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Total syntheses of echinopines A and B, sesquiterpenes with a unique tetracyclic [3-5-5-7] skeleton

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1. Introduction

The synthesis of natural products of unique structure often allows innovation in strategy and can afford opportunities to develop new methodology. In this context, terpenoids occupy a unique position and pose significant synthetic challenges.

Echinopines A (**1**) and B (**2**), are two novel sesquiterpenoids isolated from the roots of *Echinops spinosus*, in 2008, by Shi and Kiyota.[1] These minor metabolites (0.12% yield) are characterized by an unprecedented tetracyclic [3-5-5-7] skeleton. This complex architecture features five contiguous stereogenic centers, two of them being quaternary; noteworthy, the seven-membered cycle adopts a chair-like form (Fig. 1).[2]

It has been suggested that the biosynthetic pathway of this unique echinopane framework may involve skeletal rearrangements from the guaiane type precursor **3**.[1] More particularly, a sequence including transformation of the [5–7] bicyclic ring system **4** into the [5-6-7] carbocation **5**, was proposed for the construction of the [3-5-5-7] tetracyclic echinopane skeleton (Scheme 1).

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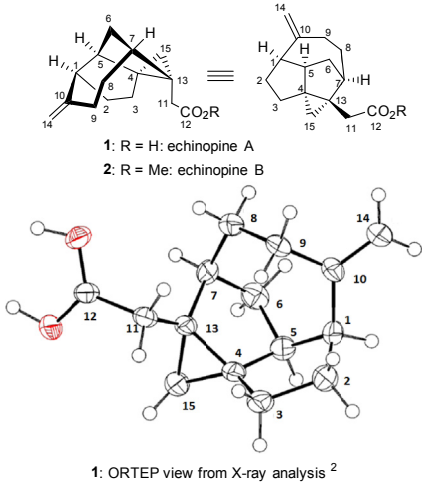
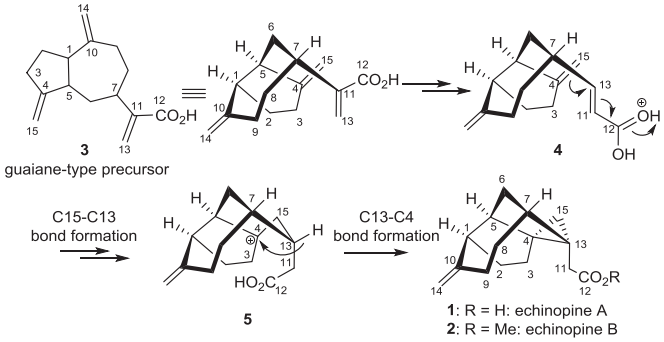


Fig. 1. Structure of echinopines A (**1**) and B (**2**).



Scheme 1. Proposed biosynthetic pathway for the echinopane skeleton.

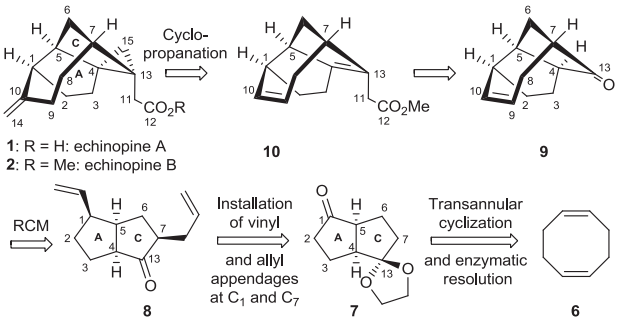
Although no biological activity has been uncovered so far, the original and complex structure of these natural products has motivated several research groups to embark on their total synthesis. Hence, only one year after their isolation, in 2009, Magauer, Mulzer and Tiefenbacher reported the first enantioselective total synthesis and determined the absolute configuration of these sesquiterpenes.[2] Thereafter, in 2010, 2011 and 2012, Nicolaou, Chen and Vanderwal described four total or formal bioinspired syntheses of these two natural products.[3–7] More recently, in 2013 and 2015, Liang and Misra, respectively, achieved one total and one formal synthesis proceeding through original sequences.[8,9] However, it is important to note that only the first syntheses, developed by Tiefenbacher et al., Nicolaou and Chen have been performed in asymmetric form.[2–6]

Design of strategies for the stereoselective synthesis of such complex skeletons is particularly challenging. Thus, in this review, which surveys the synthesis of echinopines, emphasis will be laid on the strategies and ring-forming sequences. An overview of the methods developed for the stereoselective construction of stereogenic centers in the echinopane skeleton will also be presented.

2. Magauer, Mulzer and Tiefenbacher first total synthesis (2009)

The first total synthesis of echinopines A (**1**) and B (**2**) was achieved by Magauer, Mulzer and Tiefenbacher in 2009.[2] The strategy was based on the elaboration of the diquinane **8** bearing two *cis*-appendages at C1 and C7 (numbering identical to the final compounds). This intermediate was found suitable to build up the seven-membered ring by RCM and led to the tricyclic [5-5-7] intermediate **9**.

In turn, the precursor **7** of bicycle **8**, was easily prepared following a known procedure including a palladium chloride-mediated transannular cyclization and subsequent enzymatic resolution from commercially available cyclooctadiene **6**.[10] Installation of the cyclopropane ring was accomplished at the end of the synthesis from [5-5-7] framework **10** (Scheme 2).



Scheme 2. Magauer, Mulzer and Tiefenbacher total synthesis: retrosynthetic analysis.

The synthesis started by converting cyclooctadiene **6** to optically active ketone **7** on multigram scale. Then, preparation of the RCM precursor **8** from bicyclic allylic alcohol **11** involved two key steps. The stereoselective installation of the vinyl moiety at C1 on the concave side of the bicyclo[3.3.0]octane core **11** was carried out through Myers [3,3]-sigmatropic rearrangement to give diastereomer **12** in 66% yield and 3.5:1 *dr*.[11] The stereochemical outcome of this efficient reductive transposition of allylic alcohol **11** could be rationalized by steric interactions with the adjacent cyclopentane ring. Then, allylation at C7, next to the ketone function of **12**, followed by epimerization under basic conditions, allowed the formation of the desired pure *cis*-diastereomer **8** (an easily separable 2.3:1 diastereomeric mixture was obtained).

The RCM reaction of the highly strained seven-membered ring of **8** smoothly occurred to yield tetracyclic adduct **9**. With **9** in hand, late-stage functionalization began with the unusual Pd-catalyzed C2-homologation of a vinyltriflate with a ketene silyl acetal (formation of ester **10**),[12] followed by regioselective cyclopropanation to afford the tetracyclic derivative **13**. Compound **13** was finally transformed into the target echinopines **1** and **2** (Scheme 3).

The total syntheses of echinopines A (**1**) and B (**2**) were achieved in an overall 1% yield for 20 (21) steps. The relative configuration of **1** was confirmed by single crystal analysis, whereas the absolute configuration of **1** and **2** unambiguously follows from the synthesis.

3. Nicolaou and Chen total synthesis (2010) 'Chen's first generation synthesis'

In 2010, inspired by the bond forming sequence suggested by the biosynthetic proposal of Shi and Kiyota,[1] Nicolaou and Chen considered a chemically equivalent intramolecular cyclopropanation process ,i.e., a late stage transformation of the [5-6-7] tricyclic ring system **5** into [3-5-5-7] echinopane skeleton of **1** and **2**. Unfortunately, this strategy met with failure primarily due to difficulties associated with the preparation of a suitable intramolecular cyclopropanation precursor. Therefore, in their first generation synthesis, they opted for a revised strategy that involved the simultaneous formation of the cyclopropane and one cyclopentane rings by means of a carbenoid intramolecular addition to the exocyclic olefinic bond of α-diazo-β-ketoester **15**, to afford the tricyclic [3-5-5] aldehyde **16**.[3] The cycloheptane was generated at a later stage through an intramolecular SmI_2-mediated pinacol