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First synthesis of achilleol A using titanium(III) chemistry

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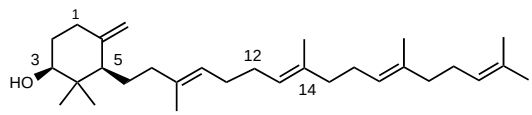
Abstract—Described herein is a straightforward synthesis of the monocyclic triterpene achilleol A using as key step titanium(III) chemistry. This synthesis confirms the previously described structure based on spectroscopic methods. © 2002 Elsevier Science Ltd. All rights reserved.

Achilleol A (**1**), the first monocyclic triterpenoid found in the nature, was originally isolated from *Achillea odorata*, where it occurs together with achilleol B (**2**).[1,2] Achilleol A and some esterified derivatives have subsequently been found in other plants belonging to different families (Umbelliferae,[3] Theraceae,[4] Asteraceae[5] and Gramineae[6]), suggesting that it may be a relatively widespread metabolite within the plant kingdom. The chemical structure of achilleol A (achillane skeleton) points to a biosynthesis based on an unusual monocyclization of 2,3-oxidosqualene. This hypothesis is supported by the finding of **1** among the products formed from 2,3-oxidosqualene via the action of a mutant oxidosqualene cyclase.[7,8] Nevertheless, achilleol A co-occurs with the structurally related sesquiterpenoid elegansidiol (**3**) in *Santolina elegans*,[5] and so other biosynthetic pathways cannot be ruled out. Therefore, doubts concerning the biosynthesis of **1** and its potential relationship with the mechanism of metabolic cyclizations catalyzed by oxidosqualene cyclases remain unanswered. In fact the coexistence of achilleol A together with achilleol B, the bicyclic structure of which is identical to that of the D and E rings of some pentacyclic triterpenes (oleanane skeleton), may well provide evidence for a non-concerted mechanism for triterpene cyclases.[2,9]

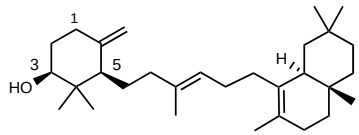
The structure and relative stereochemistry of achilleol A were both established in 1989 by spectroscopy[1] but since then the chemical synthesis of **1** has remained unpublished despite biological interest in this compound. We have carried out the stereoselective synthesis of **1** to confirm the arrangement of the isoprene units in the side chain and the relative configuration of the cyclohexanol moiety. The key step in this synthesis relies upon the Cp_2TiCl[10] mediated carbocyclization of epoxypolyprenes,[11] discovered recently in our laboratory (Fig. 1).

Bearing in mind the co-occurrence of **1** and **3** in *S. elegans*, the synthesis of **1** was planned on the basis of a C_{15}+C_{15} convergent strategy (Scheme 1). This strategy could facilitate a further chemical correlation between **1** and (−)-elegansidiol, in order to establish the absolute configuration of natural (−)-achilleol A.[12]

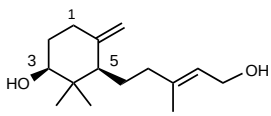
The C_{15} synton **I** (closely related to **3**) has a cyclohexanol ring with an exocyclic double bond and a 1,3-*cis* relationship between the hydroxyl group and the iso-



Achilleol A (**1**)



Achilleol B (**2**)



Elegansidiol (**3**)

Figure 1. Chemical structures of **1**–**3**.

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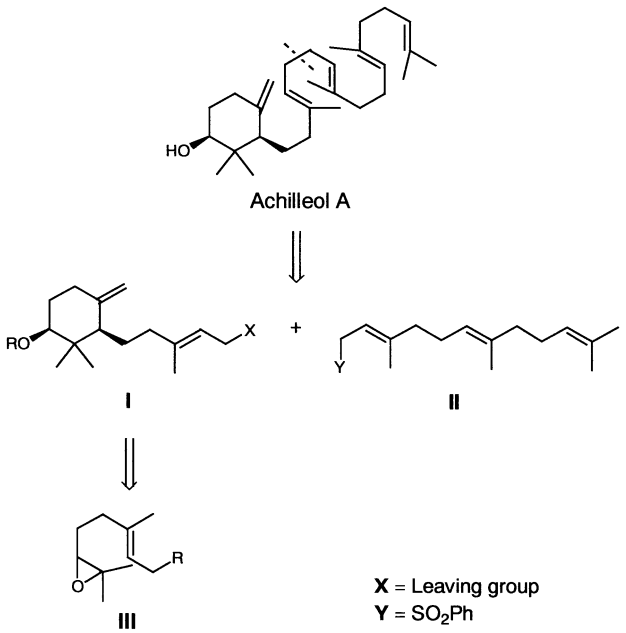


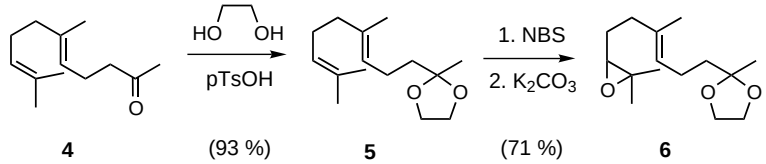
Scheme 1. Retrosynthetic analysis of **1**.

prenoid side chain. This kind of cyclohexanol has previously been prepared by the acid-catalyzed opening of 6,7-epoxygeranyl derivatives via carbocationic chemistry.[13] Nevertheless, this procedure gives only moderate yields of the desired exocyclic alkene.[14] An alternative to the more usual cationic opening is to use the transition-metal-centered radical Cp_2TiCl,[15] which selectively leads to the 1,3-*cis*-cyclohexanol with the exocyclic double bond.[11] Thus, **I** could be obtained by the free-radical-mediated cyclization of an epoxide such as **III**, followed by the transformations required to introduce an adequate X-leaving group. As far as the second C_{15} synthon **II** is concerned, its close structural relationship with farnesol is evident, and in fact nucleophilic syntons such as **II** have been prepared in the past from commercially available farnesyl chloride.[16]

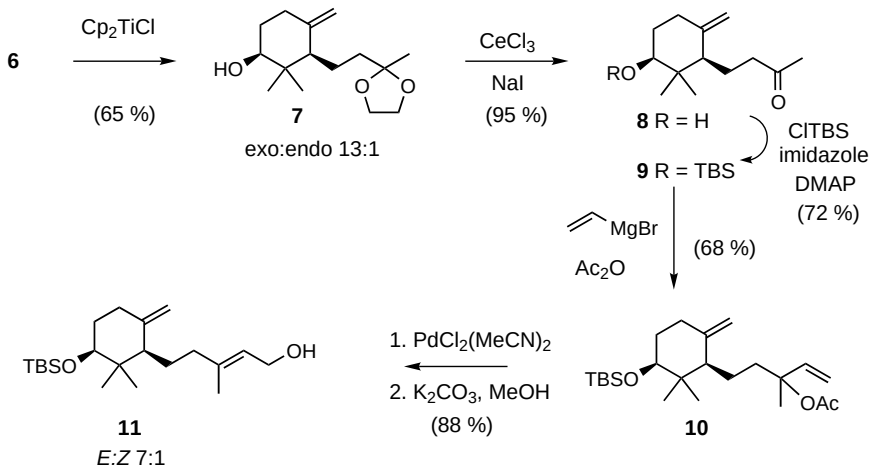
10,11-Epoxyfarnesol might be considered a priori to be an adequate raw material for the synthesis of monocyclic sesquiterpenoids such as **I**, but our previous work has shown that the Ti(III)-promoted rearrangement of 10,11-epoxyfarnesyl derivatives actually leads to bicyclic sesquiterpenoids with a drimane skeleton.[11] Neither did epoxygeranylacetone (**III**, $R = CH_2COCH_3$) prove to be a useful starting material because it also gave bicyclic by-products. We finally obtained satisfactory results with oxirane **6** prepared from geranylacetone (**4**) using the protection of the carbonyl group as an ethylenketal (**5**) and subsequent treatment with aqueous NBS and K_2CO_3 (Scheme 2).[17]

As was foreseen in retrosynthetic Scheme 1, the Cp_2TiCl-mediated cyclization of oxirane **6** gave cyclohexanol **7**,[18] with high degrees of regio- and stereoselectivity (Scheme 3).

Ketone **8** was obtained by treating ketal **7** with $CeCl_3$/NaI in CH_3CN[19] under neutral conditions to avoid any isomerization of the exocyclic double bond. Protection of the secondary alcohol **8** gave the silylether **9**, which was transformed into the elengasidiol derivative **11** (60% overall yield) via a three-step procedure previously developed in our laboratory.[13a] During the second of these steps a catalytic quantity of Pd(II) was



Scheme 2. Synthesis of oxirane **6**.

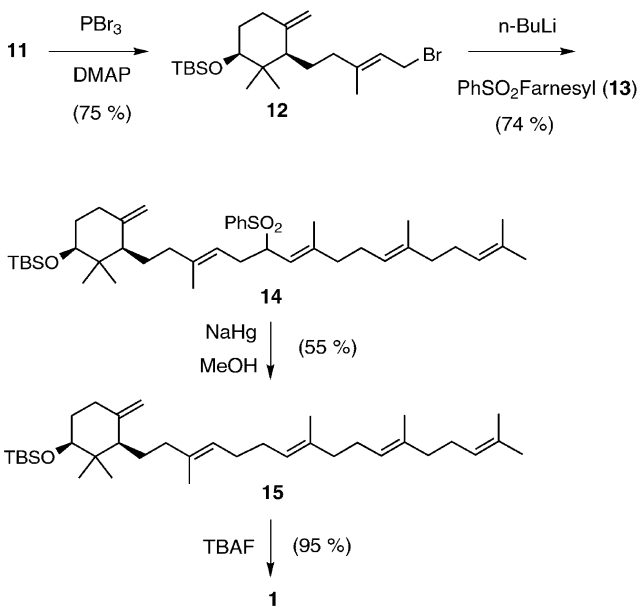


Scheme 3. Stereoselective synthesis of elegansidiol derivative **11**.

used to rearrange the tertiary acetate **10** towards the acetyl derivative of **11**, which was subsequently solvolyzed to the corresponding primary alcohol (**11**), thus obtained as a mixture of 3*E* and 3*Z* isomers at a significant ratio of 7:1 (Scheme 3).

Alcohol **11** was converted into allylic bromide **12** (Scheme 4), which was then used to alkylate the sulfone **13** described above,[16] providing a 75% yield of the polyene **14** (10:1 mixture of 3*E*/3*Z* stereoisomers). This polyene already possesses all the carbon atoms and stereogenic centers present in achilleol A. The desulfonation of **14** gave a mixture of polyprene **15** (55% yield) and a regioisomer (22%) with a double bond at Δ^6 instead of Δ^7. Lastly, achilleol A was obtained from **15** by removing the protective silyl ether with TBAF. MS, ^{1}H and the ^{13}C NMR spectra of synthetic **1** concurred with those of the natural metabolite. A revision of the ^{13}C NMR spectrum of natural achilleol A revealed a mistake in the hitherto reported spectrum:[1] the methyl signal reported at 26.8 ppm in fact resonates at 16.1 ppm.[20]

In summary, we describe here for the first time the synthesis of a monocyclic triterpenoid with an achillane skeleton. This synthesis serves to confirm the structure and relative stereochemistry of achilleol A, which seems to be a relatively widespread metabolite in the plant kingdom. The key step in the synthesis is a free-radical-mediated cyclization of an epoxypolyprene, which provides a highly stereoselective methylencyclohexanol. Our results suggest that this procedure may well prove to be a generally useful method for the synthesis of natural terpenoids and steroids. We are currently working on the enantiospecific synthesis of natural (–)-achilleol A, in order to establish its absolute configuration and also the chemical preparation of achilleol B and other natural terpenoids using free radical chemistry.



Scheme 4. Convergent C_{15}+C_{15} synthesis of achilleol A.

Acknowledgements

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