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Total Syntheses of (+)-Echinopine A and B: Determination of Absolute Stereochemistry

Thomas Magauer,* Johann Mulzer, and Konrad Tiefenbacher*

University of Vienna, Institute of Organic Chemistry, Währingerstrasse 38, 1090 Vienna, Austria

thomas.magauer@univie.ac.at; konrad.tiefenbacher@univie.ac.at

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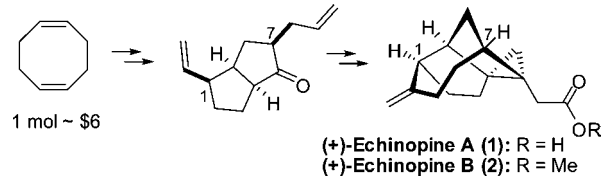
ABSTRACT



The first total syntheses of the novel 3,5,5,7-sesquiterpenoids (+)-Echinopine A (1) and B (2) were achieved. Thereby the proposed structures were confirmed, and the absolute stereochemistry was determined. The key features are (1) the stereoselective installation of the vinyl-moiety on the concave side of the bicyclo[3.3.0]octane core via Myers' [3,3]-sigmatropic rearrangement, (2) the finding that the substituent on the C7 position next to the ketone can be epimerized to the desired concave face under basic conditions, (3) the closure of the highly strained seven-membered ring via RCM, and (4) the unusual C2-homologation of a vinyltriflate with a ketene silyl acetal.

Echinopine A (**1**) and B (**2**) were isolated in 2007 by Shi and Kiyota during their screening for biologically active compounds from *Echinops spinosus*.[1] The structures of these novel, unprecedented sesquiterpenoids were elucidated by ^{1}H, ^{13}C, 2D-NMR and HRMS. Their molecular framework consists of a unique 3,5,5,7-membered ring skeleton (Figure 1), which is believed to arise from a guaiane-type precursor

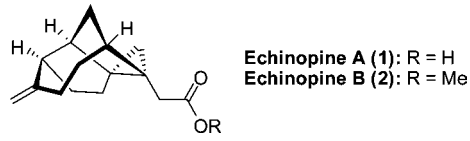


Figure 1. Structures of Echinopine A and B.

via skeletal rearrangement. The complex tetracyclic architecture features five contiguous stereocenters, two of which are quaternary.

Because of the scarcity of the natural product source, the biological activity has not satisfactorily been uncovered so far. Additionally no X-ray crystallographic analysis or chemical derivatization could be performed.[1] The absolute configuration is unknown, and the assignment of the relative stereochemistry is solely based on ^{1}H NMR spectroscopy.

The unprecedented structure and the unknown biological profile motivated us to embark on the total synthesis of **1** and **2**.

For a retrosynthetic analysis (Scheme 1) we considered two alternatives (I and II), leading to bicyclic precursors **P1** and **P2**, respectively. **P1** is a *cis*-fused AB-guaianolide system in which both rings C and D might be generated in a one-step cyclopropanation. However, this approach would be jeopardized by a potential *cis-trans*-isomerization, if for instance X = O. Alternatively, for X = CH_2 there would be a regio problem in the cyclopropanation as well as a high risk of double bond migration. Therefore we preferred route II, which goes back to a diquinane AC precursor **P2** with two *cis*-appendages R′ and R″, suitable for closing the seven-membered ring C via RCM.

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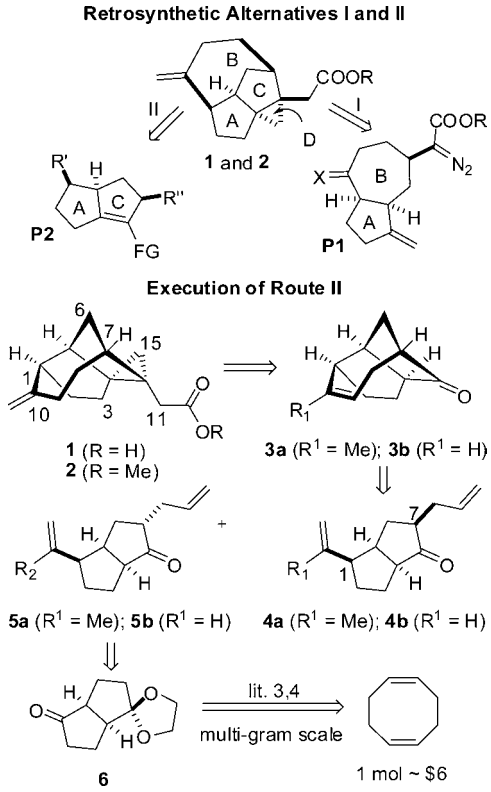
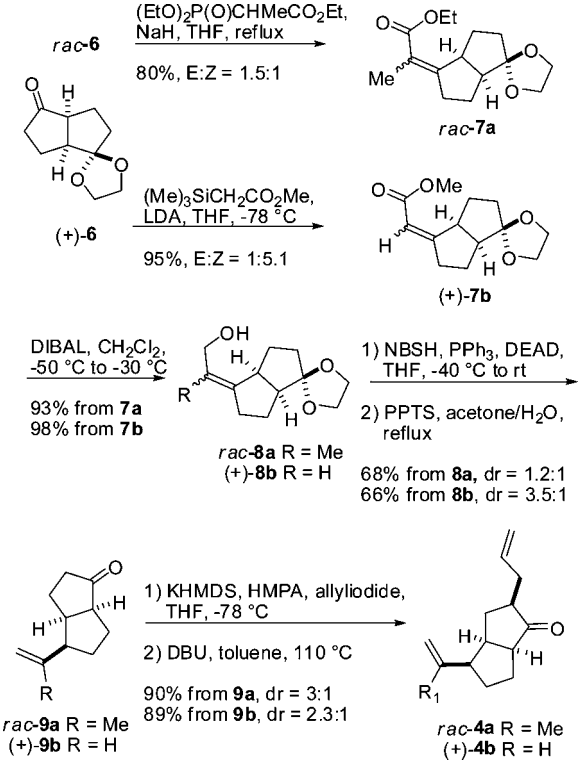
Scheme 1. Retrosynthetic Analysis of **1** and **2**



Thus, the *exo*-methylene group at C10 was retrosynthetically shifted to the *endo*-position. The cyclopropane and the acetic acid side chain were to be grafted on ketone **3**, which in turn should be elaborated from bis-alkene **4**. The synthesis of **4** was not trivial as both the vinyl/isopropenyl group at C1 (numbering identical to the final compounds) and the allyl group at C7 are located on the sterically encumbered concave face of the bicyclo[3.3.0]octane core. We therefore decided to explore a DRCM (dynamic ring closing metathesis), which has been described only once so far.[2] Equilibration of the kinetically allylated ketone **5** to RCM precursor **4** and in situ RCM should therefore deliver tricycle **3**. Ketone **5** in turn should be accessible from known racemic[3] or optically active[4] bicycle **6**, which can be easily prepared in multigram quantities from inexpensive 1,5-cyclooctadiene.

The synthesis of the RCM precursors (Scheme 2) *rac*-**4a** and (+)-**4b** started by converting ketone **6** to unsaturated

Scheme 2. Preparation of RCM Precursors **4a**/**4b**



esters **7a** and **7b** via Horner−Wadsworth−Emmons[5] and Peterson[6] olefination. Initial efforts to force the C1 side chain on the more hindered concave face by hydrogenating either the unsaturated esters or allylic alcohols resulted in 1:1 diastereomeric mixtures. Careful experimentation, however, revealed that the allylic alcohols **8a** and **8b** could be converted to the desired vinyl appendages by Myers' [3,3]-sigmatropic rearrangement protocol.[7] The stereochemical outcome can be rationalized by steric interactions with the adjacent cyclopentane ring (Figure 2), which is larger for the (*Z*)- than for the (*E*)-isomer. In fact, after separating the **8a** *Z*/*E* mixture, (*Z*)-**8a** afforded after deketalization a 10:1 ratio in favor of diastereomer **9a**, whereas the ratio dropped to 1.2:1 for (*E*)-**8a**. For compound **8b** (Z/*E* 5.1:1**)**, the effect was less pronounced, giving **9b** as an easily separable 3.4:1 diastereomeric mixture.

Having secured gram quantities of both **9a** and **9b**, we finished the preparation of the RCM precursors. Allylation with KHMDS (only 1.05 equiv, otherwise bisallylation was observed) and excess allyliodide gave **5a** and **5b** in excellent yield and as single diastereomers.

The envisaged DRCM strategy was investigated under a variety of RCM catalysts, bases, Lewis acids, and solvents (Grubbs II, Grubbs Hoveyda II, "Grubbs III",[8] DBU, Schwesinger's *t*-Bu-P_4-base, $ZnCl_2$, $AlCl_3$,[9] toluene, CH_2Cl_2). After extensive experimentation, we realized that DRCM was

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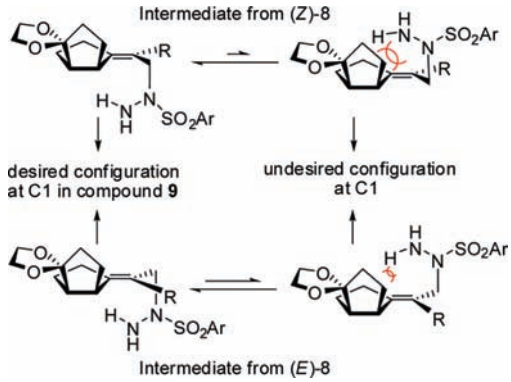


Figure 2. Models for the stereoselective [3,3]-sigmatropic rearrangement.

ineffective. However the DRCM experiments revealed that DBU (toluene, 110 °C) efficiently epimerized both **5a** and **5b** to mixtures of **4a**/**5a** (dr = 3:1) and **4b**/**5b** (dr = 2.3:1) with the desired *cis*-diastereomers in excess. The undesired diastereomers could be easily separated by HPLC and recycled.

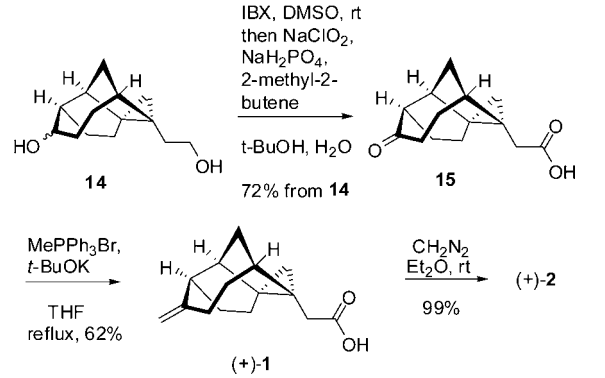
Next RCM was applied to **4a** and **4b**. To our surprise all attempts to close the seven-membered ring from **4a** failed, under a variety of reaction conditions (Grubbs II, Grubbs Hoveyda II, "Grubbs III", CH_2Cl_2, toluene, 2,6-dichlorobenzoquinone[10]). Only homodimers across the allylic units were observed. Gratifyingly the less hindered **4b** was smoothly converted to the desired core framework **3b** when exposed to Grubbs II catalyst (5 mol %) in refluxing CH_2Cl_2 (Scheme 3). As **5b** gave only polymers under these conditions, we streamlined our synthesis by submitting the **4b**/**5b** mixture to the RCM reaction, from which **3b** was readily isolated as the only monomeric product. In principle, the material can be carried through from **7b** to **3b** without separation as **4b** is the only diastereomer capable of RCM.

With **3b** in hand we started the installation of the remaining functionalities. We envisioned the introduction of the C2 side chain stepwise (path A) or directly (path B). In either case, the procedure commenced with the formation of the vinyltriflate with KHMDS/$PhNTf_2$ and a Pd(0)-mediated coupling reaction. As one-step formylation[11] failed, path A was focused on the well-established C1 elongation protocol with CO/MeOH in DMF,[12] which afforded the α,β-unsaturated methyl ester in excellent yield. Stereoselective Corey−Chaykovsky cyclopropanation[13] furnished ester **10**, and primary alcohol **12** was obtained after C1 elongation. Functionalization of the disubstituted double bound of **12** was accomplished by epoxidation with DMDO (which gave higher yields than *m*CPBA) and regioselective epoxide opening with LAH at elevated temperature to give **14** as a 16:1 diastereoisomeric mixture. Efforts to introduce appropriate functionality at C-10 in **12** via ene reactions with singlet oxygen[14] or formaldehyde[15] resulted only in the recovery of starting material.

In a more direct access to **14** (path B) we extended related methodology of Musco and Santi[16] to the vinyltriflate derived from ketone **3a**. Indeed, reaction with (1-methoxyvinyloxy)trimethylsilane and $Pd(PPh_3)_4$ furnished methyl ester **11** in 54% yield (not optimized). Regioselective cyclopropanation with modified Furukawa−Simmons−Smith's reagent[17] afforded the tetracyclic intermediate **13** in excellent yield. Epoxidation and LAH reduction gave **14** as before.

Oxidation of **14** (Scheme 4) first with IBX and then with $NaClO_2$[18] furnished ketoacid **15**, whose Wittig methylenation

Scheme 4. Completion of the Syntheses



in refluxing THF led to (+)−**1** ($[\alpha]^{22}_D$ = +26 (*c* 0.70, $CHCl_3$), lit.[1] $[\alpha]^{22}_D$ = +23 (*c* 0.11, $CHCl_3$)). The acid was converted to (+)-**2** ($[\alpha]^{22}_D$ = +22 (*c* 0.60, $CHCl_3$), lit.[1] $[\alpha]^{22}_D$ = +21 (*c* 0.14, $CHCl_3$)) with diazomethane. The analytical data for **1** and **2** (HRMS, ^1H and ^{13}C NMR, $[\alpha]^{22}_D$) matched those reported by Shi and Kiyota in all respects. The relative configuration of **1** was also confirmed by single crystal analysis, whereas the absolute configuration of **1** and **2** follows unambiguously from the synthesis.

In summary, the first total synthesis of Echinopine A (**1**) and B (**2**) was achieved in optically active form in 15 steps from known ketone **6** in 7% overall yield. The sequence is easy to perform and scaleable and starts from

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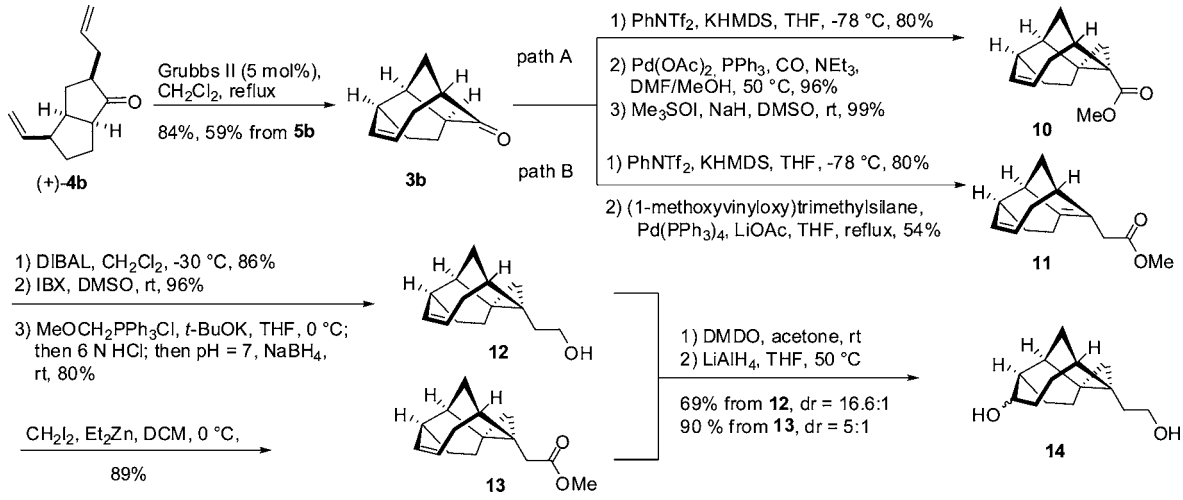
Scheme 3. Construction of the Polycyclic [3,5,5,7] Skeleton



inexpensive material. Notable chemical features of the synthesis are (1) the stereoselective installation of the vinyl moiety on the concave side of the bicyclo[3.3.0]octane core via Myers' [3,3]-sigmatropic rearrangement, (2) the finding that the C7-substituent next to the ketone (see **4** and **5** in Scheme 1) can be epimerized to the desired concave face under basic conditions, (3) the closure of the highly strained seven-membered ring via RCM, and (4) the unusual C2-homologation of a vinyltriflate with a ketene silyl acetal.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds and crystal data of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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