Enantioselective Annulation Using Nazarov Reagent: Synthesis of (+)-Preoleanatetraene

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Abstract: The enantioselective synthesis of preoleanatetraene (**1**) has been accomplished via a convergent approach of two C-15 synthons. The key step of this synthesis has been an interesting enantioselective variant of the Robinson annulation using the Nazarov reagent and a chiral enamine to obtain the bicyclic moiety A. This asymmetric methodology opens the access to other irregular triterpene skeletons whose biogenetic implication should not be underestimated.

Key words: preoleanatetraene, annulation, asymmetric synthesis, terpenoids, natural products, total synthesis

Since the isolation of achilleol A (**2**) and achilleol B (**3**) from *Achillea odorata* by our group in 1990,[1] a number of partially cyclized triterpenes – some of them, as **1** and **4**, possessing only two or three rings of the usually fully cyclized pentacyclic system – have been described (Figure 1).[2] Recently, two compounds, **5** and **6**, with a new related tetracyclic triterpene skeleton have been reported.[2d] The occurrence of these irregular triterpenes in nature suggests the existence of enzymes able to promote cyclizations at different levels from both 2,3-oxide squalene cyclase (OSC) and squalene cyclase (SC).[3] Furthermore, the description of most of these compounds during the last decade permits to suggest that with the development of isolation and identification techniques, new examples of these irregular triterpenes, are likely to be reported in the near future.

The importance of these natural products for a deeper understanding of the biogenetic pathways of living organisms prompted us to find an expedient route to most of these compounds, a challenge that we started to face with the synthesis of preoleanatetraene (**1**). Prior to this work, we have reported the synthesis of the monocyclic triterpene achilleol A (**2**) through a radical cyclization mediated by Ti(III) of an epoxide precursor.[4]

Our retrosynthetic planning to these types of natural products is based on the convergent approach of a common bicyclic precursor (**A**) and the corresponding C-15 moiety (Scheme 1). The key step in the synthesis of this common bicyclic system was projected to be an enantioselective variant of the Robinson annulation using the Nazarov

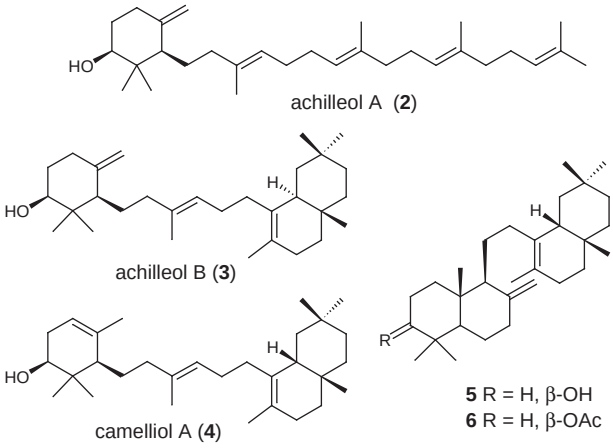
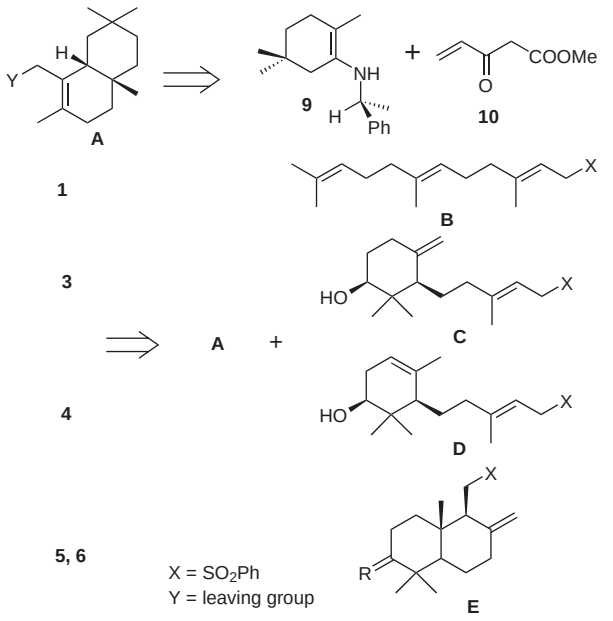


Figure 1 Chemical structures of **2**–**6**.



Scheme 1 Rethrosynthetic analysis for **1**, **3**, and **4**–**6**.

reagent, despite the noticeable absence of precedents from literature of asymmetric versions of this reaction.[5] Revision of the literature led us to two previous syntheses of derivatives of **A** by van Tamelen[6] and Heathcock[7] in their approaches to the synthesis of β-amyrin. Although the relevance of the work developed by the mentioned authors is undoubted, it was limited to obtain **A** in a racemic way.[8]

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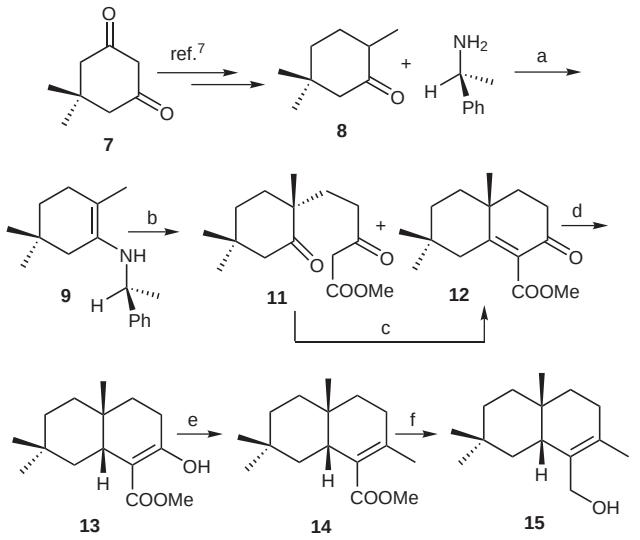
Thus, our objective was not only to achieve the synthesis of **A** enantioselectively but also to improve the efficiency of some of the transformations described in the precedent reports.



Scheme 2 *Reagents and conditions*: a) benzene, molecular sieves, 48 h, 74%; b) methyl 3-oxo-4-pentenoate (**10**), benzene, 1 h, 70 °C, 21% of **11**, and 20% of **12**; c) KF, MeOH, Δ, 6 h, quantitative; d) H_2-Pd/C, EtOAc, 72 h, 91%; e) (i) Tf_2O, $(i\text{-}Pr)_2EtN$, CH_2Cl_2, –78 °C to –50 °C, 30 min; (ii) $CuBr{\cdot}SMe_2$, MeLi, THF, –15 °C, 30 min, 91% in two steps; f) LAH, Et_2O, 0 °C, 30 min, 79%.

Basing ourselves on the work of Heathcock, ketone **8** was obtained starting from dimethyl dimedone **7** (Scheme 2). Once large quantities of **8** were at disposal, it was decided to study the feasibility of obtaining the conjugated keto ester **12** using an enantioselective version of the Robinson annelation with the Nazarov reagent. With the assumption of preoleanatetraene (**1**) possessing an absolute configuration *R* at C-10, enamine **9** was prepared (in equilibrium with the corresponding imine) by treating **8** with (*S*)-phenylethylamine.[9] Treatment of **9** with freshly prepared Nazarov reagent **10**[10] led to a mixture of the desired keto ester **12** and its acyclic precursor.[11] Quantitative cyclization was achieved by treatment of **11** with KF in MeOH. The global yield in the enantioselective Robinson annulation process was 41%, the enantiomeric excess obtained being 80%.[12]

Moving forward with the synthetic planning, the catalytic reduction of **12** with H_2-Pd/C at 3 atm led stereoselectively to *cis*-decaline **13**, which according to its NMR spectra appears in solution as the enolic form of the ketone carbonyl group. The introduction of the methyl group on the double bond was initially tried by treatment of **13** and of its phosphate derivative with Me_2CuLi. Unfortunately, under different conditions tested, the reaction did not work. The desired conversion was carried out by treating the corresponding enol triflate with MeLi in the presence of the complex $CuBr{\cdot}SMe_2$.[13] Reduction of the conjugated ester with $LiAlH_4$ afforded finally the bicyclic alcohol **15**. This achievement permitted the conversion of **12** into **15** in four steps with a yield of 63%, which improves previously described procedures considerably.

A complete spectroscopic study of **14** including 1D and 2D NMR allowed us to confirm both the structure and the *cis*-interannular junction presented in this compound.[14] The stereochemistry assigned to **14**, together with a selection of NOEs observed for this compound, is depicted in Figure 2. Fundamental for the assignment of the relative stereochemistry at C-4a and C-8a were the NOE-DIFF correlations between H-8a and the methyl group at C-4a and the β-methyl group at C-7, which also defines the major conformation in solution.

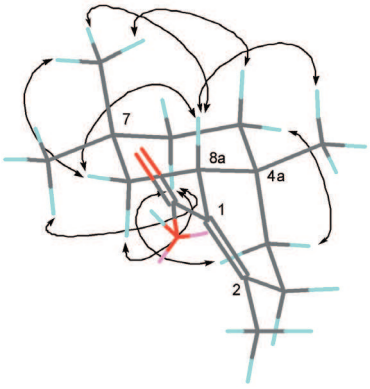
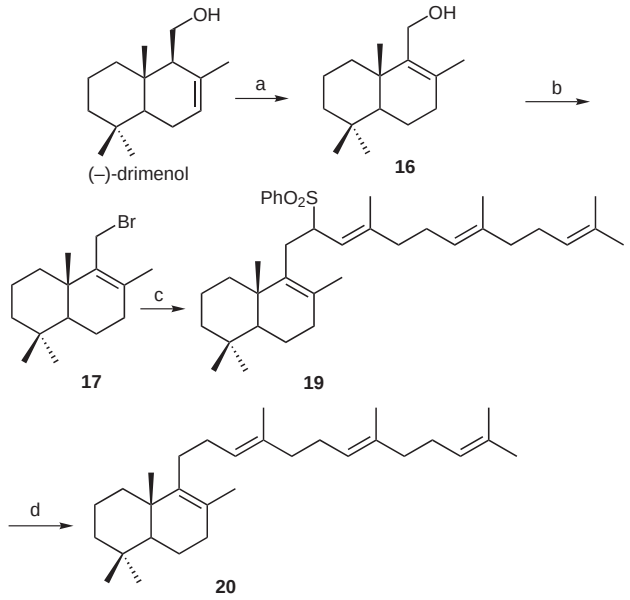


Figure 2 Relative configurations and selected NOEs for **14**.

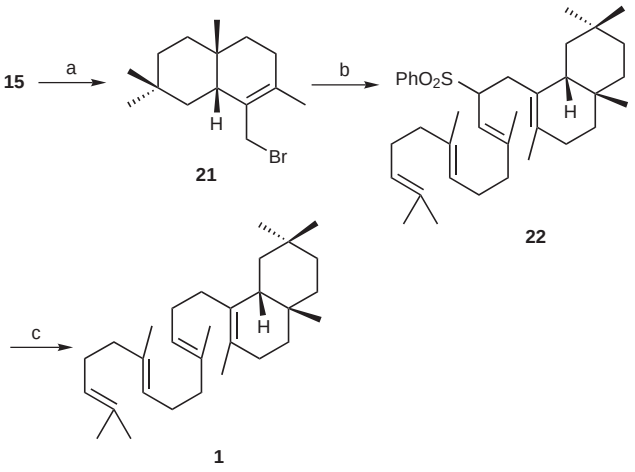
At that moment, we decided to test the coupling step using an easily accessible model. With this purpose, we turned our efforts to achieve an enantioselective access to the non-natural β-polypodatetraene **20**,[15] a bicyclic triterpene also involved in mechanistic studies of the biosynthesis of polycyclic triterpenoids, as 2,3-monoepoxide has been reported to enzymatically cyclize to onocerane derivatives.[16]

The bicyclic synthon **17** was prepared from (–)-drimenol (Scheme 3). As anticipated, the coupling process between **17** and the lithium derivative from farnesylphenylsulfone (**18**) proceeded smoothly in 72% yield. Reductive elimination of the phenylsulfonyl group using sodium-amalgam gave **20** in 44% yield; when this reaction was achieved with Li-ethylamine, the yield was improved up to 79%.

Once the conditions for the final steps of the synthesis of **1** were established, we proceeded to react allylic bromide **21** with the corresponding anion of farnesylphenylsulfone[17] to gratifyingly obtain the desired diastereomeric mixture of sulfones **22** in good yield. Finally, exposure of **22** to Li-$EtNH_2$ led to the formation of preoleanatetraene. MS, ^1H NMR and ^{13}C NMR spectroscopy of this compound coincided completely with those of the natural product. The sign of the optical rotation $[\alpha]_D$ of both the synthetic and the natural polypodatetraene were coincident {$[\alpha]_D$ value for natural **1**: +13.9 ($CHCl_3$); $[\alpha]_D$ value for synthetic **1**: +11.0 ($CHCl_3$)}, which let us assign the absolute stereochemistry of the natural product to that shown in Scheme 4.



Scheme 3 *Reagents and conditions*: a) (i) PCC, CH_2Cl_2, 50 min; (ii) K_2CO_3, MeOH, 2 h; (iii) $NaBH_4$, MeOH, 2h, 46% in three steps; b) PBr_3, Et_2O, 0 °C, 30 min, 90%; c) **18**, *n*-BuLi, THF, –78 °C, 10 min, then **17**, 4 h, 72%; d) Li, $EtNH_2$, THF, –78 °C, 2 h, 79%.



Scheme 4 *Reagents and conditions*: a) PBr_3, Et_2O, 0 °C, 30 min, 90%; b) **18**, *n*-BuLi, THF, –78 °C, 10 min, then **21**, 4 h, 72%; c) Li, $EtNH_2$, THF, –78 °C, 2 h, 89%.

In conclusion, with the synthesis of **1**, we have proved that reasonable ee could be obtained using an enantioselective variation of the Robinson annulation with a Nazarov reagent. With the aim of widening the scope of this reaction, new chiral amines and different annulation conditions are projected to be attempted. On the other hand, we have also opened an enantioselective approach to irregular triterpenes possessing the bicyclic moiety **A**, the syntheses of some of them are currently being addressed in our laboratory. Furthermore, the assignment of the absolute configuration of (+)-preoleanatetraene has also been described.

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(11) **Procedure for the Enantioselective Variant of the Robinson Annulation Using the Nazarov Reagent and a Chiral Enamine: Synthesis of Bicyclic 12.**
A stirred solution of enamine **9** (486 mg, 2 mmol) and

Nazarov reagent 10 (256 mg, 2 mmol) in dry benzene (2 mL) was heated at 65–70 °C for 1 h. Then was added 0.5 mL of a solution of 125 g of NaOAc, 25 mL of H_2O and 25 mL of HOAc. The mixture was heated for 1 h, washed with H_2O, sat. aq $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (hexane–*t*-BuOMe, 4:1) to afford 150 mg of **11** (20%) and 106 mg of **12** (21%). Keto ester **12** was isolated as colorless oil. $[\alpha]_D$ –49.7 (*c* 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 2.52 (ddd, *J* = 5.4, 14.3, 17.0 Hz, 1 H), 2.40 (dt, *J* = 3.9, 17.0 Hz, 1 H), 2.15 (d, *J* = 14.6 Hz, 1 H), 1.98 (dd, *J* = 1.3, 14.6 Hz, 1 H), 1.86 (td, *J* = 4.6, 13.7 Hz, 1 H), 1.78 (dq, *J* = 3.2, 13.6 Hz, 1 H), 1.47–1.67 (m, 3 H), 1.28–1.37 (m, 1 H), 1.23 (s, 3 H), 1.00 (s, 3 H), 0.82 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.0, 167.7, 166.4, 132.3, 52.0, 43.0, 37.8, 37.1, 34.4, 34.0, 33.5, 32.4, 32.0, 24.6, 22.3. IR (film): 2945, 2866, 1735, 1671, 1617, 1465, 1353, 1227, 1131, 1008 cm^{-1}. HRMS–FAB: *m*/*z* calcd for $C_{15}H_{22}O_3Na$ $[M + Na]^+$: 273.1467; found: 273.1463.

(12) The enantioselectivity of the annelation reaction could be measured after treating **15** with (*S*)-2-acetoxypropionyl chloride. The diastereomeric ratio of the corresponding lactates was determined by ^{1}H NMR (800 MHz) spectroscopy, by integrating the AB quartets of the major and minor components.

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(14) All new compounds gave satisfactory analytical and spectroscopic data.
Compound **14**: colorless oil. $[\alpha]_D$ +30.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6): δ = 3.51 (s, 3 H), 2.68 (dd, *J* = 2.9, 12.4 Hz, 1 H), 2.03 (s, 3 H), 1.97–2.07 (m, 2 H), 1.84 (ddd, *J* = 6.8, 11.8, 24.5 Hz, 1 H), 1.57–1.65 (m, 2 H), 1.35 (dt, *J* = 3.9, 13.6 Hz, 1 H), 1.25 (td, *J* = 3.4, 13.6 Hz, 1 H), 1.15 (br d, *J* = 13.6 Hz, 1 H), 1.08 (t, *J* = 13.0 Hz, 1 H), 1.02 (s, 3 H), 0.93 (s, 3 H), 0.93 (s, 3 H), 0.73 (dd, *J* = 6.9, 14.7 Hz, 1 H). ^{13}C NMR (100 MHz, C_6D_6): δ = 169.0, 142.8, 129.3, 50.7, 43.8, 40.0, 36.5, 34.8, 33.1, 31.4, 31.1, 31.0, 27.0, 26.3, 24.1, 21.9. IR (film): 2949, 2922, 2851, 1713, 1640, 1464, 1258, 1063, 804 cm^{-1}. HRMS–FAB: *m*/*z* calcd for $C_{16}H_{26}O_2Na$ $[M + Na]^+$: 273.1831; found: 273.1830.

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