# The Growing Impact of Titanocene(III)-Mediated Radical Epoxide Opening on the Synthesis of Natural Products

J. M. Cuerva, J. Justicia, J. L. Oller-López, B. Bazdi and J. E. Oltra*

*Department of Organic Chemistry, Faculty of Sciences, Campus Fuentenueva s/n, University of Granada, E-18071, Granada, Spain*

**Abstract:** This review describes recent developments in the homolytic ring opening of epoxides mediated and catalysed by titanocene(III) complexes, with special emphasis on their applications for the synthesis of natural products.

**Keywords**: Epoxides, titanocene, free radicals, synthetic methods, natural products.

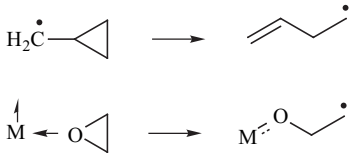
## 1. INTRODUCTION

Epoxides (oxiranes) constitute one of the most versatile intermediates in organic synthesis as they can be prepared without difficulty from alkenes, carbonyl compounds and other easily accessible starting materials and subsequently transformed into many other functional groups [1]. Moreover, the successful methods for asymmetric epoxidation developed by Sharpless, Katsuki, Jacobsen, Shi and others, have resulted in epoxides becoming crucial intermediates for enantioselective synthesis [2].

It has been known for a long time that when treated with acidic reagents [3] or carbon nucleophiles [4] epoxides undergo heterolytic ring opening, thus facilitating C-C bond formation *via* carbocation- or carbanion-type chemistry respectively. Within this context, reports published by RajanBabu and Nugent between 1988 and 1994 introduced a novel concept into epoxide chemistry: homolytic ring opening mediated by titanocene(III) complexes [5]. Among other transformations, this method facilitates C-C bond-forming reactions *via* free-radical chemistry and when Gansäuer and co-workers developed its first catalytic version [6] it emerged as a really powerful synthetic tool. Since then both the stoichiometric and catalytic versions have been objects of active research and several excellent reviews have covered the results reported up until 2003 [7]. Over the last year or so, however, relevant new findings have been published and the method has been applied to the synthesis of a wide array of natural products. This review, therefore, is not meant to be exhaustive but rather focuses on the most recent observations and the increasing scope of applications that the titanocene(III)-based procedure is being put to in the synthesis of natural products. We also present the basic concepts of the method to facilitate and encourage further discussions.

## 2. BASIC CONCEPTS AND NEW FINDINGS

In 1988, on the basis of an analogy to the rearrangement of cyclopropylmethyl radicals to homoallyl radicals, Nugent and RajanBabu reported a fundamental hypothesis: that a σ-complex of an epoxide with a transition metal possessing a half-filled *d* orbital might undergo C-O bond cleavage to release ring strain (Scheme **1**) [5a].



**Scheme 1.** Analogy realised by Nugent and RajanBabu.

Experimental evidence provided by the authors confirmed their hypothesis and proved that the treatment of epoxides with an excess of bis(cyclopentadienyl)titanium(III) chloride ($Cp_2TiCl$) can be used not only for selective reduction and deoxygenation reactions but also for C-C bond forming processes such as the cyclisation of 6,7-epoxyalkenes and 6,7-epoxyalkynes, and intermolecular additions to activated olefins (Scheme **2**) [5]. It is worth noting that as the reaction mechanism generally proceeds *via* the most substituted (i.e. energetically most stable) radical, the regiochemistry is the opposite (and complementary) to that which is normally to be expected for conventional $S_N2$-type epoxide openings with hydride reagents [8] or carbon nucleophiles.

The titanocene(III) complex used by RajanBabu and Nugent can either be prepared separately as described previously [9], or generated by electroreduction methods [10] or (most commonly) generated *in situ* by simply stirring commercially available $Cp_2Ti^{IV}Cl_2$ with reductive metals such as Mn, Zn, Mg or Al [11]. Curiously, the question concerning the true nature of the active form of this [$Ti^{III}$] reagent has been the subject of controversy for quite some time [12]. It is known that the complexes obtained by the reduction of $Cp_2TiCl_2$ with metals crystallize as trinuclear species $(Cp_2TiCl)_2MCl_2$ (M = Mn, Zn, Mg) [11c,d], a phenomenon which has been claimed to be responsible for the diastereoselectivity observed in the pinacolization of aromatic and α,β-unsaturated aldehydes [13]. Nevertheless, cyclic voltammetry and kinetic measurements carried out by Skrydstrup's and Daasbjerg's group have finally confirmed that the complexes generated by $Cp_2TiCl_2$ reduction with metals in tetrahydrofuran (THF) solution actually take the form of an equilibrium mixture of the mononuclear species $Cp_2TiCl$ and its dimer $(Cp_2TiCl)_2$ whatever the reductive metal used [12c]. Therefore, in this review we have

*Address correspondence to this author at the Department of Organic Chemistry, Faculty of Sciences, Campus Fuentenueva s/n, University of Granada, E-18071, Granada, Spain; E-mail: joltra@ugr.es

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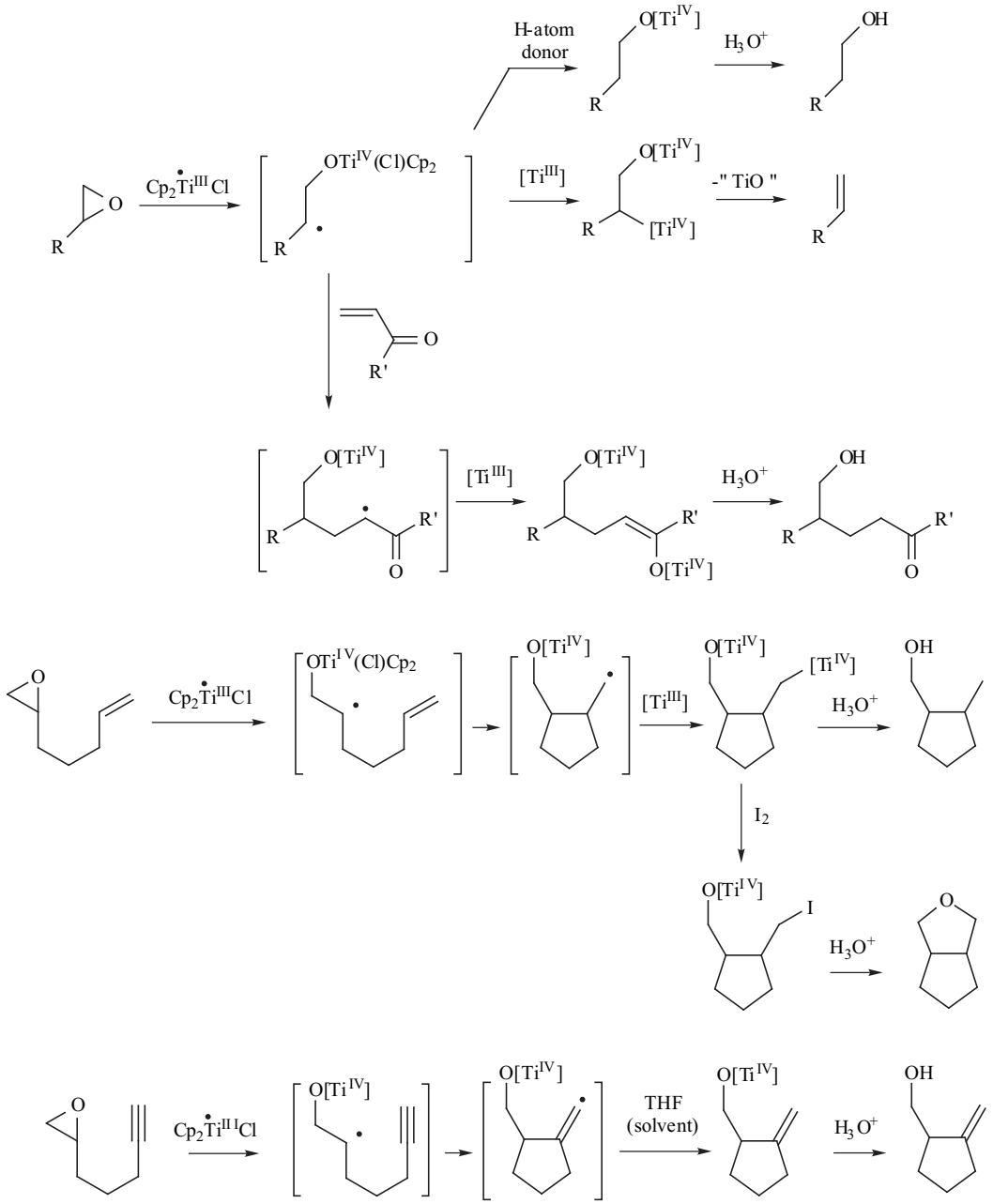
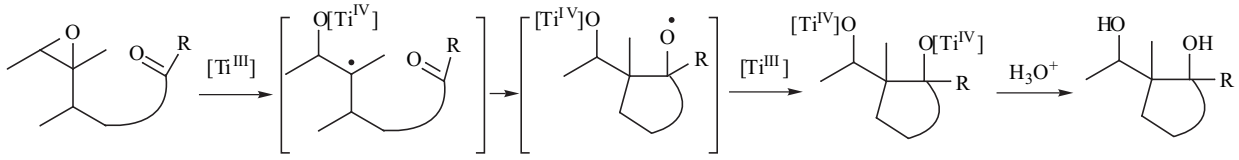


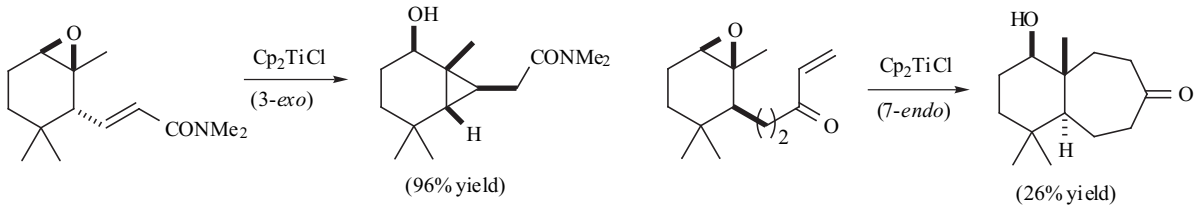
**Scheme 2.** Basic titanocene-promoted transformations reported by RajanBabu and Nugent [5].

represented the titanocene(III) complex either as the mononuclear species or simply as [$Ti^{III}$] for clarity's sake.

Apart from the original report by RajanBabu, Nugent and Beattie [5c], among the processes employing stoichiometric proportions of $Cp_2TiCl$ there have been numerous studies dealing with reductions and deoxygenations of different epoxides, including epoxy alcohols, epoxy ketones and epoxy-carvone derivatives [14]. Very importantly, five years ago Fernandez-Mateos *et al.* published the titanocene-promoted intramolecular addition of epoxides to carbonyl groups, a new radical reaction affording compounds ranging from cyclopropanols to cyclohexanols (Scheme **3**) [15]. This procedure has subsequently been extended to the cyclisation of epoxynitriles to give β-hydroxycycloalkanones [16].



**Scheme 3.** 1,3-cycloalkanediols from epoxy-carbonyl compounds [15].

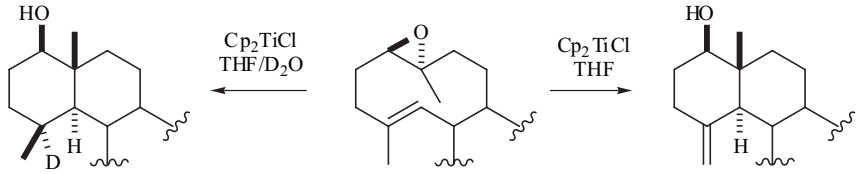



**Scheme 4**. Intramolecular additions of epoxides to activated olefins [19].

Some descriptions of titanocene-promoted intermolecular additions of epoxides to α,β-unsaturated chromium- and tungsten-carbene complexes [17] and other activated alkenes [18] have been published by different authors. More recently, the intramolecular version of the addition of epoxides to activated olefins has been independently developed by the groups of Fernandez-Mateos and Gansäuer, employing stoichiometric and catalytic quantities of titanocene respectively [19]. This method allowed the construction of three- to six- and eight-membered carbocycles at medium to high yields, although those reported for the synthesis of seven-membered rings were considerably lower (Scheme **4**) [19b].

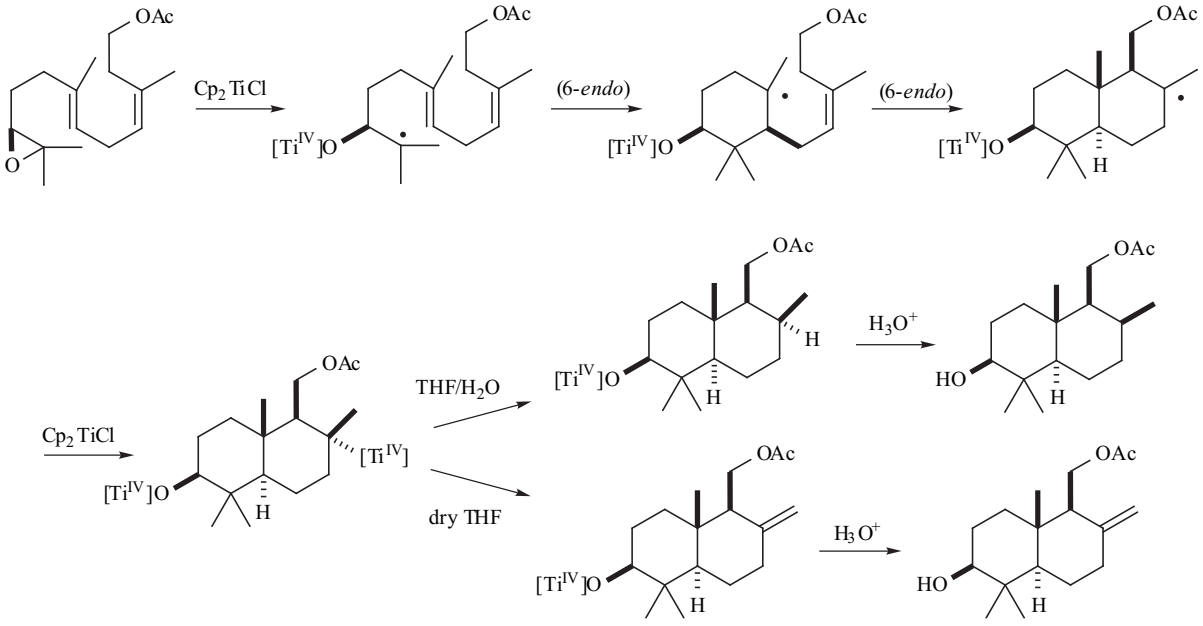
To study the effects of water and other solvents on titanocene(III)-mediated processes we used the transannular cyclisation of epoxygermacrolides as a model reaction [20]. selectively to decalins with an exocyclic double bond. In an aqueous medium, however, the main product was a reduced decalin (Scheme **5**). In the presence of $Cp_2TiCl$, water (either $H_2O$ or $D_2O$) proved to be more effective than the toxic and expensive hydrogen-atom donor 1,4-cyclohexadiene for the reduction of tertiary radicals. This is an unusual phenomenon in free-radical chemistry [21], which might be exclusive for processes mediated by single-electron-transfer metals.

Some controversy remains concerning contemporary radical chemistry as to whether radical cascade cyclisations take place in a concerted or stepwise fashion [21a]. Within this context we have recently reported theoretical and experimental evidence to support the idea that titanocene(III)-promoted cascade cyclisation of epoxypolyprenes takes place in a non-concerted fashion *via* discrete carbon-centred

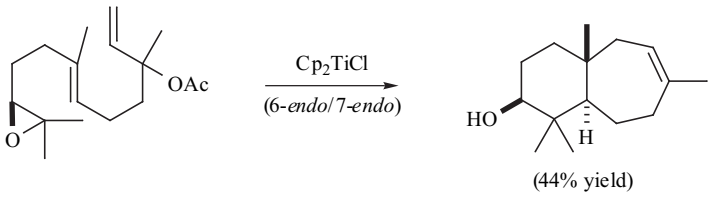



**Scheme 5**. Titanocene(III)-mediated transannular cyclisation of epoxygermacrolides [20].

Thus we found that in anhydrous, nonhalogenated solvents such as THF, benzene and toluene the reaction led radicals [22]. The 6-*endo* consecutive cyclisations proceed stereoselective and the end step can easily be controlled to




**Scheme 6**. Titanocene(III)-promoted cascade cyclisation of epoxypolyprenes [22, 23].

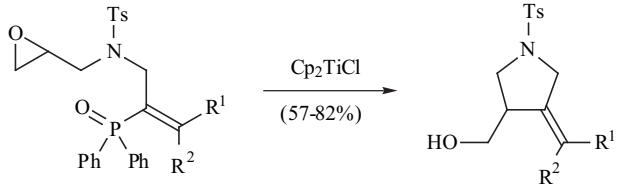



**Scheme 7**. Titanocene(III)-promoted cyclisation of epoxy-nerolidyl acetate [23].

give exocyclic alkenes or reduction products by simply excluding or adding water to the medium (Scheme **6**). Cascade cyclisations promoted by stoichiometric quantities of titanocene [23], however, require high dilution conditions to avoid the premature trapping of intermediate radicals by an excess of $Cp_2TiCl$ that results in decreased yields. As we shall see later, this drawback is circumvented and the yields are improved considerably by using the catalytic version of the process [22].

With a judicious placement of double bonds and an acetate group in the starting material (mimicking for example that of natural nerolidyl pyrophosphate), stoichiometric amounts of titanocene can be also employed to achieve tandem 6-*endo*/7-*endo* cyclisations (Scheme **7**) [23]. There is, as yet, no clear explanation for this unusual cyclisation mode but it is possible that the steric hindrance introduced by the tertiary acetate group helps to retard the alternative 6-*exo* process. In any case, the yield of nearly 50% can be regarded as satisfactory, especially when compared to that of the simple 7-*endo* cyclisation depicted in Scheme **4**.

Titanocene(III)-mediated intramolecular vinylations based upon the elimination of β-phosphinoyl radicals have recently been reported by Leca *et al.* [24]. The procedure, which is new to organic synthesis, has proved to be useful in synthesising alkylidenepyrrolidines (Scheme **8**).

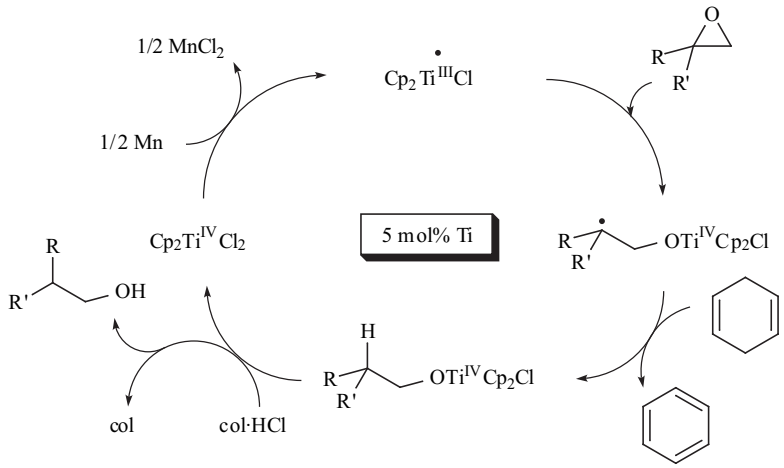



**Scheme 8**. Titanocene-mediated preparation of alkylidenepyrrolidines [24].

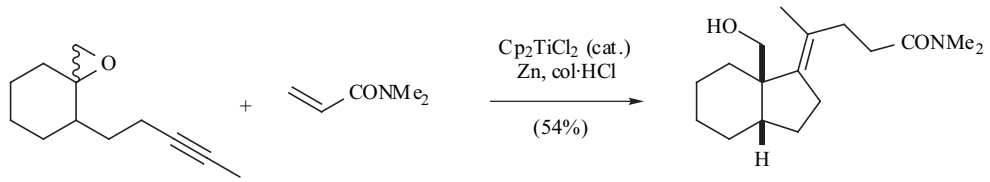
## 3. TITANOCENE(III)-CATALYSED EPOXIDE OPENING

In 1998, ten years after the pioneering report by Nugent and RajanBabu [5a], Gansäuer *et al.* described the first catalytic procedure to achieve homolytic epoxide openings [6]. Their method was based on regenerating the pre-catalyst $Cp_2TiCl_2$ by protonating the titanium-bound oxygen atom. Subsequent *in situ* reduction by the stoichiometric reductant (Mn or Zn) once more gives the active titanium(III) complex, and closes the catalytic cycle (Scheme **9**). The acid employed in this process must be weak enough not to open the epoxide in a heterolytic form, but strong enough to protonate O-$Ti^{IV}$ bonds [6c]. The authors anticipated that Brønsted acids, with an interval of $pK_a$ values between 5.25 and 12.5, would be suitable. In fact, both pyridine hydrochloride and 2,6-lutidine hydrochloride proved to be capable of maintaining the catalytic cycle, but it was 2,4,6-collidine hydrochloride (col·HCl) ($pK_a$ = 7.43) which gave the best results [6].

This titanocene-catalysed procedure was immediately extended by Gansäuer *et al.* to the enantioselective opening of *meso*-epoxides employing substoichiometric quantities of titanocene complexes with chiral ligands [25]. It has also been applied in racemic form not only for reductive epoxide openings [6, 26] and intermolecular additions to α,β-unsaturated carbonyl compounds [6, 27], but also to achieve 3-*exo* [19a], 4-*exo* [19a] and 5-*exo* cyclisations [6, 28], as well as tandem cyclisation addition reactions featuring vinyl radicals (Scheme **10**) [29].




**Scheme 9.** Titanocene-catalysed reductive epoxide opening [6, 7a].



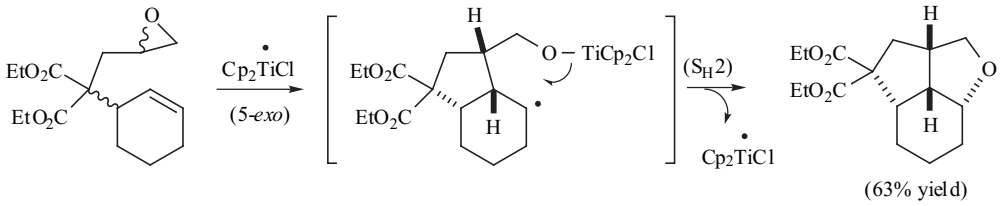

**Scheme 10**. Titanocene-catalysed tandem reactions with alkynes in EtOAc [29].

Another novel titanocene-catalysed tandem reaction reported by Gansäuer *et al.* provides a straightforward way of synthesising structurally complex tetrahydrofurans in only one step (Scheme **11**) [30]. In the final step of the process a homolytic, concerted substitution reaction ($S_H2$) closes the tetrahydrofuran ring and regenerates the [$Ti^{III}$] catalyst.

When we assayed col·HCl as the titanocene-regenerating agent for achieving a catalytic version of the transannular cyclisation of epoxygermacrolidesn [31], instead of the desired excocyclic alkene **3**, we obtained a high proportion of the reduction product **2**, presumably deriving from the protonation of an intermediate C-$Ti^{IV}$ bond (Scheme **12**).

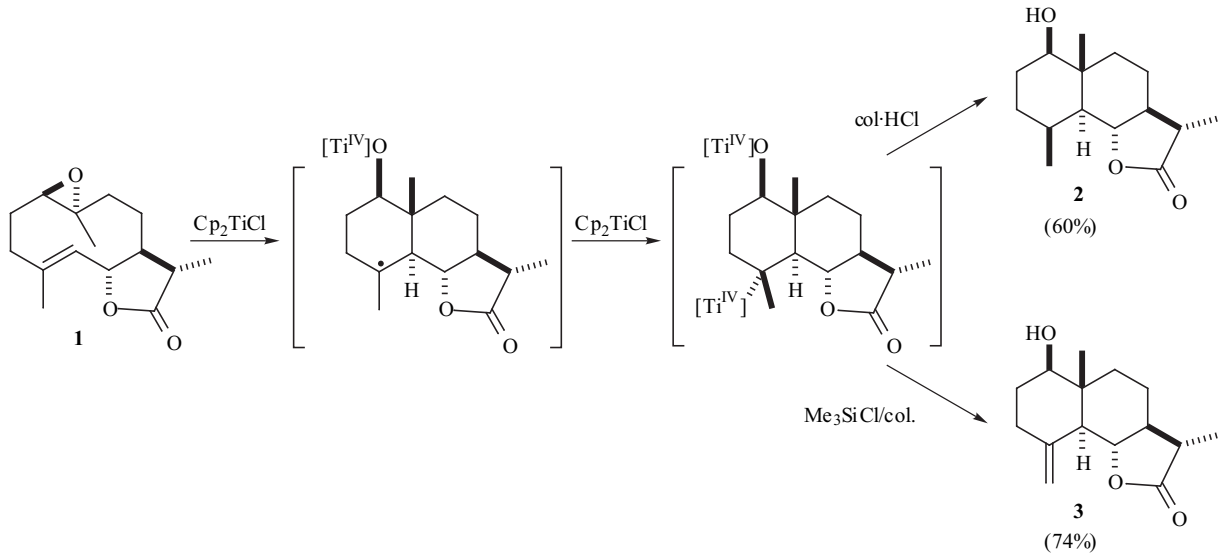
To avoid this undesired background we introduced a new titanocene-regenerating agent, the combination of $Me_3SiCl$ and 2,4,6-collidine (col.), which presumably generates *in situ* the non-protic reagent 2,4,6-trimethyl-1-trimethylsilylpyridinium chloride, which is both compatible with epoxides and capable of regenerating $Cp_2TiCl_2$ not only from oxygen-bound titanium atoms, including $Cp_2Ti(Cl)OAc$, but also from $Cp_2Ti(Cl)H$ formed by β-hydride elimination reactions from alkyl-$Ti^{IV}$ complexes towards alkenes. Therefore, as we expected, the titanocene-catalysed cyclisation of **1** with this novel reagent gave improved proportions of exocyclic alkene **3** (Scheme **12**) [31].

The combination $Me_3SiCl$/col. has also proved to be a suitable regenerating agent for titanocene-catalysed cascade cyclisations of epoxypolyprenes. Thus the catalytic cyclisation of epoxyfarnesyl acetate (**4**) (Scheme **13**) [22], for example, provided substantially increased yields of alkene **5** (40% *versus* the 25% obtained by the stoichiometric version) whilst employing lower titanocene proportions and dilution levels by one and two orders of magnitude respectively.

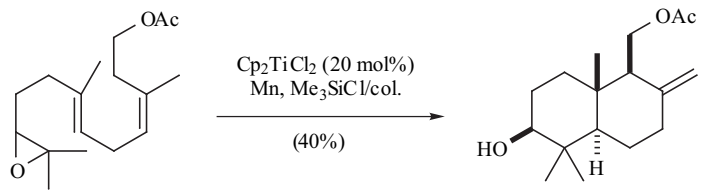



**Scheme 11**. Formation of tetrahydrofurans by a novel radical tandem cyclisation [30].

Finally, Fuse *et al.* proposed recently the use of $Et_3B$ together with 2,6-lutidine hydrochloride or 2,4,6-collidine hydrochloride to improve the capacity of the system for regenerating titanocene(III) from $Cp_2Ti(Cl)H$ in the [$Ti^{III}$]-catalysed cyclisation of 6,7-epoxygeranyl acetate [32].




**Scheme 12.** Titanocene-catalysed transannular cyclisation of epoxygermacrolides [31].

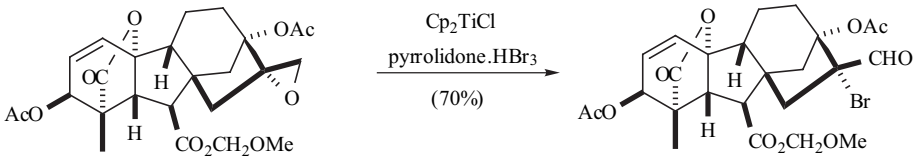



**4** **5**

**Scheme 13**. Titanocene-catalysed cyclisation of epoxy-farnesyl acetate [22].

## 4. STOICHIOMETRIC TITANOCENE IN THE SYNTHESIS OF NATURAL PRODUCTS

Methods for synthesising complex natural products require selectivity, mild experimental conditions and wide functional group tolerance. Titanocene(III)-promoted epoxide deoxygenations have been demonstrated to conform to these requirements in two especially relevant cases: the chemical correlation between cryptophycin-23 and cryptophycin-45 [33] and the synthesis of anhydrovinblastine from leurosine [34]. Moreover, titanocene-mediated reductive epoxide openings, using hydrogen-atom donors such as 1,4-cyclohexadiene or *t*-BuSH, have been the key step in the total synthesis of natural δ-lactones found in *Cryptocarya latifolia* [14h], (+)-prelactone B [14m], (+)-prelactone C [14k], and oxygenated segments of rhizoxin [14c], taxol [14d], and epothilones [14g]. Bhaskar and Mander used the titanocene-promoted opening of epoxide **6** in the presence of pyrrolidone hydrotribromide to obtain α-bromoaldehyde **7**, a crucial intermediate in the synthesis of the biologically potent gibberellin $GA_{32}$ [35].




**6** **7**

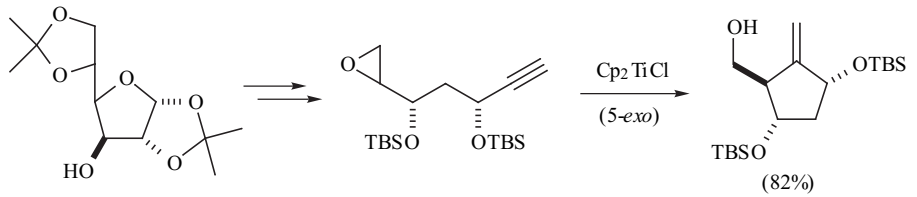
**Scheme 14**. Titanocene-promoted synthesis of bromoaldehyde **7** [35].

Titanocene-induced 5-*exo* cyclisations have been used by Clive, Magnuson *et al.* in the preparation of (±)-ceratopicanol and related sesquiterpenoids [36] and have been intensively exploited by Roy *et al.* for the total synthesis of antibiotic butyrolactones, such as (±)-methylenolactocin and (±)-protolichesterinic, (±)-dihydroprotolichesterinic and (±)-roccellaric acids [37], as well as furano- and furofuran-lignans, including (±)-sesamin, (±)-dihydrosesamin, (±)-acuminatin, (±)-eudesmin, (±)-lariciresinol, (±)-pinoresinol, (±)-piperitol, (±)-acuminatin methyl ether, (±)-sanshodiol methyl ether, (±)-piperitol methyl ether, (±)-pinoresinol monomethyl ether, (±)-lariciresinol monomethyl ether and (±)-lariciresinol dimethyl ether [38]. More recently Ziegler and Sarpong used a titanocene-promoted 5-*exo* cyclisation for the synthesis of a protected carbocyclic core of BMS-200475 (entecavir) (Scheme **15**), a nucleoside active at the nanomolar level against the hepatitis B virus [39].

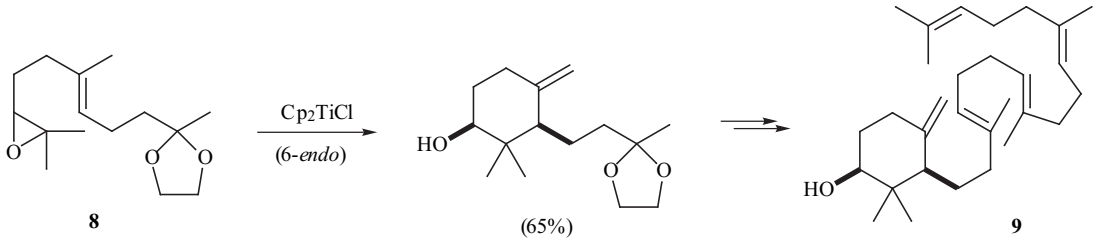
Titanocene-mediated simple 6-*endo* cyclisation of epoxygeranyl acetate was used by Takahashi *et al.* in the preparation of synthons for building the A and C rings of paclitaxel [40], and a similar cyclisation of epoxygeranylacetone derivative **8** by us for the first synthesis of achilleol A (**9**) (Scheme **16**) [41]. Thus, it was possible to confirm the chemical structure of this unusual monocyclic triterpenoid more than ten years after its discovery [42]. Interestingly, achilleol A has been recently found among the products obtained from the incubation of (3*S*)-2,3-oxidosqualene with a Gly600-deletion mutant of the enzyme squalene cyclase from *Alicyclobacillus acidocaldarius* [43].

Grande *et al*. have studied the titanocene-promoted intramolecular addition of epoxides to activated alkenes in both 5-*exo* and 6-*endo* cyclisation modes as a new way of preparing polycyclic β-lactam antibiotics [44].

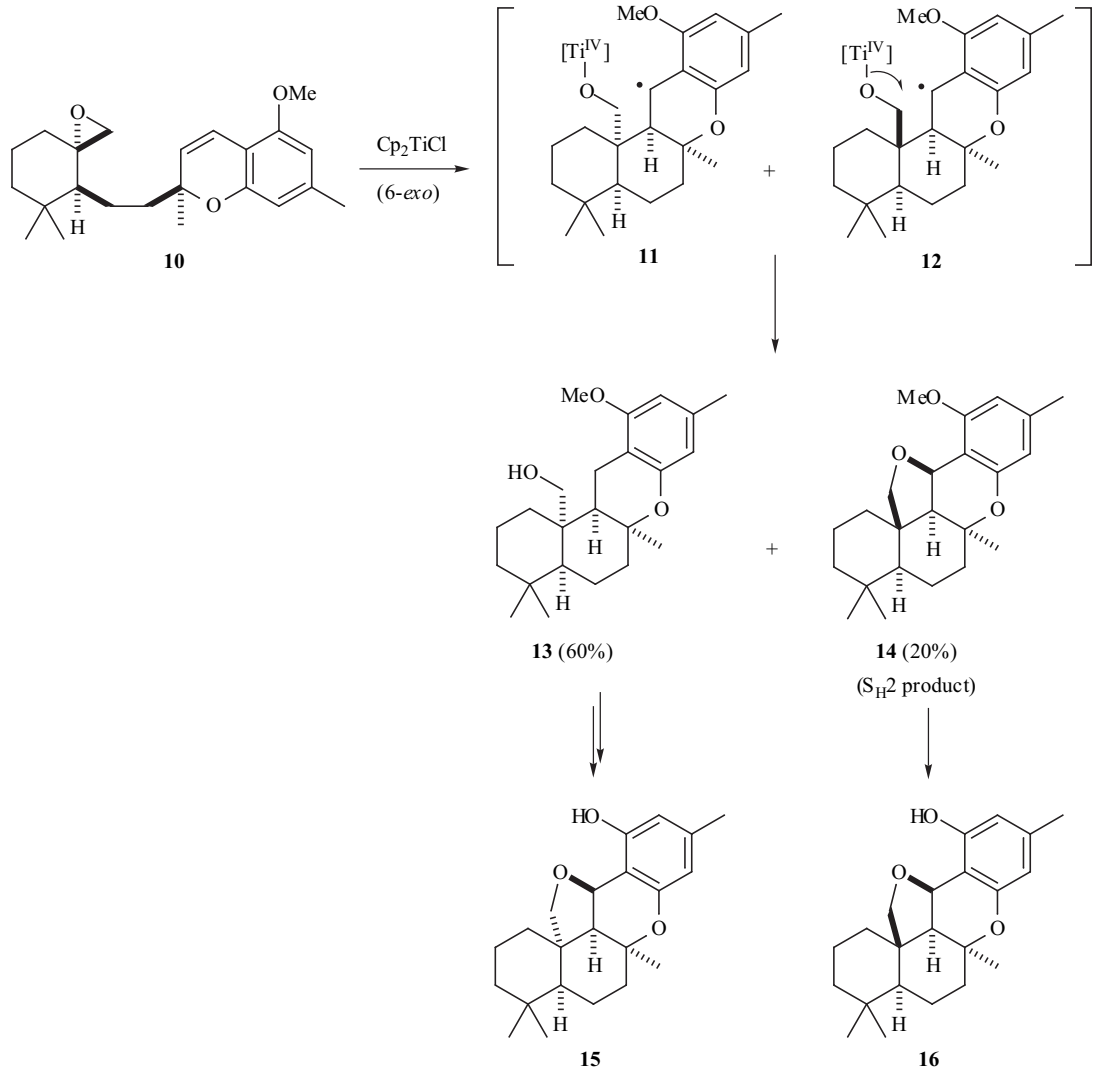
Trost *et al.* have exploited the titanocene(III)-promoted 6-*exo* cyclisation of **10** to **13** for the first enantioselective biomimetic total synthesis of the antifungal metabolite (-)-siccanin (**15**) (Scheme **17**) [45]. These authors also observed a minor amount (20%) of by-product **14**, presumably derived from the radical intermediate **12** by a process reminiscent of the $S_H2$ reaction described by Gansäuer's group [30]. They took advantage of **14** for the preparation of (-)-5-epi-siccanin (**16**) [45].



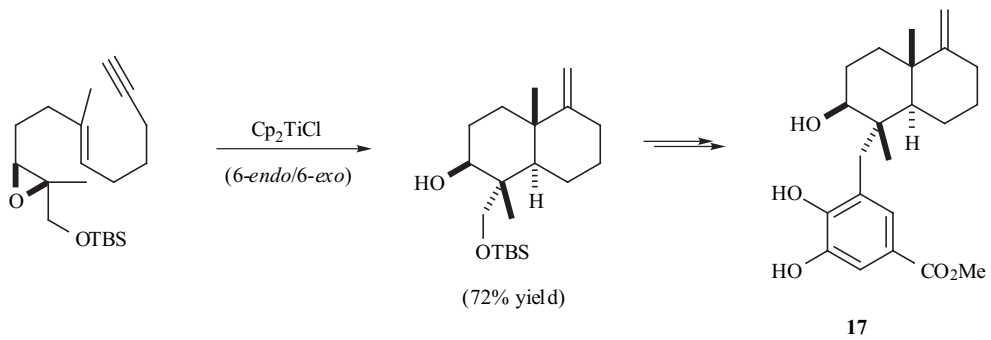

**Scheme 15**. Synthesis of a protected carbocyclic core of entecavir from D-diacetone glucose [39].



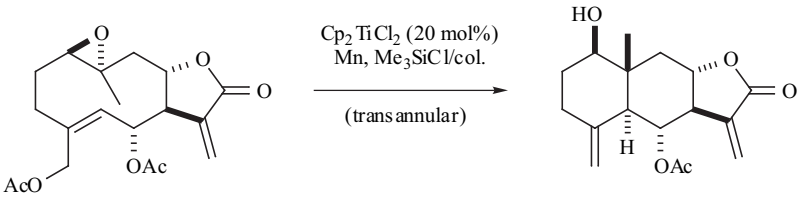

**Scheme 16**. Titanocene-mediated synthesis of achilleol A [41].




**Scheme 17**. Titanocene-promoted synthesis of (-)-siccanin (**15**) and (-)-5-epi-siccanin (**16**) [45].




**Scheme 18**. Titanocene-promoted tandem cyclisation in the synthesis of smenospondiol [46].




**18** (47%)

**Scheme 19**. Titanocene-catalysed synthesis of (+)-β-cyclopyrethrosin [31].

Stoichiometric quantities of $Cp_2TiCl$ were used by Haruo *et al.* to initiate a stereoselective tandem 6-*endo*/6-*exo* cyclisation employed for the total synthesis of the sesquiterpenoid (±)-smenospondiol (**17**) (Scheme **18**) [46].

## 5. TITANOCENE(III)-CATALYSED SYNTHESIS OF EUDESMANOLIDES

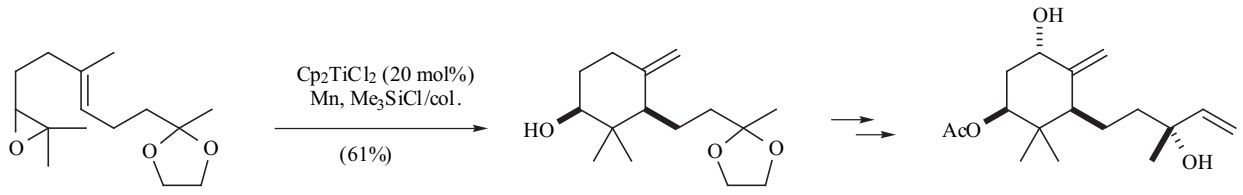
Our group found that the titanocene(III)-mediated transannular cyclisation of 1,10-epoxycostunolide, a homochiral material accessible in (multi)gram quantities, provides an straightforward way for the enantiospecific synthesis of eudesmanolides such as (+)-reynosin and (+)-3α-hydroxyreynosin [20]. We have also taken advantage of the $Me_3SiCl$/collidine combination as a titanocene-regenerating agent for developing a catalytic version of this method [31]. Thus we have been able to synthesise eudesmanolides with an exocyclic double bond such as (+)-9β-hydroxyreynosin or (+)-β-cyclopyrethrosin (**18**) using only substoichiometric proportions of commercial $Cp_2TiCl_2$ (Scheme **19**) [31]. We have also developed an improved synthetic procedure for the biologically active eudesmanolide (+)-tuberiferine [31].

## 6. TITANOCENE(III)-CATALYSED RADICAL CASCADE CYCLISATIONS IN THE SYNTHESIS OF TERPENOIDS

The increasing demand for selectivity and atom and step economy in organic synthesis will presumably have a decisive influence on the strategies employed by chemists in coming years [47]. The biosynthesis of lanosterol from squalene fits these requirements admirably, taking place as it does in only two steps: the enantioselective epoxidation of squalene followed by the stereoselective cascade cyclisation of 2,3-oxidosqualene, only one proton being lost during the process (to form the double bond at Δ[8]) [48]. Mimicking this natural transformation, Goldsmith, van Tamelen, and Corey, among others, have exploited the acid-induced cascade cyclisation of epoxypolyprenes as a powerful procedure in the construction of polycyclic terpenoids *via* carbocationic chemistry [49]. This method involves certain drawbacks, however, such as the need to attach "extra" groups to the polyene substrate to stabilize carbocationic intermediates and control termination steps, and the difficulty of synthesising compounds containing seven-membered rings which are relatively widespread among natural products. An alternative concept, radical cascade cyclisation, introduced by Breslow and Julia more than thirty years ago [50], has also proved to be an excellent method for the stereoselective synthesis of polycyclic compounds from different acyclic precursors [51]. To the best of our knowledge, however, this concept was never applied to the cyclisation of epoxypolyprenes during the last century, probably due to the lack of a suitable protocol for the radical opening of epoxides. The titanocene(III)-based procedure [5] and its catalytic versions [6, 31, 32] have catered for this need, thus opening up the possibility of mimicking the enzyme lanosterol synthase *via* free-radical chemistry. We have taken advantage of this radical-based biomimetic procedure for the straightforward synthesis of different terrestrial and marine terpenoids with various carbocyclic skeletons [22,52].

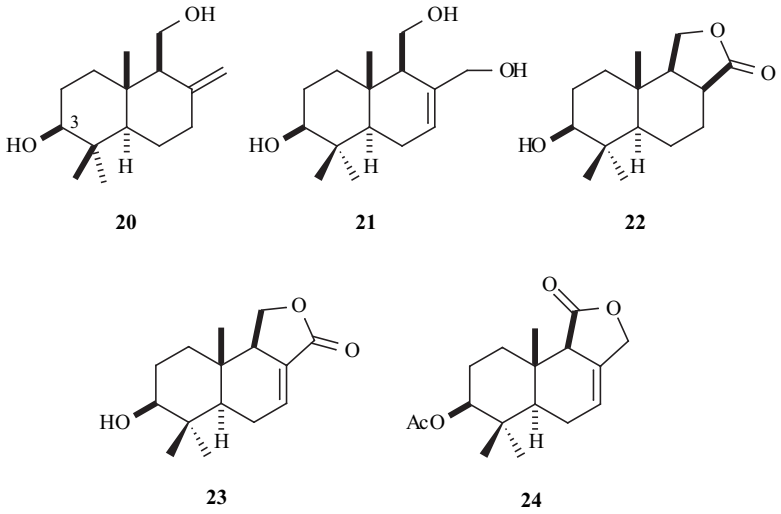
In this way, we have prepared monocyclic sesquiterpenoids, such as the metabolite **19** found in the fragrant plant *Artemisia chamaemelifolia* [53] (Scheme **20**), and monocyclic triterpenoids such as achileol A (**9**), starting from epoxygeranylacetone derivative **8** [22].

Drimanes constitute a family of bicyclic sesquiterpenoids with interesting biological properties [54]. The titanocene-catalysed 6-*endo*/6-*endo* tandem cyclisation of epoxyfarnesyl acetate (**4**) stereoselectively gave bicyclic intermediate **5** (Scheme **13**) which proved to be a suitable precursor for the total synthesis of 3-hydroxy-drimanes with different functionalization patterns, including (±)-isodrimenediol (**20**), triol **21**, (±)-3β-hydroxydihydroconfertifolin (**22**), (±)-3β-hydroxycinnamolide (**23**) and (±)-3β-acetoxydrimenin (**24**) (Scheme **21**) [22, 52c]. Interestingly, synthetic **22** showed antifeedant activity against the insect *Leptinotarsa decemlineata*, whereas the conjugated γ-lactone **23** was active against *Myzus persicae* [52c].




**8** **19**

**Scheme 20.** Titanocene-catalysed synthesis of **19** [22].

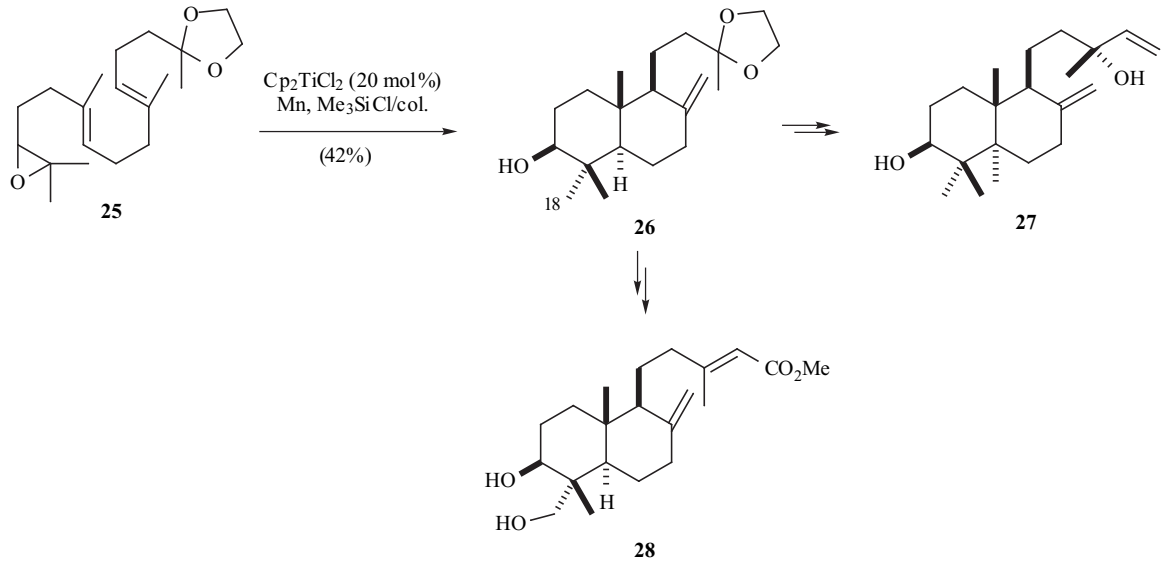


**Scheme 21**. Drimanes synthesised by titanocene-catalysed 6-*endo*/6-*endo* cyclisation of **4** [22, 52c].

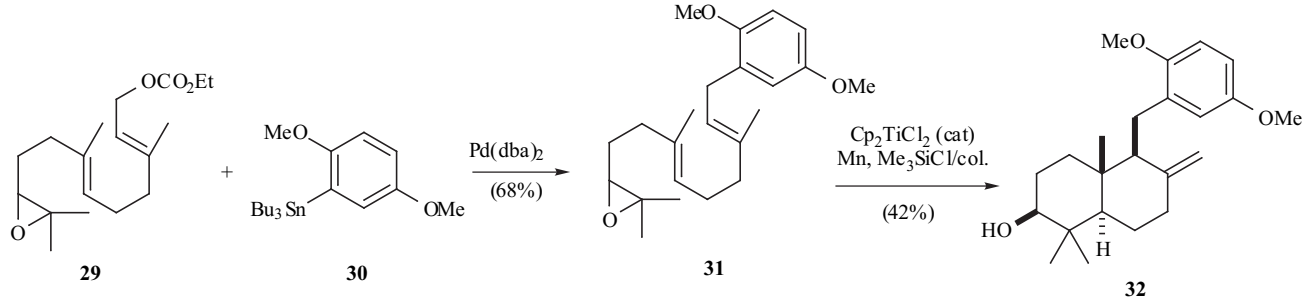
Furthermore, the titanocene-catalysed 6-*endo*/6-*endo* cyclisation of epoxyfarnesylacetone derivative **25** led to the first total synthesis of (±)-3β-hydroxymanool (**27**) (Scheme **22**) [22], a bicyclic diterpenoid with a labdane skeleton from the fern *Gleichenia japonica* [55].

The subsequent palladium-mediated, long-range functionaliztion of the C-18 methyl group of **26** allowed the first synthesis of (±)-rostratone (**28**) (Scheme **22**) [52a], a labdane diterpenoid with a characteristic γ-dioxygenated system on ring A, found in the Chilean plant *Nolana rostrata* [56].

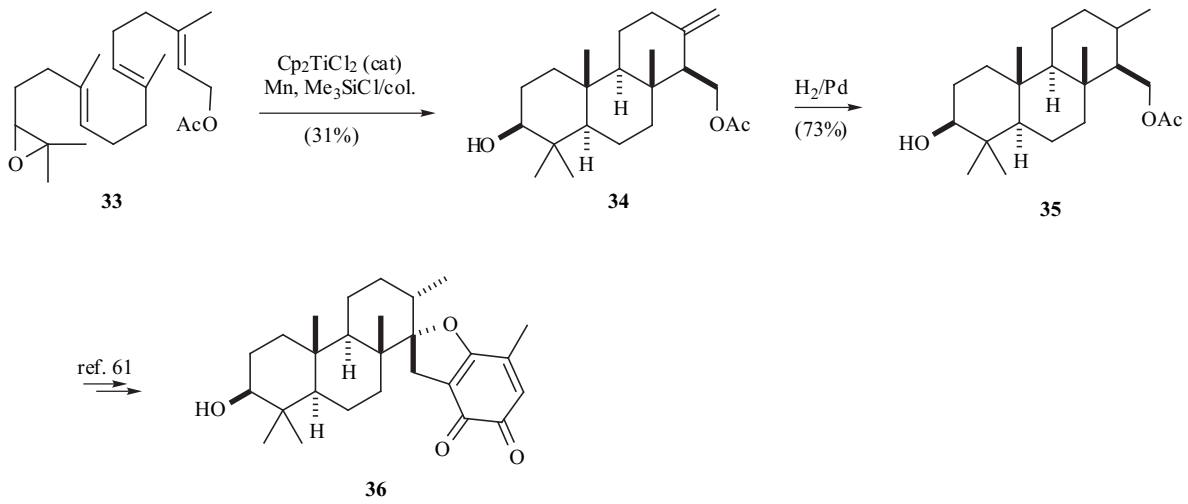
The term "meroterpenoids" is generally used to denote a wide range of natural products of mixed (polyketide-terpenoid) biogenesis [57]. The titanocene-catalysed 6-*endo*/6-*endo* cyclisation of **31**, obtained by Stille coupling between carbonate **29** and stannane **30**, stereoselectively gave



**Scheme 22**. Titanocene-catalysed synthesis of (±)-3β-hydroxymanool and (±)-rostratone [22, 52a].



**Scheme 23**. Synthesis of **32** based on Stille couplings and titanocene catalysis [52b].




**Scheme 24.** Titanocene(III)-catalysed formal synthesis of stypoldione [22].

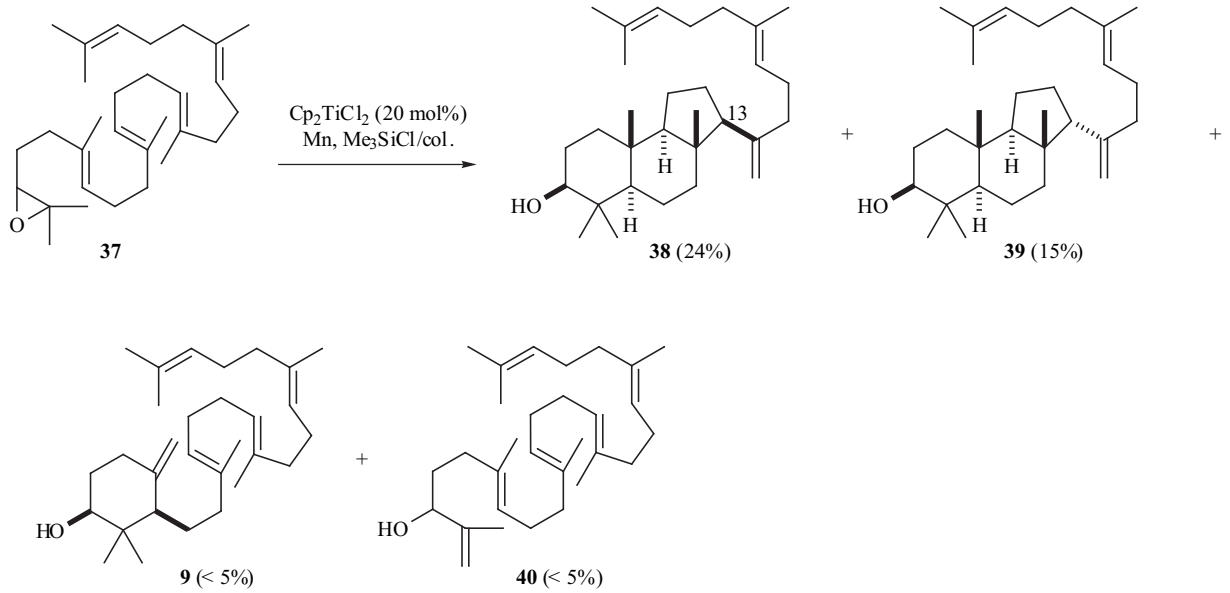
**32** [52b], an intermediate closely related to the marine meroterpenoid zonarol [58]. Interestingly, the aromatic ring of **31** and its oxygenated groups proved to be inert against the carbon-centered radicals formed during the cyclisation process [52b]. This is in contrast to what occurred in previously described cascade cyclisations towards meroterpenoids *via* carbocationic chemistry [59].

The marine metabolite stypoldione (**36**) has attracted the attention of chemists owing both to its pharmacological properties [60] and its challenging chemical structure. Xing and Demuth have recently reported an elegant synthesis of **36** *via* the tricyclic intermediate **35** [61].

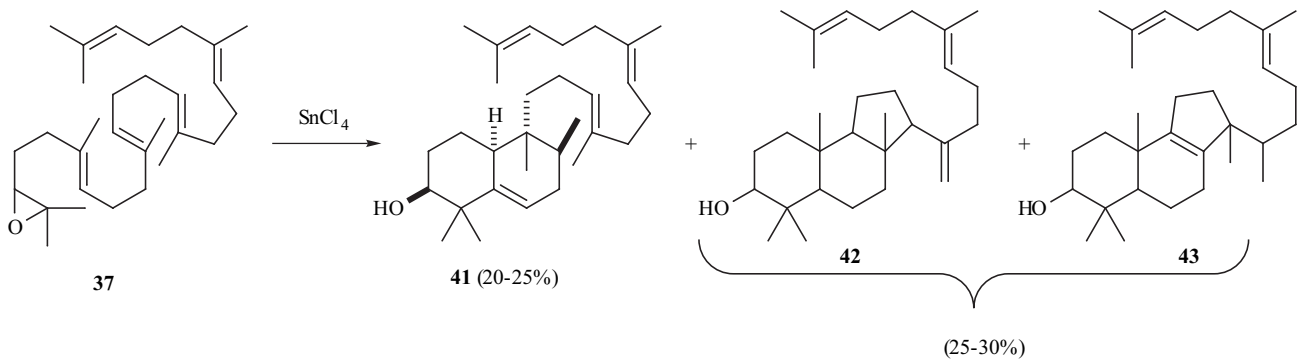
In our laboratory the titanocene-catalysed 6-*endo*/6-*endo*/6-*endo* cascade cyclisation of epoxypolyene **33**, prepared from commercial geranylgeraniol [62], gave tricyclic alkene **34** in a moderate yield of 31% [22], which can nevertheless be regarded as satisfactory when bearing in mind that the reaction selectively afforded a product (**34**) containing three fused (*trans*/*anti*/*trans*) six-membered rings, an exocyclic double bond and six stereogenic centres among more than 190 potential regio and stereoisomers. The catalytic hydrogenation of **34** gave **35** and thus the formal synthesis of stypoldione was completed [22].

Finally, the possibility of achieving the first radical cyclisation of 2,3-oxidosqualene (**37**), the known biogenetic precursor of sterols and pentacyclic triterpenoids in animals, fungi and plants [48], encouraged us to treat it with a catalytic quantity of titanocene [22]. In this case, the cascade cyclisation proceeded in a 6-*endo*/6-*endo*/5-*exo* manner, giving a mixture of malabaricane **38** and its C-13 epimer **39** (39% combined yield), together with minor amounts of achilleol A (**9**) and the acyclic alcohol **40** (Scheme **25**).

In contrast, the acid-induced carbocationic cyclisation of **37**, previously reported by van Tamelen, Sharpless and co-workers [63], gave a mixture containing bicyclic (**41**) and tricyclic products (**42** and **43**, stereochemistry not specified in the original paper) as the major components (Scheme **26**). These results suggest that in the carbocationic process the




**Scheme 25**. Titanocene(III)-catalysed cyclisation of 2,3-oxidosqualene [22].




**Scheme 26**. Acid-induced cyclisation of 2,3-oxidosqualene [63].

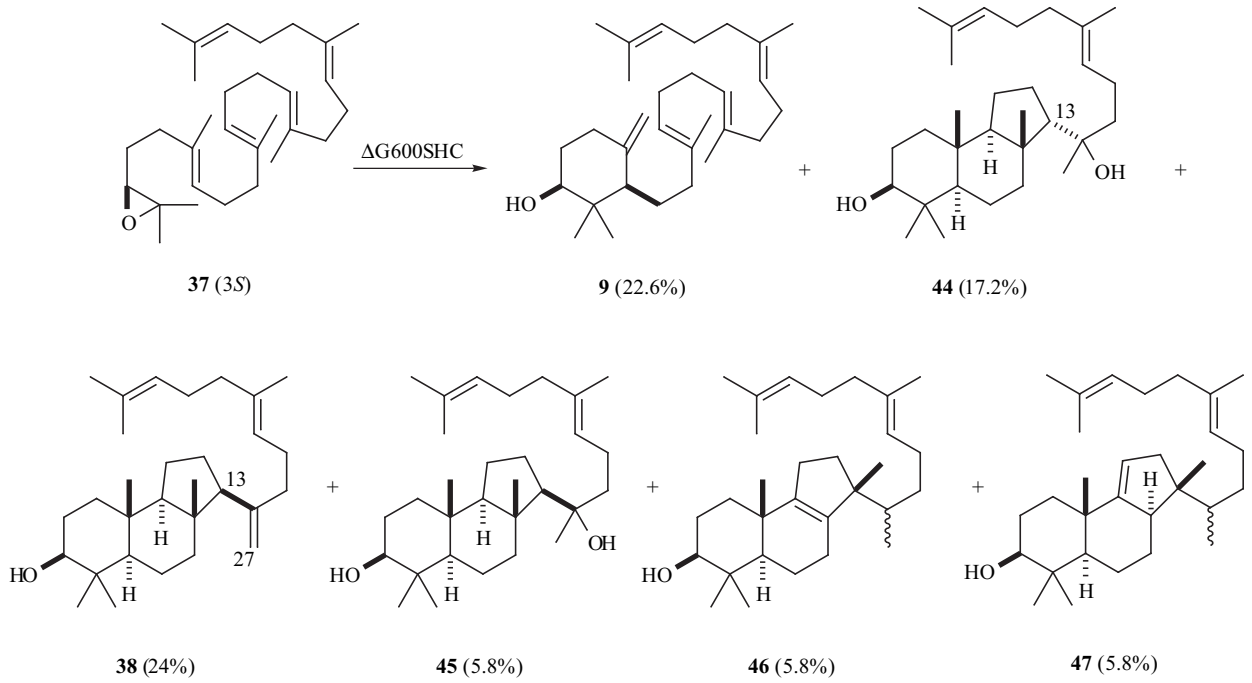
second 6-*endo* cyclisation is relatively fast but the third 5-*exo* cyclisation is quite slow. Thus, formation of the bicyclic rearranged compound **41** is allowed whereas that of monocyclic products is avoided. In the radical process, however, the second 6-*endo* cyclisation seems to be relatively slow and the third 5-*exo* cyclisation fairly fast, thus allowing the formation of monocyclic achilleol A (**9**) and avoiding bicyclic products. In other words, there are subtle but significant differences between the kinetics of radical and carbocationic cyclisations of 2,3-oxidosqualene that are reflected in the skeletal profile of the products obtained (monocyclic and tricyclic skeletons in the former case *versus* bicyclic and tricyclic ones in the latter).

In this context Hoshino *et al.* have very recently reported the cyclisation of (3*S*)-2,3-oxidosqualene catalysed by a Gly600-deletion mutant (ΔG600SHC) of the enzyme squalene-hopene cyclase (SHC) from *Alicyclobacillus acidocaldarius* (Scheme **27**) [43].

The enzymatic biotransformation gave monocyclic (**9**) and tricyclic triterpenoids (**38** and **44**-**47**), but no detectable bicyclic products. Despite the authors' biogenetic proposal of a conventional carbocationic pathway [43], the skeletal profile of the biotransformation products reported closely resembles that expected for a radical-type cyclisation.

## 7. CONCLUSIONS

Since the discovery of titanocene(III)-mediated radical epoxide opening, both stoichiometric and catalytic versions of the method have been used in the synthesis of about fifty natural products and advanced synthons. At first, owing to its selectivity and the extremely mild experimental conditions employed, the procedure was chosen for deoxygenation and reductive epoxide opening on densely functionalised substrates but during the past years it has been increasingly employed to achieve radical cyclisations, affording straightforward strategies for the synthesis of complex natural products. In these fields the method has already largely proved its synthetic usefulness. Nevertheless, titanocene-mediated intermolecular additions of epoxides to activated olefins, 7-*endo* cyclisations and some recent findings such as the Gansäuer's tetrahydrofuran reaction,




**Scheme 27**. 2,3-Oxidosqualene cyclisation catalysed by a mutated squalene cyclase [43].

have as yet been scarcely applied. It is presumably, however, that these promising titanocene-based transformations will be demonstrated to be powerful synthetic tools in the near future.

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