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Total Synthesis of Valerenic Acid, a Potent GABA$_A$ Receptor Modulator

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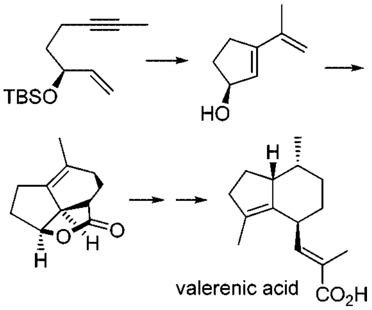
ABSTRACT



The first total synthesis of the sesquiterpenoid valerenic acid, a constituent of *Valeriana officinalis*, is described. The compound is a potent modulator of the GABA$_A$ receptor and may thus be useful in the treatment of various dysfunctions of the central nervous system. The synthesis is enantio-, diastereo-, and regiocontrolled and utilizes an enyne-RCM, a metal-coordinated Diels−Alder reaction, a hydroxy-directed Crabtree hydrogenation, and a Negishi methylation as key steps.

γ-Aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the mammalian brain and mediates its action by interaction with GABA type A (GABA$_A$) receptors representing a ligand-gated chloride channel, second messenger linked GABA$_B$ receptors that are coupled to Ca^{2+}- and K$^+$-channels via G-proteins and GABA$_C$ receptors.[1] There is clear evidence for specific expression of certain GABA$_A$ receptor subtypes (with different subunit compositions) in different regions in the central nervous system (CNS).[2] The subunit composition determines the GABA-sensitivity and the pharmacological properties of the GABA$_A$ receptor.[3] Searching for molecules selective for a certain GABA$_A$ receptor subtype is, therefore, a promising approach to develop new therapeutics.

Valerenic acid (**1**), isolated from the roots of *Valeriana officinalis*,[4] has recently been shown to selectively modulate GABA$_A$ receptor subtypes.[5] These data suggest that **1** is a subunit-specific allosteric modulator of GABA$_A$ receptors and as a drug, might be applicable against a variety of CNS dysfunctions, such as panic disorders, hyperactivity, poor motor coordination, learning deficits, spontaneous epileptic seizures, and abnormal facial development. Therefore, as more extensive and elaborate structural variations are envisaged, an efficient total synthesis of **1** appeared of importance. This intention seemed all the more worthwhile to us as, despite some fruitless efforts in the past,[6] no total synthesis of **1** has been reported so far.

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(5) Khom, S.; Baburin, I.; Timin, E. N.; Hohaus, A.; Sieghart, W.; Hering, S. *Mol. Pharmacol.* **2002**, *69*, 640–649.

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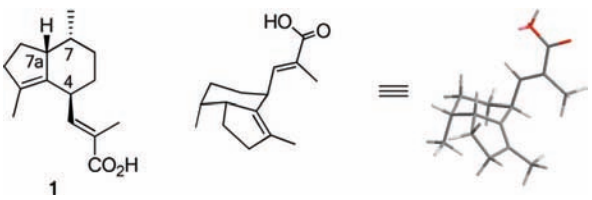
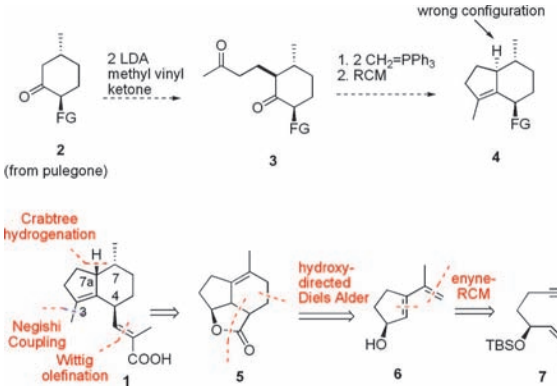


Figure 1. Structural features of valerenic acid (**1**).

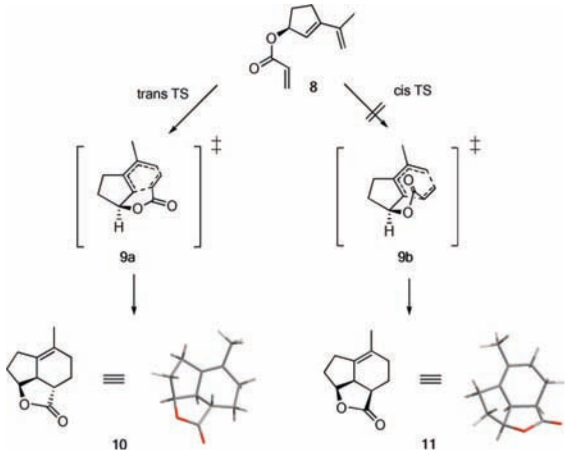
Structurally, **1** is a sesquiterpene featuring an indanyl core with three stereogenic centers and two double bonds (Figure 1). A particular challenge in a total synthesis lies in the diaxial arrangement[7] of two onring substituents, which had to be installed without subsequent epimerization.[6b]

Scheme 1. Retrosynthetic Analysis of **1**



From the retrosynthetic perspective (Scheme 1), an obvious route to **1** might start from a pulegone-derived cyclohexanone such as **2** and attach the cyclopentene ring via alkylation to **3** and olefination/ring closing metathesis (RCM) to **4**. However, enolate additions to **2** are known[8] to favor the trans-diastereomer, which would generate **4** with the wrong configuration at the ring juncture. Therefore, we decided to prepare the bicyclic core from an acyclic precursor **7** via an enyne-RCM[9]-IMDA (IMDA = intramolecular Diels−Alder addition) sequence via **6** to generate lactone **5**. The relative configuration at C-7/7a should be created via hydroxy-directed catalytic hydrogenation. As the ultimate steps of our synthesis we considered a Negishi-coupling to introduce the methyl substituent at C-3, whereas the exocyclic enoate appendage at C-4 should be formed by an *E*-selective Wittig olefination. This plan had two main unknowns: (a) the stereochemical outcome of the IMDA reaction generating **5** and (b) the possibility to achieve the correct relative configuration at C-7/7a with respect to C-4.

Scheme 2. Stereochemical Implications of the IMDA Reaction of **8**



The IMDA reaction of ester-linked trienes such as **8** is known to proceed exclusively via the so-called trans (= exo) transition state **9a** (Scheme 2).[10,11] Because of great distortion and steric hindrance the electronically normally preferred cis (= endo) transition state **9b** is clearly disfavored and, thus, product **10** should be formed. On the other hand, this outcome would be *contra*-thermodynamic, as **10**, according to STO 3-21G calculations, is 13.2 kcal•mol^{-1} higher in energy than product **11**.

Our synthesis (Scheme 3) started with readily available racemic 3-OTBS-oct-1-en-6-yne (**7**),[12] which smoothly underwent RCM to cyclopentene **12** with Grubbs' first generation catalyst, if the reaction was carried out under an ethylene atmosphere (Mori's conditions).[13] Several other conditions such as using an argon atmosphere instead of ethylene or PtCl$_2$ as catalyst led to no conversion or decomposition. In situ deprotection and acylation furnished acrylic ester **8** as the envisaged IMDA substrate. However, all attempts to achieve cycloaddition under thermal conditions just led to decomposition. After this failure we switched to a metal-coordinated Diels−Alder reaction[14] of alcohol **6** and methyl acrylate with MgBr$_2$ as the template. This reaction furnished lactone **11** stereoselectively.[15] The transition state (**13**) of this Diels−Alder reaction now resembles the electronically favored *endo*-arrangement **9b** and furnishes lactone **11** as the thermodynamically more stable product, so that all disadvantages of the covalently tethered acrylate are now reversed.

The synthesis was continued (Scheme 4) by installing the side chain at C-4 via reduction to the lactol **14** (not isolated)

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[7] Cf. the crystal structure of valerenolic acid: Birnbaum, G. L.; Findlay, J. A.; Krepinsky, J. L. *J. Org. Chem.* **1978**, *43*, 272–276.

[8] Touriya, Z.; Santelli-Rouvier, C.; Santelli, M. *J. Org. Chem.* **1993**, *58*, 2686–2693.

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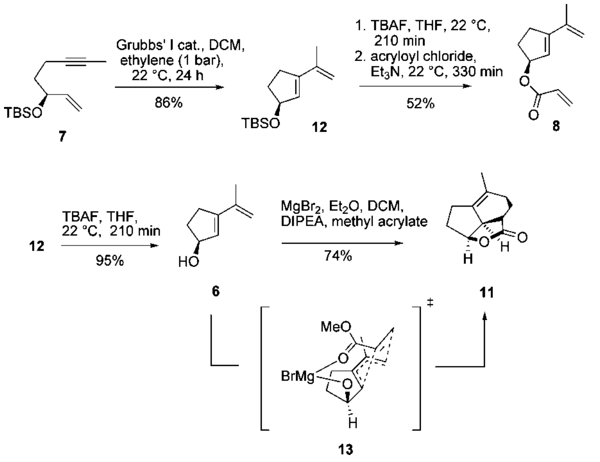
[13] Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388–12389.

[14] Barriault, L.; Thomas, J. O. D.; Clement, R. *J. Org. Chem.* **2003**, *68*, 2317–2323.

[15] The relative configuration of **11** was secured via 2D NMR techniques (see the Supporting Information).

Scheme 3. Preparation of Lactone **11**[a]

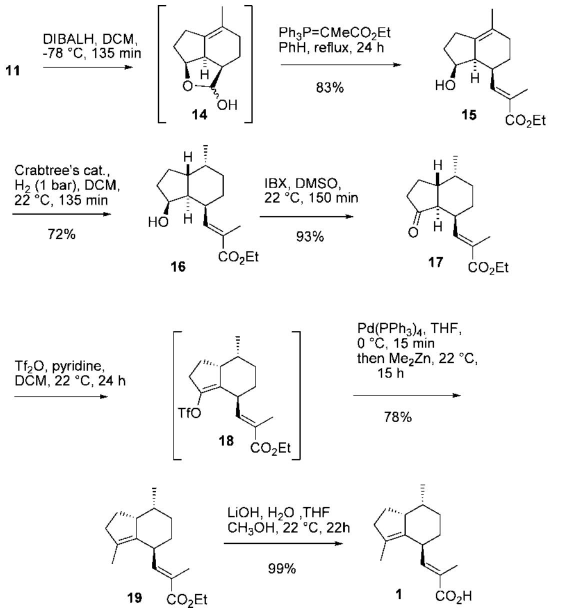


[a] Abbreviations: DCM = dichloromethane, DIPEA = diisopropylethylamine.

and Wittig reaction to form enoate **15**. The free OH group was now used as an anchoring group for Crabtree's catalyst,[16] which delivered dihydrogen in a *syn* fashion to generate hydrindane **16** stereo- and chemoselectively. Oxidation to ketone **17** was followed by deprotonation to the thermodynamically more stable enolate, formation of vinyl triflate **18** (not isolated), and Negishi coupling[17] with dimethyl zinc. From this sequence the tetrasubstituted olefin **19** was obtained with >90% regioselectivity. Base-catalyzed ester hydrolysis led to *rac*-**1**. After that, the synthesis was repeated with enantiomerically pure (*S*)-**7**[18] to provide the natural enantiomer (−)-**1**. All analytical data of *rac*-**1** and (−)-**1** were in full agreement with those of an authentic sample (see the Supporting Information).

In conclusion we have achieved a concise stereo- and regiocontrolled synthesis of valerenic acid (**1**) in racemic (8 steps from **7**, 26% overall yield) and optically pure form (13 steps from (*R*)-glycidol, 8% overall yield). Remarkably, the initial stereochemical information introduced with the carbinol center in compound **7** is used in a relay-manner to control the stereogenic centers in the target molecule. After that it is discarded in favor of an endocyclic double bond. The route is flexible and should be applicable to a variety of derivatives, suitable for SAR investigations.

Scheme 4. Completion of the Synthesis[a]



[a] Abbreviations: DCM = dichloromethane, IBX = 2-iodoxybenzoic acid.

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

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[18] (*S*)-**7** was prepared via a stereo-unambiguous route from (*R*)-glycidol in five steps and 32% overall yield (see the Supporting Information).