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First Total Synthesis of (−)-Achilleol B: Reassignment of Its Relative Stereochemistry

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ABSTRACT

The first total synthesis of (−)-achilleol B was achieved using a convergent approach with a longest linear sequence of 14 steps. Three key steps were employed, including an enantioselective Robinson annelation for the construction of the bicyclic moiety. The monocyclic synthon was prepared through a Ti(III)-mediated cylization of a chiral monoepoxide obtained via asymmetric dihydroxylation of geranylacetone. The asymmetric preparation of these subunits also permitted us to achieve the enantioselective synthesis of elegansidiol, achilleol A, and farnesiferol B.

Achilleol B (**1**) is a triterpene isolated in 1990 from *Achillea odorata* (Asteraceae).[1] It possesses a tricyclic skeleton which could be encompass in a group of triterpenes which could be described as irregular. Other examples of these irregular triterpenes are achilleol A (**2**),[2] camelliols C and A (**3** and **4**),[3] preoleanatetraene (**5**),[4] *seco*-oleananes **6** and **7**,[5] and *seco*-amyrins **8** and **9** (Figure 1).[6] All are structurally characterized by possessing less rings than those usually found in the oxidosqualene (OS) cyclizations catalyzed by OS cyclases. Thus, in the case of **2** and **5**, their biosynthesis could be rationalized by considering an incomplete cyclization of OS[7] initiated at the oxirane ring. In this sense, it was recently proven that the *Arabidopsis thaliana* OS cyclase At1g78955 mainly makes camelliol C (**3**) and minor quantities of achilleol A and β-amyrin (**10**) (0.2%).[8] Recently, a new biosynthetic mechanism toward *seco*-triterpenes such as compounds **6**−**9** has been proposed. This new route involves a first cyclization and subsequent rearrangements to the corresponding pentacyclic structure present in the oleanane or ursane skeletons, followed by a retrocyclization process starting from a carbenium ion located at C-13 which

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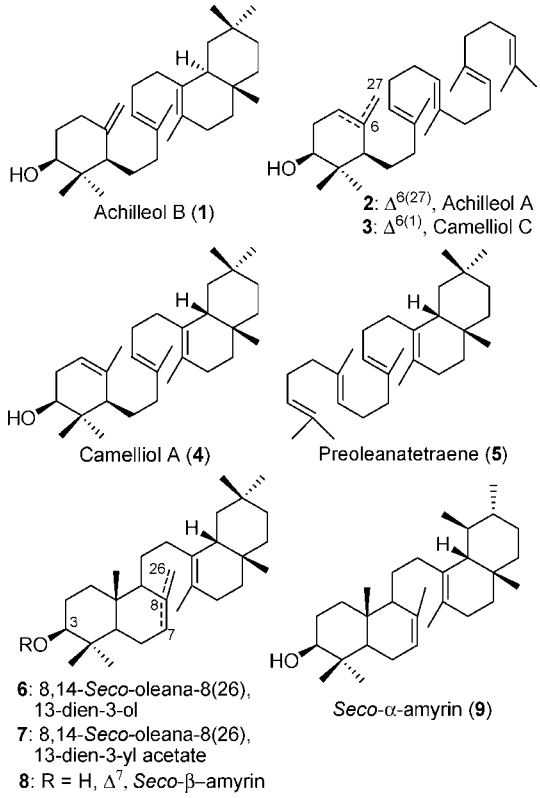


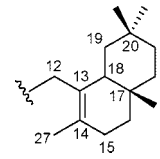
Figure 1. Irregular triterpenes.

would provoke the breaking of the C8−C14 bond.[6] In this sense, a triple rethrocyclization process initiated at the oleanyl cation would account for the biosynthesis of preoleanatetraene (**6**).

Our interest of this kind of molecule, together with the discrepancy observed in the interannular ring junction stereochemistry present in achilleol B and in structures **4**–**9** prompted us to re-examine the stereochemistry assigned to achilleol B.[1] This stereochemistry was initially described as trans due to the lack of NOE effect between the methyl and proton located at the interannular carbons. To help clarify this point, a comparative study of the ^{13}C NMR chemical shifts of the carbons of the bicyclic system present in **4**−**6** and **1** was undertaken.

Following this comparison (Table 1), it was suspected that the actual stereochemistry of the bicyclic system in achilleol B (**1**) was cis. With the aim of both confirming this hypothesis and establishing unambiguously the structure and absolute stereochemistry of achilleol B, the enantioselective synthesis of this compound was addressed. Thus, we anticipated that the tricyclic achillane skeleton might arise from the coupling of two C15 chiral synthons, namely, **A** (nucleophilic where X = phenylsulfone) and **B** (electrophilic with Y = Br) (Scheme 1).

Table 1. ^{13}C Chemical Shifts of the C−D Rings



carbon	achilleol B (**1**)	camelliol A (**4**)	preoleana-tetraene (**5**)	*seco*-C oleanane (**6**)
12	31.6	31.6	31.7	30.8
13	133.7	133.9	133.6	134.3
14	123.9	123.9	123.9	123.5
15	26.6	29.5	29.5	29.5
17	31.4	31.4	31.4	31.5
18	42.3	42.3	42.3	42.9
19	43.0	43.0	43.0	42.9
20	31.0	31.0	31.0	31.0
27	18.6	18.7	18.6	18.8

The syntheses of **A** and **B** were projected in accordance to the absolute configuration found in the normal enantiomeric series in triterpenes, that is, 3*S*,5*R*,17*R*,18*R*; the numbering of the target product was considered. Synthon **A** could be disconnected along the olefin bond through a Horner−Emmons condensation. The enantioselective synthesis of the monocyclic C-13 moiety would involve a radical carbocyclization of the oxirane intermediate **C**. This Cp_2TiCl-mediated reaction would lead to the hoped-for methylenecyclohexanol with the lateral chain possessing the appropriate stereochemistry. Further retrosynthesis of oxirane **C** through an asymmetric dihydroxylation indicated commercially available geranylacetone as a suitable starting material. The use of the premixed catalyst AD-mix-β would originate, after selective mesylation and basic treatment, the 3*S* monoepoxide, which after Ti(III)-induced cyclization should lead to the corresponding 3*S*-hydroxymonocycle.

Once we had the required **A** synthon in hand, the asymmetric synthesis of related natural products such as elengasidiol (**11**),[9] its coumarine derivative farnesiferol B (**12**),[10] and achilleol A **2**[2] could be easily achieved after straightforward transformations.

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(17) Yields obtained in the preparation of B synthon were improved with respect to those obtained in ref 11. In particular, the efficiency in the generation of the alcohol derivative of **23** by reduction of the corresponding α,β-unsaturated ester improves from 79% to 94% yield when DIBALH is used instead of LAH.

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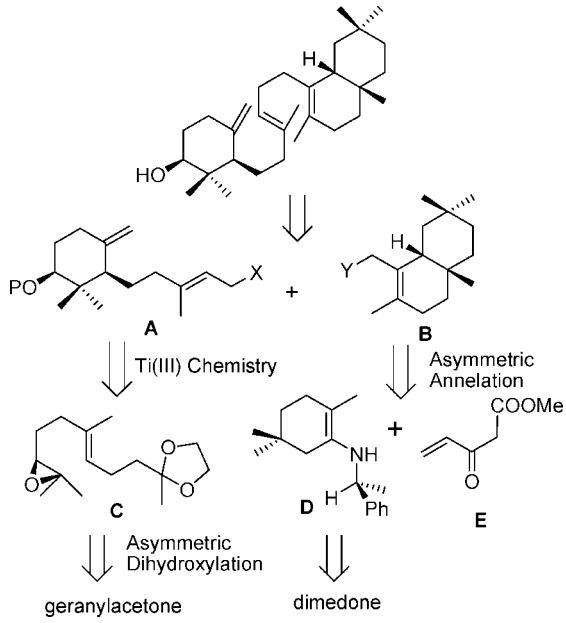
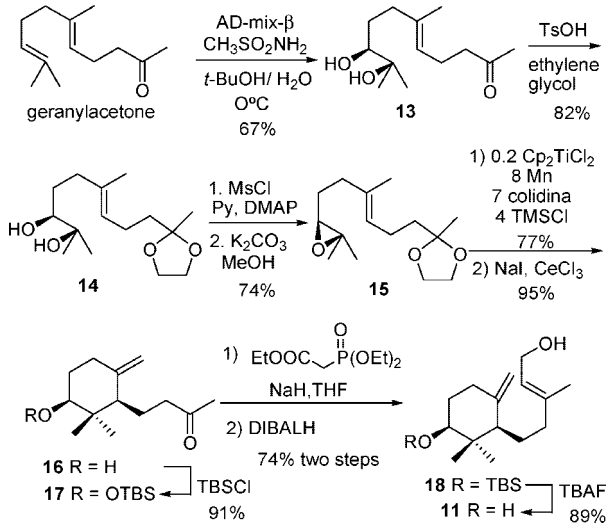
Scheme 1. Rethrosynthetic Analysis for Achilleol B



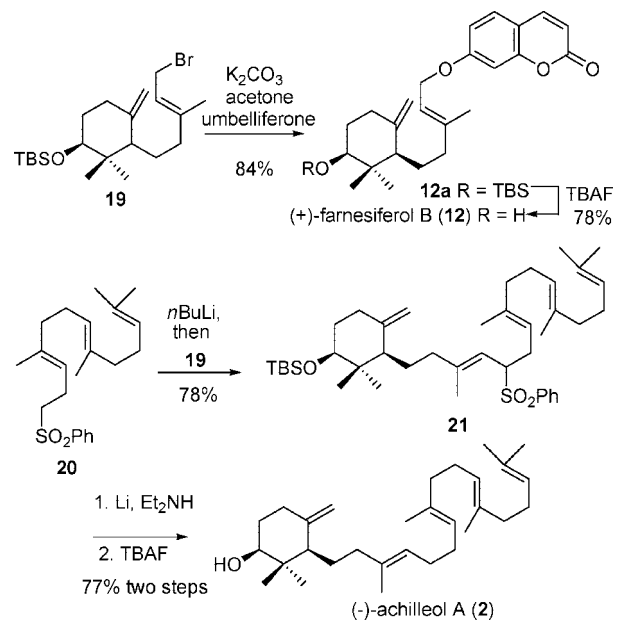
On the other hand, synthon **B** would derive from an interesting enantioselective variant of the Robinson annulation using the Nazarov reagent and a chiral enamine.[11] In this sense, the use of 2*S*-phenylethylamine should permit access to the bicyclic system with the appropriate stereochemistry.

Scheme 2. Synthesis of A Synthon



Sharpless asymmetric dihydroxylation[12] of geranylacetone led, with acceptable selectivity and efficiency, to diol **13**.[13] Protection of the carbonyl group led only to 85% of the ketal **14** (based on recovered starting material). Reaction of diol **14** with mesyl chloride and subsequent treatment with base gave rise to oxirane **15** in 74% global yield. When this epoxide was reacted with 0.2 equiv of Cp_2TiCl_2 and Mn in excess (8 equiv) in the presence of 7 equiv of the Ti(III) regenerator TMSCl-collidine,[14] the cyclization took place efficiently and the monocyclic alcohol was obtained after acid workup. Only the exocyclic isomer was detected. Deprotection of the ketyl group led to ketoalcohol **16**. Application of the Horner−Wadsworth−Emmons protocol to the silyl derivative **17** furnished the requisite two-carbon homologation. The corresponding unsaturated ester was reduced with DIBALH to give **18**, thus completing the synthesis of the **A** synthon. Simple deprotection of the silylether in **18** led to the natural sesquiterpene (−)-elegansidiol (**11**) (Scheme 2).

Scheme 3. Enantioselective Synthesis of (−)-Achilleol A and (+)-Farnesiferol B

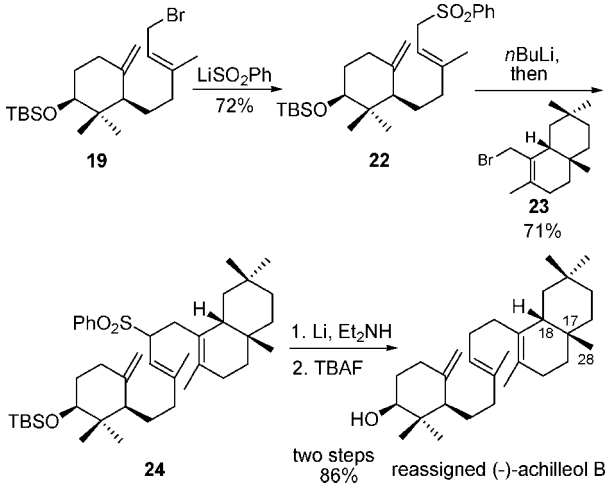


The targeted (−)-achilleol B and (+)-farnesiferol B were efficiently assembled as follows. Alcohol **18** was brominated with PBr_3 to give the allylic bromide **19**. Then, alkylation of the potassium salt of commercial umbelliferone with bromide **19** afforded the silyl ether derivative of farnesiferol B which, after TBAF-mediated deprotection, yielded (+)-farnesiferol B (**11**). On the other hand, and as anticipated, the coupling process between **19** and the lithium derivative from farnesylphenylsulfone (**20**) proceeded smoothly in 78% yield. Reductive elimination of the phenylsulfonyl group using Li-ethylamine and subsequent deprotection of the silyl group with TBAF afforded (−)-achilleol A (**2**) in a yield of 77% for the two steps. Although racemic protocols to farnesiferol B[15] and achilleol A[16] have been reported, our synthesis supposes the first enantioselective preparation of these two natural compounds. These stereocontrolled syntheses proved the absolute configuration of both compounds. In this sense, the stereostructure of natural (+)-farnesiferol B (**12**) is the opposite of that described by Caglioti and coworkers.[10]

The **B** synthon preparation was previously communicated by us in our enantioselective synthesis of preoleanatetraene.[17] Following a synthetic route parallel to that used with achilleol A, we proceeded to make allylic bromide **23** react with the corresponding anion of phenylsulfone **22** to gratifyingly obtain the desired diasteromeric mixture of sulfones **24** in good yield. Finally, exposure of **24** to Li-EtNH_2 and subsequent deprotection of the silyl ether led to the formation of **25**. MS and ^{1}H and ^{13}C NMR of our synthetic achilleol B coincide completely with those of the natural product. Noteworthy is the existence of a NOE effect between H-18 and the CH_3−C17. The sign of the optical rotation $[\alpha]_D$ of synthetic achilleol B (−10.9, *c* 0.9, $CHCl_3$) matched that of the natural compound (−8.1, *c* 1.1, $CHCl_3$).

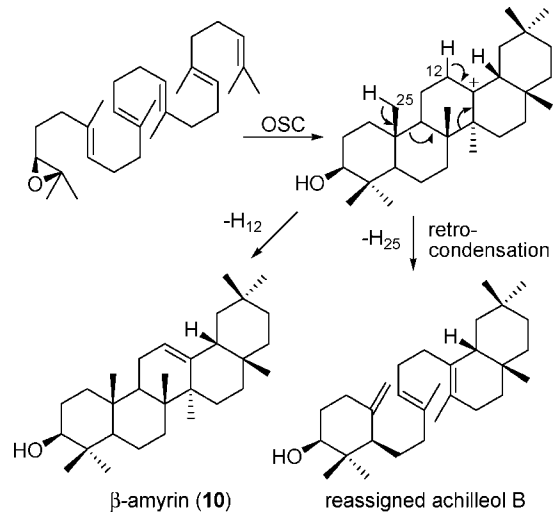
All of the above allowed us both to reassign the stereochemistry of the interannular junction of the bicyclic system in achilleol B and also to establish absolute stereochemistry of the natural product as that shown is Scheme 4.

Scheme 4. Synthesis of Reassigned Achilleol B



With regard to the biosynthetic origin of achilleol B, a cyclization−rearrangement−retrocondensation[6] process is proposed, a hypothesis that is supported by the coexistence

Scheme 5. Biogenetic Proposal for Achilleol B



in *Achillea odorata* of achilleol B and the oleanane *β*-amyrin (Scheme 5).[18]

In conclusion, the first enantioselective synthesis of achilleol B has been efficiently completed with a longest linear sequence of 14 steps. This work has also allowed us to reassign the structure of this natural triterpene. Furthermore, this asymmetric protocol enabled us to complete the synthesis of achilleol A, elegansidiol, and farnesiferol B in 10, 8, and 9 steps and 12, 17, and 13% overall yield, respectively.

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Supporting Information Available: Experimental procedures and spectroscopic data of new compounds and ^{1}H and ^{13}C NMR spectra of **12**−**18**, **22**, and those of natural and synthetic (−)-elegansiol (**11**), (−)-achilleol (**2**), and (−)-achilleol B. This material is available free of charge via the Internet at http://pubs.acs.org.

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