products with *exo* double bonds. Nevertheless, the control of the final oxidative ending was not good, also giving the corresponding *endo* double bonds and reduction products (Scheme 31). The formation of an *exo* double bond was lately assigned to a mixed disproportionation reaction between the organic

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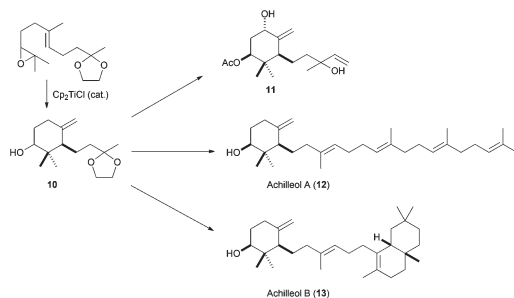
Scheme 32 Synthesis of achilleol A, B, and **11** from products obtained by Cp$_2$TiCl-catalysed epoxyolefin cyclisation.
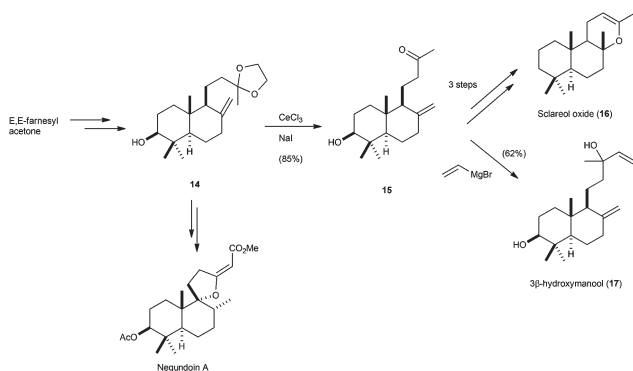
Scheme 33 Synthesis of sclareol oxide, 3β-hydroxymanool, and negundoin A *via* Cp$_2$TiCl-catalysed epoxypolyprene cyclisation.

Scheme 34 Synthesis of furanoditerpenoids **20** and **21** *via* Cp$_2$TiCl-catalysed cyclisation of **18**.

Scheme 35 Synthesis of 3β-drimanes from cyclization product **22**.

Scheme 36 Hydroxyl-promoted epoxidation strategy and application to natural products synthesis.

radicals and Cp$_2$TiCl.[13] On the other hand, the presence of reduced products was due to a very efficient hydrogen atom transfer (HAT) process from a titanocene(III) aquocomplex, formed by the presence of adventitious water, to the corresponding carbon-centred radical.[9,53]
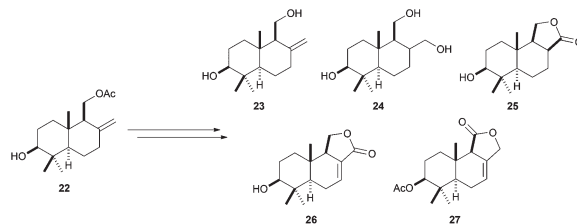
Similar results were obtained by Takahashi's group in an approximation to the synthesis of taxol based on the monocyclisation of epoxygeranyl acetate and other closely related functionalised derivatives.[54]

The methodology developed by Cuerva *et al.* was used to confirm the structure of monocyclic triterpene achilleol A (**8**),[55] a metabolite from *Achillea odorata*,[56] taking advantage of the excellent characteristics of this kind of radical cyclisation to generate exocyclic double bonds (Scheme 32). In this case, the key intermediate is monocycle **10**, which presents the required exocyclic double bond and derives from the corresponding epoxide of protected geranylacetone. This monocyclic compound was transformed into achilleol A (**12**) in a few steps. This cyclic synthon **10** was subsequently used in the synthesis of the cyclofarnesane terpenoid **11**[11] and achilleol B (**13**).[57]
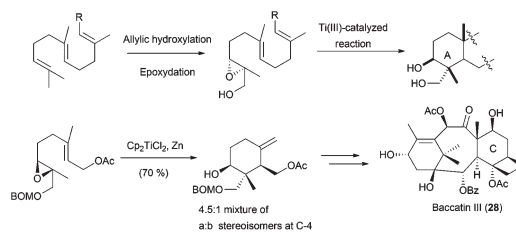
Additionally, other bicyclic terpenes, such as labdane 3β-hydroxymanool,[11] isolated from *Gleichenia japonica*, or sclareol oxide,[58] were synthesised by similar procedures, but using the corresponding cyclisation product derived from the epoxide of protected farnesylacetone (Scheme 33). Recently, Álvarez-Manzaneda *et al.* have also used compound **14** in the total synthesis of negundoin A.[58b]

Synthesis of natural terpenes based on higher polycyclisations has been also described, such as furanoditerpenoids **20** and **21**, prepared from Cp$_2$TiCl-catalysed cyclisation of geranylgeranyl acetate previously described by Cuerva *et al.*,[11] to yield the tricyclic compound **19**, which could be transformed into the furanoditerpenoids **20** and **21** in a few steps (Scheme 34).[59]

The versatility as building blocks in terpene synthesis of compounds generated by titanocene(III)-catalysed cyclisations of simple epoxypolyprenes is also revealed in the preparation of several bicyclic compounds from the family of drimanes. Taking advantage of the exocyclic double bond in drimanic skeleton **22**, Cuerva *et al.* prepared a collection of 3β-hydroxydrimanes with different functionalisations, as isodrimenediol (**23**), drimane (**24**), 3β-hydroxydihydroconfertifolin (**25**), 3β-hydroxycinnamolide (**26**), and 3β-acetoxydrimenin (**27**) (Scheme 35).[60]

Besides the hydroxyl group at C-3, it is very common in nature to find terpenes with additional oxygenated functions in different parts of the skeleton.[61] A frequent arrangement is a γ-dioxygenated system on the A ring. The introduction of this hydroxyl group in non-functionalised cyclisation products is not trivial, and procedures based on allylic oxidations, remote functionalisations or microbiological oxidations normally give low yields or mixtures of compounds, also presenting an important lack of chemoselectivity.[62] To overcome these problems, some approximations have been developed. Thus, a

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two-step protocol consisting of allylic oxidation of the methyl group in terminal alkene of the starting polyprene followed by an epoxidation yields the corresponding hydroxylated epoxy-polyprenes. After protection of the hydroxyl group, these compounds were cyclised using Cp_2TiCl, generating the corresponding cyclisation products with a γ-dioxygenated system on the A ring, but normally with low yields and moderate stereoselectivities. This strategy has been used by several authors in the preparation of different compounds. In this sense, the synthesis of the taxol-related compound baccatin III (**28**) was accomplished using a γ-dioxygenated system derived from geranyl acetate (Scheme 36).[63] In the same way, mechanistic studies about the cyclisation of these functionalised epoxypolyprenes have been performed.[64]

An alternative to this methodology for the synthesis of the γ-dioxygenated system on the A ring was developed by Cuerva *et al.*, using the hydroxyl group located at C-3 as a template to achieve a remote C–H activation.[65] The placement at C-3 of an oxime and subsequent treatment with Na_2PdCl_4 allows the formation of a five-membered palladium complex, involving the oxime and the equatorial methyl group at C-4. The final oxidation of this complex generated regioselectively the introduction of an acetoxy group at that position (Scheme 37).

Using this procedure, the authors carried out the functionalisation of several mono-, bi- and even tricyclic terpenic skeletons. Some of these compounds were used in the short and efficient synthesis of natural terpenoids. Thus, rostratone, isolated from *N. rostrata*,[65] was prepared from cyclisation compound **29**, which was transformed in **30** using simple transformations (see Scheme 38). Finally, the bicyclic compound was functionalised using the Pd-based methodology and a subsequent transesterification yield rostratone (**32**). Additionally, formal total syntheses of complex natural terpenes aphidicoline and pyripyropene A were also accomplished.
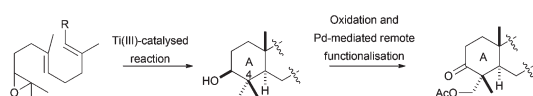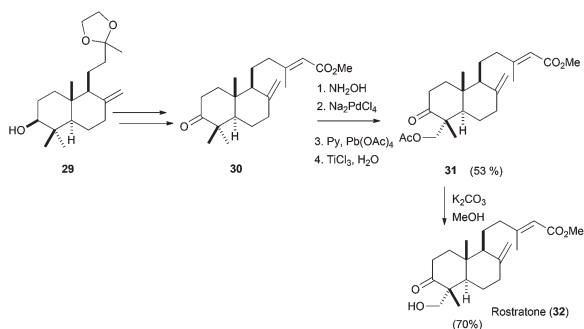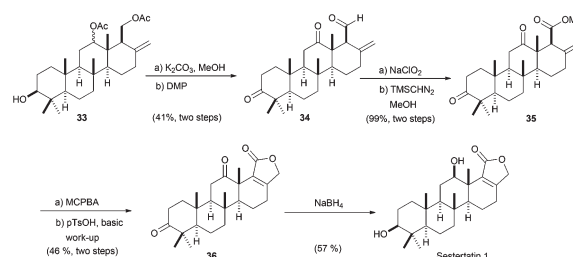
Bioinspired Cp_2TiCl-promoted processes have also allowed the synthesis of several terpenic structures hydroxylated in different positions of the terpenic frameworks, such as C-1, C-7 or C-12. These polyhydroxylated structures are also very common in natural terpenes. In this context, Cuerva's group has applied the versatile chemistry of titanocene(III) complexes to the development of a new methodology to gain access to such polyhydroxylated structures.[66a] It consists of an initial Cp_2TiCl-promoted Barbier reaction of appropriate α,β-unsaturated aldehydes with simple allyl bromides (as prenyl, geranyl or farnesyl bromides) to generate the corresponding hydroxylated polyprenes (Scheme 4). Then, after subsequent protection of the hydroxyl group and regioselective epoxidation, a Cp_2TiCl-catalysed cyclisation of the corresponding polyhydroxylated epoxypolyprenes generates the desired mono-, bi-, tri- and tetracyclic polyhydroxylated terpenes with moderate to good yields. Some of these polycyclic products were used in the synthesis of complex natural terpenes, such as sestertatin 1 (see Scheme 39) and C,D rings of the marine natural product aspergilloxide. Sestertatin 1 and aspergilloxide are tetracyclic sesterterpenoids isolated from the sponge *Hyrtios erecta*[67a] and an undescribed member of a fungus from the genus *Aspergillus*,[67b] respectively. A similar protocol has been recently used in the preparation of (+)-apotrisporin E and (+)-apotrientriols A–B.[66b]

Another important aspect in the synthesis of natural products is the development of methodologies which allow the enantioselective access to the desired compounds. In this sense, Cp_2TiCl-catalysed bioinspired radical cyclisations of epoxypolyprenes have been shown to be an excellent procedure for the enantioselective synthesis of natural terpenoids. This is because the correct absolute configuration present in the natural terpene can be placed in the starting polyprene by an enantioselective epoxidation process. In this sense, Sharpless dihydroxylation[68] has been used for the preparation (after the corresponding epoxide ring closing) of enantioenriched epoxypolyprenes, which retain the enantiomeric excess after the corresponding cyclization. This method has been used in the preparation of several interesting natural terpenes, such as achilleol B (**13**),[57] myrrhanol (**39**),[69] (+)-seco-C-oleanane (**38**),[70] and β-onocerin (**37**),[7] starting from enantioenriched farnesyl epoxide. β-Onocerin was also prepared using a Cp_2TiCl-catalysed Wurtz-type dimerisation of allylic halides (Scheme 40).[71]

Scheme 37 Post cyclisation oxidation of products obtained *via* Cp_2TiCl catalysed epoxypolyene cyclisation.

Scheme 38 Synthesis of rostratone from epoxypolyene cyclisation product **29**.

Scheme 39 Total synthesis of sestertatin 1 from cyclisation product **33**.

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Scheme 40 Synthesis of myrrhanol A, (+)-seco-C-oleanane, and β-onocerine *via* Cp$_2$TiCl promoted epoxypolyene cyclisation.

Scheme 41 Approach to fomitellic acid based on a Cp$_2$TiCl-mediated epoxypolyene cyclisation.

Sharpless epoxidation of allylic alcohols has been also used in the preparation of labdane-type compounds with complex structure.[72] Another example of this application was the synthesis of tetracyclic fomitellic acid (**40**), a very interesting compound due to its biological activity as an inhibitor of calf DNA polymerase α, rat DNA polymerase β, and human DNA topoisomerases I and II.[73] The synthesis of A,B rings of fomitellic acid was performed using a stereoselective Cp$_2$TiCl-mediated cyclisation of the corresponding enantioenriched epoxide precursor (Scheme 41).

Nevertheless, Sharpless dihydroxylation is not efficient in some substrates, presenting several problems concerning the enantiomeric purity as well as selectivity. To overcome these drawbacks, Cuerva *et al.* used Jacobsen epoxidation in the synthesis of the bicyclic natural terpene (−)-α-ambrinol (**42**),[74] an odorous component of ambergris. The epoxidation of protected geranylacetone using this methodology, and subsequent cyclisation catalysed by Cp$_2$TiCl, yielded the corresponding monocyclic product **41**, which after a few simple steps was transformed in (−)-α-ambrinol (**42**) (Scheme 42).

All the cyclisation processes depicted above are characterised by a 6-*endo*-trig cyclisation mode, similar to the related cationic processes. Nevertheless, in nature it is also possible to find compounds which present a cycloheptane in their
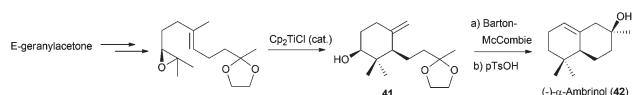
structures, such as laukarlaool (**44**) or barekoxide (**45**). Additionally, tricyclic compounds from the valparane family also have this kind of seven-membered carbocycles. Although the biosynthesis of these compounds has been proposed to take place by sequence 6-*endo*, 6-*endo*, 7-*endo* cationic cyclisations, this biogenetic hypothesis involves the formation of secondary cationic intermediates.[75] In fact, this kind of cationic cyclisation has not been reproduced in the laboratory even using enzymes,[76] showing a lot of uncertainties about the real nature of 7-*endo* cyclisations. In this context, Cuerva's group has studied the cyclisation of several epoxypolyprenes derived from linalyl, nerolidyl and geranyl linalyl acyclic terpenes.[77a] The cyclisation of these epoxypolyprenes generated the corresponding cyclisation products presenting a 7-membered ring in good yields. These cyclisation products were subsequently used by the authors in the straightforward synthesis of several natural terpenes containing 7-membered rings, such as laukarlaool (**44**), barekoxide (**45**) and valparadiene (**46**). The syntheses were extremely short and effective. Thus for example, valparadiene (**46**) was prepared in only four steps from commercial geranyl linalool, with an overall yield of 21%. Recently, Cuerva *et al.* have studied the reason for this regioselectivity, concluding that the substitution in the double bond involved in the final cyclization reaction drives the reaction to the exclusive formation of six- or seven-membered rings (Schemes 43 and 44).[77b]

It is worth noting that the epoxide can be placed in other positions of the epoxypolyprene. Thus for example, Barrero *et al.* took advantage of this possibility in the preparation of chokols, a 2,6-cyclofarnesane compound isolated from *Phleum pratense*.[78] The titanocene(III)-mediated cyclisation of an epoxide derivative of nerolidol led to the 5-*exo*-trig cyclisation product, used by the author in the synthesis of chokols

Scheme 43 Cp$_2$TiCl catalysed 7-*endo* cyclisations in epoxypolyene cyclisations. Synthesis of laukarlaool, barekoxide and valparadiene.

Scheme 42 Synthetic approach to (−)-α-ambrinol.

Scheme 44 Selectivity in Cp$_2$TiCl catalysed 6-*exo* vs. 7-*endo* cyclisations of epoxypolyenes.
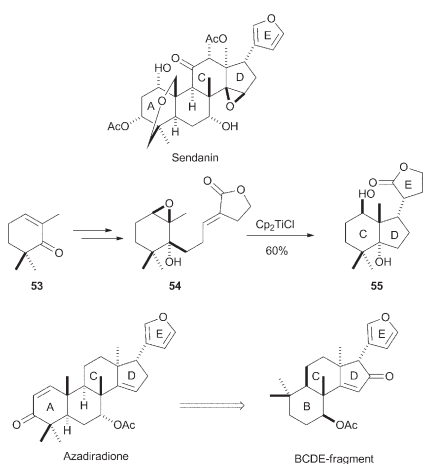
Scheme 45 Synthesis of chokol K mediated by titanocene(III).

Scheme 46 Preparation of (+)-tuberiferine (**50**) and (+)-brachylaenolide (**52**) by titanocene(III) chemistry.

Scheme 47 Synthesis of CDE fragment of sendanin, and BCDE fragment of azadiradione by Cp₂TiCl-mediated cyclisation.

derivatives (see Scheme 45). This unexpected cyclisation takes place due to a coordination between the titanocene complex, the epoxide and the trisubstituted hydroxyl group in vicinal position.

The complex Cp$_2$TiCl has not been only used in the synthesis of polycyclic terpenes with the regular skeletons shown before. It is also useful for the preparation of other terpenes with different structures. Thus, this methodology was used in the synthesis of eudesmanolide-type compounds, such as (+)-tuberiferine (**50**) and (+)-brachylaenolide (**52**), via titanocene(III)-catalysed cyclisation of the corresponding epoxygermacrolides.[79a] Additionally, an extensive study about the titanocene-promoted cyclization of structurally related epoxidated germacrones has been recently described (Scheme 46).[79b]

Recently, Fernández-Mateos et al. have performed a remarkable synthesis of CDE molecular fragments related to natural terpenoids sendanin, a limonoid triterpene,[80a] using stoichiometric amounts of Cp$_2$TiCl (see Scheme 47). In this case, the epoxide is placed in a cyclic structure as **54**, which is based on

Scheme 48 Synthesis of fragranol catalysed by a titanocene(III) complex **56**.
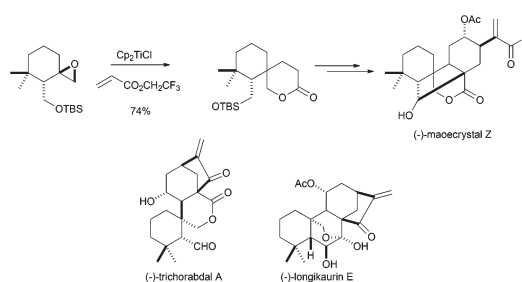
Scheme 49 Synthesis of maoecrystal Z and related compounds via titanocene(III)-catalysed epoxide opening and lactonisation.

a terpene substructure derived from trimethylcyclohexenone **53**. The subsequent cyclisation of **54** mediated by Cp$_2$TiCl yields a polycyclic compound **55** with a structure similar to the CDE fragment present in the mentioned limonoid. A similar strategy has been used by the same authors in the synthesis of BCDE molecular fragments of the limonoid azadiradione.[80b]

Additionally, Gansäuer et al. described a new approach to the synthesis of fragranol, a monoterpene isolated from the roots of Artemisia fragrans Willd, based on a radical 4-exo-cyclisation catalysed by the new titanocene complex **56**. This synthesis introduced a new concept in titanocene(III)-promoted cyclisations, a template effect from the complex to control the process (Scheme 48).[81]

Other complex structures have been also prepared using titanocene(III)-promoted cyclisations. In this sense, Reisman's group has recently synthesised (−)-maoecrystal Z, an unusually rearranged 6,7-seco-ent-kauranoid natural terpenoid isolated from Isodon eriocalyx.[82a] In this synthesis, the authors used the ability of the radical generated from a Ti(III)-catalysed epoxide opening to give an addition reaction over acrylates, and the subsequent lactonisation reaction (Scheme 49). Additionally, an approximation to the synthesis of related compound maoecrystal V has recently been reported by Thomson's group.[82b] Other related compounds, such as (−)-trichorabdal A and (−)-longikaurin E, have been also prepared using this methodology.[82c]

Beyond the use of Cp$_2$TiCl in the synthesis of cyclic or polycyclic terpenoids, acyclic terpenes can be also prepared. Thus for example, very efficient Wurtz- and Barbier-type reactions have been used in the synthesis of some natural acyclic terpenes. Cp$_2$TiCl-catalyzed Wurtz-type coupling of farnesyl bromide has been used in the synthesis of squalene, an important natural terpene (Scheme 4).[71] Recently, Cuerva et al. have
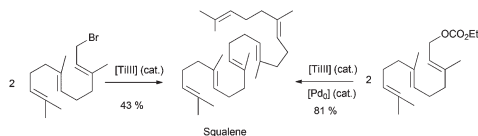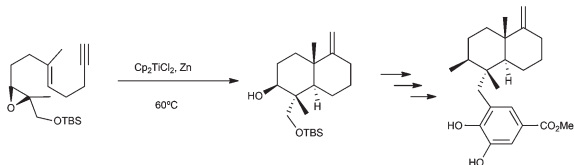
Scheme 50 Synthesis of squalene by Wurtz type reactions from farnesyl bromide or farnesyl ethyl carbonate.
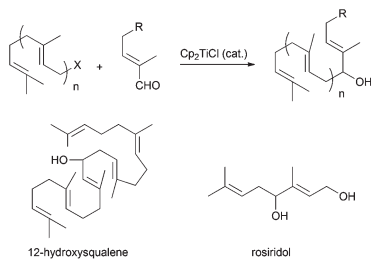
Scheme 51 Preparation of acyclic hydroxylated terpenes using Cp$_2$TiCl-catalyzed Barbier type reactions.

**Scheme 52** Synthesis of (±)-smenospondiol using titanocene(III) chemistry.

published a modification of this process, using farnesyl carbonate as the starting material in a similar Wurtz-type coupling reaction catalysed by titanocene(III) and Pd(0).[12a] This new method allowed the use of more handle starting materials (Scheme 50).

Barbier-type reactions between prenyl halides and α,β-unsaturated aldehydes have also been used in the synthesis of hydroxylated acyclic terpenes (Scheme 4). In this sense, Cuerva's group performed the preparation of 12-hydroxysqualene, the major product from the biotransformation of presqualene diphosphate, and rosiridol, a monoterpenoid isolated from several plants, using these kinds of reactions (Scheme 51).[6] Thus, 12-hydroxysqualene was synthesised in good yield by an α-regioselective Barbier reaction catalysed by titanocene(III) between farnesal and farnesyl chloride. On the other hand, rosiridol was prepared from prenyl bromide and the corresponding α,β-unsaturated aldehyde and subsequent transesterification.[6]

All the chemistry shown above points out that Cp$_2$TiCl is a powerful tool for the synthesis of natural acyclic and polycyclic terpenes, allowing access to this kind of compounds by straightforward strategies, using few synthetic steps and under mild conditions.

Meroterpenes

Meroterpenes are compounds of mixed biosynthesis with a common structural feature: they are formed by sesquiterpene
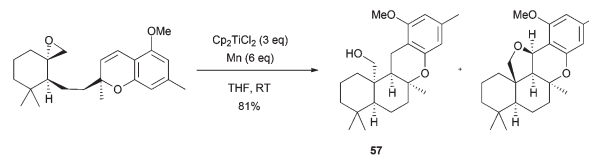
**Scheme 53** Preparation of **57**, key intermediate in the synthesis of (−)-sicannin.

units linked to aromatic structures, mostly substituted phenols. Most of the procedures described to synthesize these compounds using Cp$_2$TiCl involve radical cyclizations starting from epoxipolyprenes and a great majority employ stoichiometric quantities of Ti(III).

One example of this strategy was reported by Takahashi in the total synthesis of (±)-smenospondiol. The bicyclic skeleton was constructed by a Cp$_2$TiCl-mediated 6-*endo*,6-*exo* tandem radical cyclization of an epoxyenyne, yielding the bicyclic structure as the major product (Scheme 52).[83]

Trost *et al.* used Cp$_2$TiCl in the first enantioselective biomimetic total synthesis of (−)-sicannin. In this case, cationic cyclization using Lewis acids did not occur whereas Ti(III)-mediated cyclization afforded the desired tetracyclic compound **57** together with the 5-*epi*-sicannin in a 81% combined yield (Scheme 53).[84]

The construction of the DEF-ring terpenoid fragment of terpendole E was achieved with a combination of Cp$_2$TiCl$_2$ and Zn, starting from an epoxi-derivative of the commercially available farnesyl acetate.[85] In the total synthesis of (±)-platencin (**58**), Cp$_2$TiCl promoted a highly stereoselective radical cyclization of a trisubstituted epoxide to an α,β-unsaturated ketone, yielding a single stereoisomer in 87% yield (Scheme 54).[86]

The group of Omura and Nagamitsu proposed a stereoselective 6-*exo*-dig cyclization to a nitrile group, obtaining the corresponding diketoalcohol in 61% yield, which was later used in the total synthesis of pyripyropene A (Fig. 3).[87]
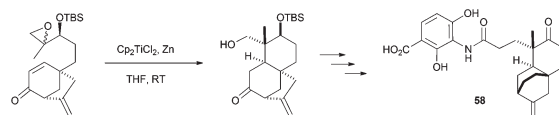
Scheme 54 Synthesis of (±)-platencin (**58**) *via* Cp$_2$TiCl-mediated cyclisation.
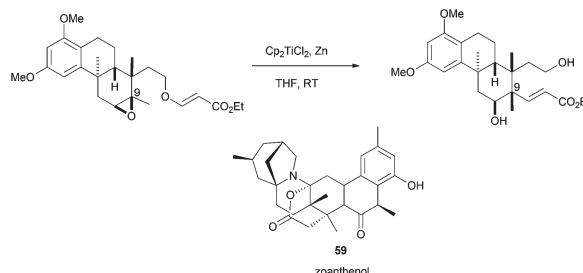
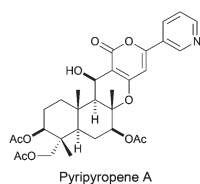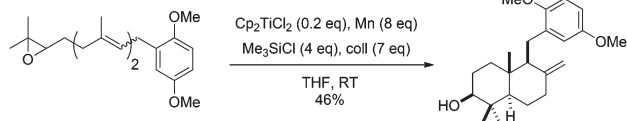**Scheme 55** Approximation to the synthesis of zoanthenol (**59**).

Fig. 3   Structure of pyripyropene A.

Scheme 56   Straightforward access to meroterpenes.

Recently, Yamashita *et al.* have described how Cp_2TiCl is able to promote radical-induced atom transfer. In this case, the acryl ester moiety is transferred from an oxygen to a carbon, leading to the efficient construction of a quaternary center and the configurational inversion of C-9.[88] Such a structure is an approximation to zoanthenol (**59**) (Scheme 55).

All the procedures described above involve the use of stoichiometric quantities of the titanium reagent. Nevertheless, the regenerating system introduced in our group, the chlorotrimethylsilane/2,4,6-collidine mixture, allowed the use of substoichiometric amounts of Ti(III). Thus, we have applied this methodology to the synthesis of different polycyclic meroterpenoids from aryl epoxypolyprenes (see Scheme 56), under mild conditions and with high stereo- and regioselectivities.[89]

It is worth noting that the aromatic subunits remain unchanged after radical cyclization, which represents a significant difference not only to carbocationic processes but also to radical cyclizations promoted by other transition metals, such as Mn(III).

Antibiotics

Pharmaceuticals, and among them antibiotics, are another important group of compounds which have been synthesized using Cp_2TiCl-mediated free radical chemistry. In this sense, the group of Roy has synthesised polysubstituted tetrahydrofuran anti-tumor antibiotics such as methylenolactocin (**60**),[90] protolichesterinic acid (**61**),[90] roccellaric acid (**62**)[91] and dihydroprotolichesterinic acid (**63**)[91] (Fig. 4).

The synthetic strategy for the preparation of **60** and **61** consists of an intramolecular radical cyclization of the epoxyalkyne derivatives **64** to give the tetrahydrofuran ring with a
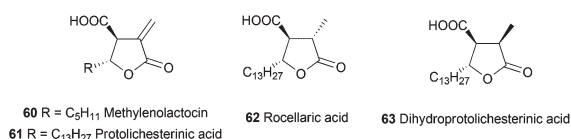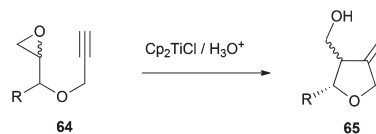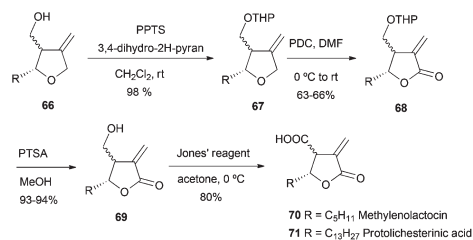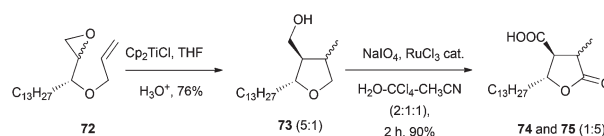

60 R = C_5H_{11} Methylenolactocin
61 R = $C_{13}H_{27}$ Protolichesterinic acid
62 Rocellaric acid
63 Dihydroprotolichesterinic acid

Fig. 4   Anti-tumor antibiotics with tetrahydrofuran structures.

Scheme 57   Preparation of intermediate **65** *via* titanocene(III)-mediated cyclisation.

Scheme 58   Synthesis of **70** and **71**.

Scheme 59   Synthesis of **74** and **75**.

terminal alkene, which is characteristic of these antibiotics. (Scheme 57).

The final compounds were obtained by a short sequence of steps, which implied protection of the hydroxyl group, oxidation with PDC to give the lactone, and deprotection and oxidation of the hydroxyl group to carboxylic acid with Jones reagent (Scheme 58).
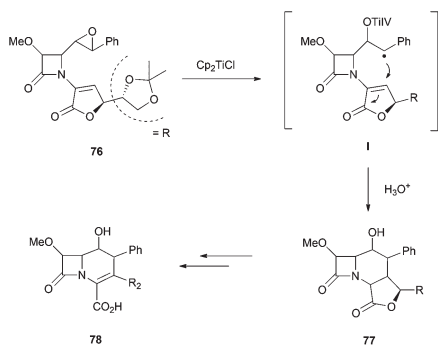
The synthesis of **74** and **75** was carried out by an intramolecular radical cyclisation of the epoxyalkyne **72**, followed by an oxidation with $NaIO_4$ and a catalytic amount of $RuCl_3$ to give the mixture of the final compounds (Scheme 59).

Recently, the same group has achieved the enantioselective synthesis of (−)-methylenolactocin and (−)-protolichesterinic acid starting with D-mannitol as a chiral precursor.[92]

Another group of antibiotics of broad spectrum and widely used are the β-lactam antibiotics, which contain a β-lactam ring in their molecular structures. The group of Grande has focused on the development of novel β-lactam derivatives by radical cyclisations using Cp_2TiCl. A first approximation was the synthesis of highly functionalized chiral tricyclic β-lactams as very convenient intermediates to achieve chiral 3-substituted carbacephem antibiotics.[93] The carbacephem skeletons were obtained by an intramolecular radical cyclisation of the corresponding enantiopure epoxides by addition to α,β-unsaturated lactones (Scheme 60).

The reaction of the epoxy β-lactams with Cp_2TiCl generated *in situ* with Cp_2TiCl_2 and zinc dust in THF afforded a mixture of three products in which the tricyclic β-lactams were the most abundant (Fig. 5).

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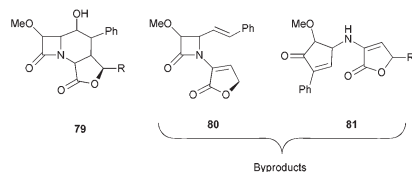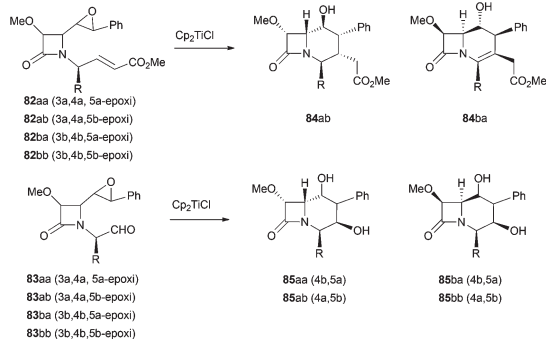**Scheme 60** Synthesis of β-lactams skeletons mediated by Cp$_2$TiCl.

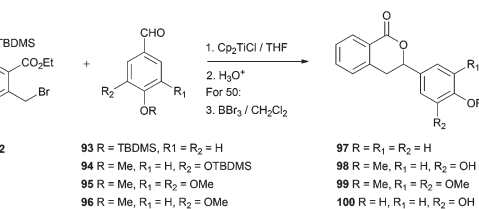**Fig. 5** Mixture of products in the cyclisation step.
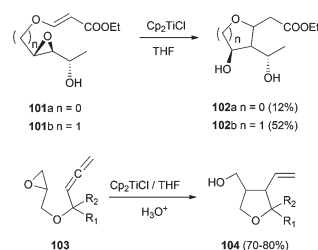

Scheme 61 Synthesis of novel carbacephems.

This strategy has been extended to the synthesis of stereospecific polyfunctionalized bicyclic β-lactams. In this case, the intramolecular radical cyclisation mediated by Cp$_2$TiCl was conducted over four isomeric epoxyacrylates **82** and epoxyaldehydes **83**. While the four isomeric epoxyaldehydes gave exclusively the respective carbacephems **85**, under the same reaction conditions, only two isomeric epoxyacrylates gave the cyclisation products **84ab** and **84ba** together with the elimination products (all isomers)[94] (Scheme 61).

More recently, the same group has reported the synthesis of new bi- and tricyclic β-lactams by the radical cyclisation of δ- and ε-epoxynitrile-2-azetidinones **86** and **87**. The intramolecular radical cyclisation between the homolytic opening of the epoxide and the cyano group afforded, after hydrolysis, bi- and tricyclic hydroxyketo-β-lactams[95] (Scheme 62).

The authors proved that a 7-*exo*-radical cyclisation of ε-epoxynitrile-2-azetidinones promoted by Cp$_2$TiCl is possible and new tricyclic β-lactams could be synthesised. This reaction was

Scheme 62 Cp$_2$TiCl mediated radical cyclisation of δ- and ε-epoxynitrile-2-azetidinones.

applied for the first time to benzonitrile acceptors to give the first examples of homobenzocarbacephems **91** reported in the literature.[95a]

Miscellaneous

Another group of natural products which have been synthesized using Cp$_2$TiCl as a radical initiator are 3,4-dihydroisocumarins. The group of Roy has achieved the synthesis of hydrangenol **97**, phyllodulcin **98**, macrophyllol **99**, and thunberginol G **100**.[96] The mixture of the ethyl 2-bromomethyl-benzoate derivative **92** and the corresponding benzaldehyde (**93–96**) was treated with Cp$_2$TiCl in THF at room temperature to afford the corresponding 3-phenyl-3,4-dihydroisocoumarins in good yield. The reaction proceeded *via* a Barbier-type addition followed by *in situ* lactonization (Scheme 63).

Additionally to these interesting substances, Cp$_2$TiCl has also been used for the synthesis of polyfunctionalized carbo- and heterocyclic precursors of many natural products. For example, polyfunctionalized tetrahydrofurans and pyrans[97] have been synthesized by radical cyclisation reactions of epoxyallenes[98] and epoxyacrylates ethers (Scheme 64).[97]

Scheme 63 Synthesis of 3,4-dihydroisocumarins.

Scheme 64 Synthesis of polyfunctionalised tetrahydrofurans.

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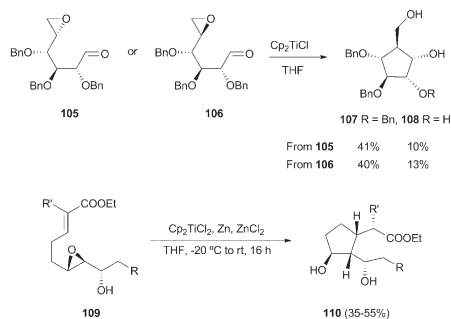
Scheme 65 Synthesis of chiral cyclopentanols.
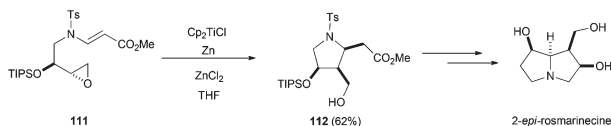
Scheme 66 Synthesis of 2-epirosmarinecine.

Scheme 67 Synthesis of oxacyclic fused rings.

Scheme 68 Synthesis of evodone.

Scheme 69 Synthesis of (±)-9,10-diepi-stemoamide **118**.

Scheme 70 Synthesis of α-aminated ketone **122**.

Scheme 71 Ti(ɪɪɪ)-catalysed synthesis of **124**, an intermediate in the preparation of entecavir.

methodology was applied to the synthesis of evodone, a furan monoterpene (Scheme 68).[104]

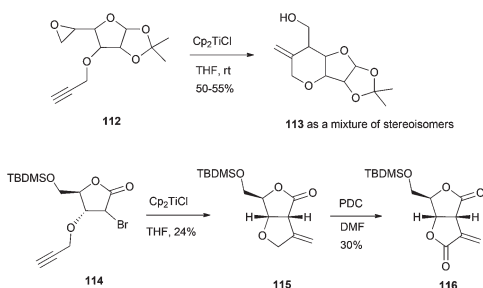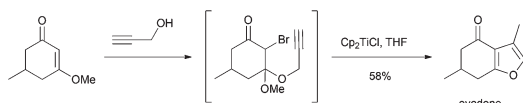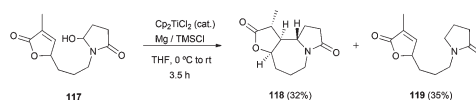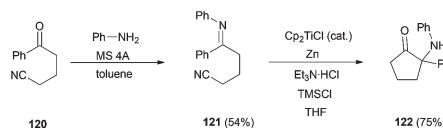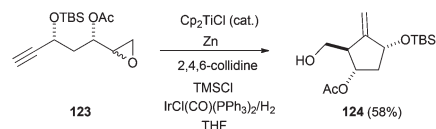Recently, the synthesis of (±)-9,10-diepi-stemoamide **118** has been reported by the group of Zheng. The key step for the synthesis of this compound is a novel dehydroxylative radical cyclisation with the activated alkene **117** catalysed by Cp₂TiCl[105] (Scheme 69).

Other important kinds of bioactive natural compounds, such as α-aminated ketones (as **122**) and pyrrolidin-3-ones, are also accessible using titanocene(ɪɪɪ) catalytic cyclization of imines over nitrile moieties, as has been recently demonstrated by Streuff *et al.* (Scheme 70).[106] This methodology is also useful in the preparation of α-hydroxyketone fragments, present in several natural compounds as barbacenic acid, cortistatin D, dragmacidin F, sieboldine A, *etc.*[107]

Cp₂TiCl-catalysed intramolecular radical addition of an epoxide to an alkyne has been used in the recent synthesis of the important drug entecavir, frequently used in the treatment of hepatitis B. The introduction of IrCl(CO)(PPh₃)₂/H₂ in the reaction conditions allowed the reduction of the final radical (Scheme 71).[108]

Five-membered carbocycles with multiple chiral centres have been achieved by intramolecular radical cyclisation of the corresponding enantiopure epoxyaldehydes[99] and epoxyacrylates (Scheme 65).[100] This strategy has been used in the total synthesis of 2-epirosmarinecine (Scheme 66).[101]

Another class of important building blocks present in a multitude of natural products are oxacyclic fused rings, such as bicyclic ethers and bis-γ-lactones. The synthesis of both types of structures has been carried out by the group of Roy. The synthesis of the bicyclic ethers **113** proceeded *via* intramolecular radical cyclisation of the corresponding epoxyalkynes **112**.[102] The synthesis of the bis-γ-lactones **116** was achieved by an intramolecular Barbier type addition of **114** followed by PDC oxidation[103] (Scheme 67).

Roy *et al.* synthesized substituted furans from α-bromo-β-keto enolethers using Cp₂TiCl as a radical source. This

Conclusions

Titanocene(ɪɪɪ)-mediated radical processes have been applied to the synthesis of natural products of diverse nature. Beyond simple functional group interconversions, radical cyclizations, mainly from epoxides, have demonstrated their utility to yield (poly)cyclic natural skeletons, which are valuable synthons in organic synthesis. This radical approach has in many cases resulted in better yields and stereoselectivities than the cationic equivalents. In particular, the synthesis at room

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temperature of stereodefined terpenic skeletons without enzymatic assistance is remarkable. In this context, the main limitation of this bioinspired approach is, in fact, its extraordinary stereoselectivity, which avoids obtaining *cis*-fused decalins and/or substituents in axial positions. Such stereochemistry is present in many interesting natural terpenes. On the other hand, as can be seen in the first part of the review, the diverse reactivity of titanocene(III) complexes derives in some functional group incompatibilities. It is expected that in near future judicious designs of new titanocene(III) complexes can resolve this drawback. In any case, the evolution of the applications of titanocene(III) in natural product synthesis suggests that these reagents can be a matter of choice in the arsenal of a synthetic organic chemist.

Acknowledgements

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