Total Synthesis of Valerenic Acid

Sascha Kopp,[a] W. Bernd Schweizer,[b] Karl-Heinz Altmann*[a]

[a] Institute of Pharmaceutical Sciences HCI H405, Swiss Federal Institute of Technology (ETH) Zürich, Wolfgang-Pauli-Strasse 10, 8093 Zürich, Switzerland

[b] Laboratory of Organic Chemistry, Swiss Federal Institute of Technology (ETH) Zürich, Wolfgang-Pauli-Strasse 10, 8093 Zürich, Switzerland
Fax +41(44)6331369; E-mail: karl-heinz.altmann@pharma.ethz.ch

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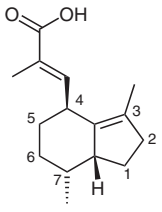
Abstract: Valerenic acid is a major constituent of valerian root. It exhibits modulatory activity on the $GABA_A$ receptor and thus represents a potential new lead structure for the discovery of new anxiolytics. Here we present the enantioselective total synthesis of valerenic acid, which departs from natural (*R*)-pulegone and proceeds through a bicyclic ketone as the central intermediate. Key transformations are the stereoselective reduction of a 3,4-disubstituted cyclohexenone and a microwave-assisted Wittig reaction.

Key words: total synthesis, natural product, valerenic acid, microwave-assisted Wittig reaction, $GABA_A$ receptor

Valeriana officinalis L. (valerian) has been used as a medicinal plant in Europe for centuries and valerian-derived phytopharmaceuticals (based on valerian root mono extracts or on combination extracts with passionflower, lemon balm, or hop) are widely used as mild sedatives for the treatment of insomnia, nervous tension, and restlessness.[1] However, in spite of their longstanding and widespread medical use, the clinical effectiveness of valerian preparations has remained a matter of debate,[2] and the molecular mechanisms underlying the purported sedative activity of valerian have not been unequivocally elucidated. Interactions of valerian constituents with relevant receptor systems in vitro have been reported for specific lignans (inverse agonistic activity on the adenosine receptor type 2A)[3] and flavonoids (modulatory activity on the $GABA_A$ receptor),[4] but the significance of these effects in humans has not been established.



Valerenic acid (**1**)

Figure 1 Structure of Valerenic acid (**1**)

Valerenic acid (**1**, Figure 1) is a sesquiterpene acid that was first isolated from valerian root in 1957.[5] It is used as an analytical marker in the quality control of valerian root extracts, but traditionally has not been associated with the drug's pharmacological effects. More recently, however, valerenic acid (**1**) was found to be an allosteric modulator of the $GABA_A$ receptor[6,7] and to act as an inverse agonist on the 5-HT_{5a} receptor,[8] thus suggesting a possible involvement in the sedative effects of valerian extracts. While such extrapolations at this point are still hypothetical, it is important to note that valerenic acid (**1**) does not interact with the benzodiazepine binding site on the $GABA_A$ receptor[6,7] and, therefore, represents an attractive lead structure for the discovery of a new type of $GABA_A$ receptor modulators (and also of 5-HT_{5a} ligands). However, natural product-based lead optimization in a first step generally requires the establishment of a synthetic route to the natural product itself. In this paper we describe the first stereoselective synthesis of valerenic acid (**1**), which provides a chemical basis for future lead optimization efforts and SAR studies.

Valerenic acid (**1**) has not been widely pursued as a synthetic target in the past, and the first stereoselective synthesis of this natural product has been reported only very recently by Ramharter and Mulzer.[9] In addition, Bohlmann and Lonitz have described the synthesis of racemic valerenic acid methyl ester, valerenal, and valerenol,[10] and a number of attempts have been reported on the construction of the bicyclic core structure of **1**.[11] However, none of these previous efforts (not including Mulzer's work) appeared to provide an attractive framework for the development of an efficient stereoselective synthesis.

As indicated above, Mulzer and co-workers have recently disclosed an elegant stereoselective synthesis of valerenic acid (**1**),[9] which utilizes a metal-coordinated intramolecular Diels–Alder reaction to establish the bicyclic core structure from a five-membered ring precursor. In this communication we summarize our own work on the synthesis of **1**, which is based on an entirely different strategy for the build-up of the 5,6-ring system.

As illustrated in Scheme 1, our retrosynthesis of valerenic acid (**1**) led to the bicyclic ketone **2** as a first key intermediate. According to our original synthetic plan, the keto group of **2**, after reduction, was to be converted into an appropriate leaving group, thus generating a purported substrate for a transition-metal-catalyzed cross-coupling reaction with a (*E*)-3-iodo-2-methyl acrylic ester. As it turned out, this strategy ultimately could not be imple-

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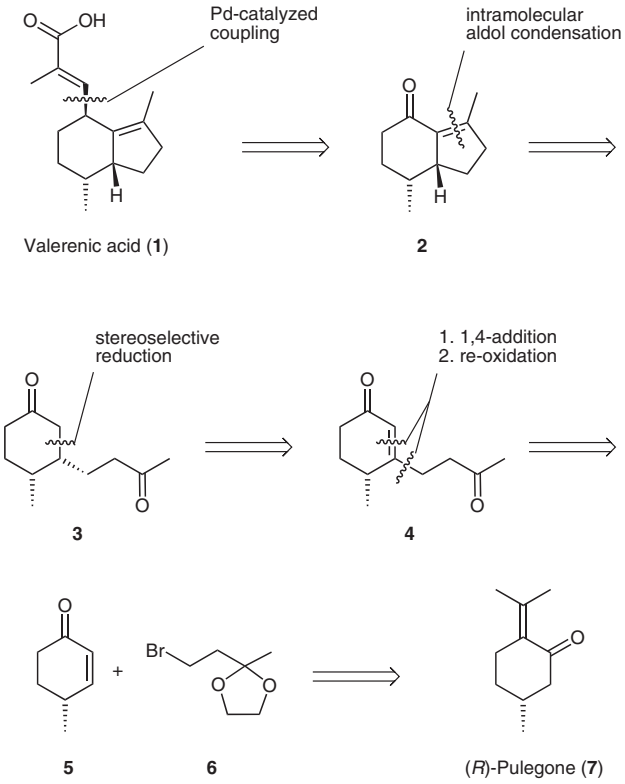
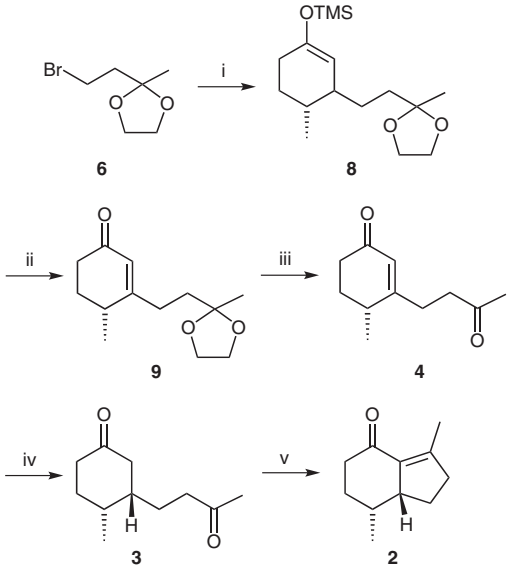
mented and in spite of extensive experimentation none of the desired coupling product could ever be isolated (vide infra). However, as will be shown below, bicyclic ketone **2** still proved to be a useful intermediate for the synthesis of **1**, even if the incorporation of the entire side chain in a single step could not be realized. Further disconnection of **2** led to diketone **3** as a substrate for an intramolecular aldol condensation. Diketone **3**, in turn, was to be obtained through the chemo- and stereoselective reduction of enone **4**, with the latter being envisaged to be the result of a 1,4-addition of a cuprate derived from bromide **6** to enone **5** followed by Saegusa oxidation.[12] Finally, cyclohexenone **5** was expected to be accessible from the chiral pool compound (*R*)-pulegone (**7**) in a six-step sequence that had been previously developed by Lee et al.[13]



Scheme 1 Retrosynthesis of Valerenic acid (**1**)

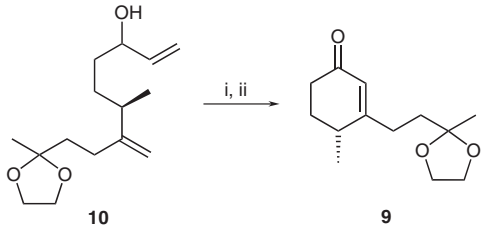
The elaboration of (*R*)-pulegone (**7**) into the desired cyclohexenone **5** proved to be straightforward and could be achieved in up to 71% overall yield [vs. 45% in ref. 13 from technical grade (*R*)-pulegone].[14]

In contrast, the subsequent 1,4-addition of a cuprate reagent derived from bromide **6** to ketone **5** (Scheme 2) required extensive optimization of the reaction conditions. Due to the instability of the intermediate TMS-enol ether **8** on silica gel, the latter could not be purified, but was directly subjected to Saegusa oxidation,[12] in order to reestablish the olefinic double bond and produce **9**. Both Grignard-derived Normant reagents as well as lithium-based Gilman cuprates were investigated for the 1,4-addition step under a variety of conditions, with Grignard-derived reagents generally giving better yields of **9**. The major problem encountered in this step was a pronounced tendency for a Wurtz-type homocoupling in the initial metalation step. The efficient suppression of this unproductive side reaction required very slow addition of bromide **6** to powdered magnesium in THF (rather than Et_2O) by means of a syringe robot at room temperature with simultaneous addition of one full equivalent of 1,2-dibromoethane (relative to **6**). Under optimized conditions for the 1,4-addition (preparation of the magnesiocuprate at –15 °C from 4 equiv of Grignard reagent and 1.2 equiv of $CuBr{\cdot}SMe_2$ followed by slow addition of 1 equiv of **5** at –78 °C) β,γ-disubstituted enone **9** could be obtained in 50% yield (from **5**).



Scheme 2 *Reagents and conditions*: (i) a) Mg, slow addition of **6**, THF, r.t., $BrCH_2CH_2Br$, 6 h; b) $CuBr{\cdot}SMe_2$, THF, –20 °C, 30 min; c) **5**, TMSCl, THF, Et_3N, –78 °C, 15 h; (ii) O_2, 20 mol% $Pd(OAc)_2$, DMSO, r.t., 24 h, 50% (2 steps); (iii) 2 N HCl, DMSO, r.t., 15 min, 85%; (iv) $[PPh_3CuH]_6$, benzene, r.t., 2 d, 76%; (v) NaO*t*-Bu, *t*-BuOH, r.t., 15 min, 71%.

Alternatively, **9** could also be prepared via diene **10** through ring-closing olefin metathesis (RCM) followed by oxidation (Scheme 3). Diene **10** was obtained in an eleven-step sequence from (4*S*,5*R*)-1,5-dimethyl-4-phenyl-3-propionylimidazolidin-2-one[15] in 6.6% overall yield. While this RCM-based approach provided cyclohexenone **9** in a reliable manner, the overall efficiency of this strategy was clearly lower than for the pulegone-based route.



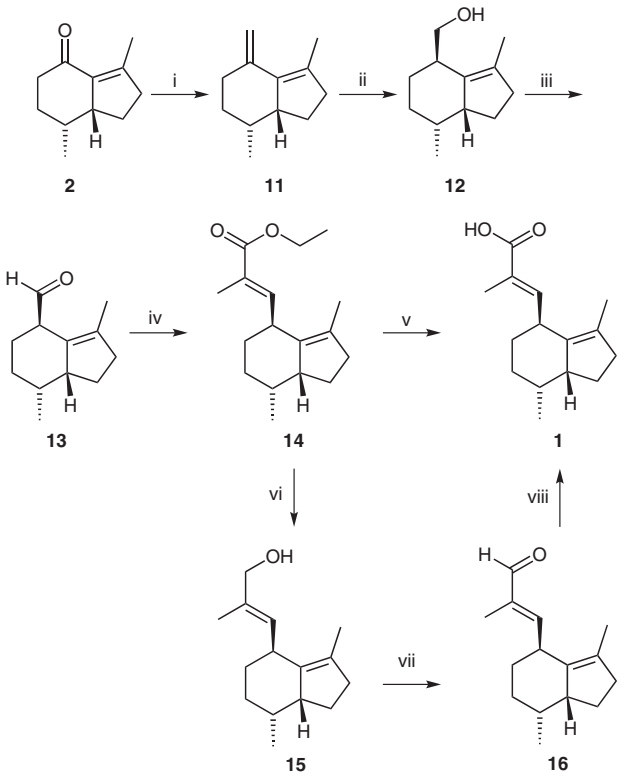
Scheme 3 *Reagents and conditions*: (i) Grubbs II cat., CH_2Cl_2, r.t., 2 h, 95%; (ii) DMP, CH_2Cl_2, r.t., 30 min, 88%.

Acidic cleavage of the ketal protecting group in **9** proceeded smoothly and gave diketone **4** in 85% yield. The latter could be reduced with $[Ph_3P(CuH)]_6$ (Stryker's reagent)[16] to produce **3** as a single isomer in 76% yield. In contrast to other cases known in the literature, where this stabilized copper hydride has been employed in a catalytic fashion,[17] the efficient conjugate reduction of **4** required slightly more than stoichiometric amounts of Stryker's reagent. Conducting the reaction under a hydrogen atmosphere either at normal or at elevated pressure (up to 12 bar) in the presence of catalytic amounts of $[Ph_3P(CuH)]_6$ (1–15 mol%) did not yield any product. Catalytic hydrogenation of **4** with Ra-Ni gave only mixtures of the desired **3** and the corresponding *trans*-isomer.

The conversion of **3** into the desired bicyclic ketone **2** proceeded without difficulty. Ring closure was achieved through treatment of **3** with NaO*t*-Bu in *t*-BuOH, which gave **2** in 71% yield.

As indicated above, the keto group of **2** had originally been planned to be converted to a suitable leaving group, which was to be followed by attachment of the complete side chain in a single step. However, while the reduction of **2** to the corresponding alcohol proceeded smoothly, all attempts to transform the latter into an allylic halide were unsuccessful (presumably due to the instability of the products). Acetylation of the secondary hydroxy group was possible, but the resulting acetate could not be induced to undergo Pd-catalyzed cross-coupling reactions.

In light of these difficulties we resorted to a stepwise strategy for the elaboration of the acrylic acid side chain onto the core structure **2**. As illustrated in Scheme 4 this alternative approach commenced with the conversion of **2** into olefin **11**, which was followed by hydroboration of the newly established exocyclic double bound to produce alcohol **12** in high yield (82%) as a single isomer! Based on HSQC-ROESY 2D-NMR experiments this product was assigned a *trans* arrangement of the methyl group at C7 and the newly formed hydroxymethyl group at C4, although the uniform stereochemical outcome of the hydroboration reaction at this point is difficult to rationalize. Oxidation of **12** with Dess–Martin periodinane (DMP) gave the volatile aldehyde **13**, which was not purified,[18] but directly submitted to Wittig reaction with $Ph_3P{=}C(Me)CO_2Et$. This transformation was carried out most efficiently under microwave conditions in MeOH, employing a heating period of 5 minutes and a reaction temperature of 140 °C. Gratifyingly, under these conditions valerenic acid ethyl ester (**14**) was obtained as the only isolable product in 62% yield for the two-step sequence from alcohol **12**, thus validating bicyclic ketone **2** as a feasible intermediate in the construction of valerenic acid (**1**). Saponification of **14** with LiOH at 40 °C provided valerenic acid (**1**) in excellent yield (97%).[19] The spectral properties (^1H and ^{13}C chemical shifts, optical rotation, IR) of synthetic **1** were fully identical with those of material obtained from a natural source.[20] Likewise, RP-HPLC analysis of a mixture of synthetic and natural material gave a single peak. Ultimate structural proof was obtained by an X-ray crystal structure of **1**.[21]



Scheme 4 *Reagents and conditions*: (i) $MePPh_3Br$, $NaNH_2$, Et_2O, 0 °C, 1 h, 75%; (ii) 9-BBN, THF, 0 °C, 3 h, oxidative workup, 82%; (iii) DMP, THF, –78 °C, 2 h; (iv) $Ph_3P{=}C(Me)CO_2Et$, MeOH, MW 130 °C, 10 min, 62% (2 steps); (v) LiOH, *i*-PrOH–H_2O, 40 °C, 10 h, 97%; (vi) LAH, THF, 0 °C, 1 h, 69%; (vii) MnO_2, CH_2Cl_2, r.t.; (viii) a) NaO*t*-Bu; b) $NaClO_2$, $Na_2HPO_4{\cdot}H_2O$, *t*-BuOH–2-methylbut-2-ene, r.t., 5 h, 75% (2 steps).

Reduction of valerenic acid ethyl ester (**14**) with LAH provided valerenol (**15**) in 69% yield. The latter is a minor constituent of *V. officinalis*, which we have previously shown to interact with the $GABA_A$ receptor with a similar affinity as valerenic acid (**1**).[7] Again, synthetic **15** proved to be identical with valerenol obtained in our laboratory by LAH reduction of natural valerenic acid.

Valerenol (**15**) could be cleanly oxidized to valerenal (**16**) with activated MnO_2.[10] Subsequent Pinnick oxidation[22] provided acid **1** in 75% overall yield for the two-step sequence from valerenol (**15**). While the reduction–oxidation route from **14** to **1** is obviously less efficient than the direct saponification of **14**, it may become of interest in the context of analogue synthesis.

In summary, we have accomplished the enantioselective total synthesis of valerenic acid (**1**), which was obtained in 6% overall yield over a sixteen-step sequence starting from (*R*)-pulegone (**7**). The chemistry developed in the course of this total synthesis now provides a basis for the synthesis of valerenic acid analogues and SAR studies. Such studies are currently ongoing in our laboratory, and the results will be reported in due course.

Acknowledgment

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References and Notes

(1) (a) *European Scientific Cooperative on Phytotherapy (ESCOP) Monographs*, 2nd ed.; Thieme: Stuttgart/ New York, **2003**, 539. (b) Kumar, V. *Phytother. Res.* **2006**, *20*, 1023.
(2) (a) Ziegler, G.; Ploch, M.; Miettinen-Baumann, A.; Collet, W. *Eur. J. Med. Res.* **2002**, *7*, 480. (b) Taibi, D. M.; Petry, H.; Landis, C. A.; Vitiello, M. V. *Sleep Med.* **2007**, *11*, 209.
(3) Schumacher, B.; Scholle, S.; Hölzl, J.; Khudeir, N.; Hess, S.; Müller, C. E. *J. Nat. Prod.* **2002**, *65*, 1479.
(4) Marder, M.; Viola, H.; Wasowski, C.; Fernandez, S.; Medina, J. H.; Paladini, A. C. *Pharmacol. Biochem. Behav.* **2003**, *75*, 537.
(5) Stoll, A.; Seebeck, E.; Stauffacher, D. *Helv. Chim. Acta* **1957**, *40*, 1205.
(6) Khom, S.; Baburin, I.; Timin, E.; Hohaus, A.; Trauner, G.; Kopp, B.; Hering, S. *Neuropharmacology* **2007**, *53*, 178.
(7) Benke, D.; Barberis, A.; Kopp, S.; Altmann, K.-H.; Schubiger, M.; Vogt, K. E.; Rudolph, U.; Möhler, H. *Neuropharmacology* **2009**, *56*, 174.
(8) Dietz, B. M.; Mahady, G. B.; Pauli, G. F.; Farnsworth, N. R. *Mol. Brain Res.* **2005**, *138*, 191.
(9) Ramharter, J.; Mulzer, J. *Org. Lett.* **2009**, *11*, 1151.
(10) Bohlmann, F.; Lonitz, M. *Chem. Ber.* **1980**, *113*, 2410.
(11) (a) Minami, T.; Usunomiya, T.; Nakamura, S.; Okubo, M.; Kitamura, N.; Okada, Y.; Ichikawa, J. *J. Org. Chem.* **1994**, *59*, 6717. (b) Baudouy, R.; Sartoretti, J. *Tetrahedron* **1983**, *39*, 3293. (c) Joseph, K. T.; Krishna Rao, G. S. *Tetrahedron* **1967**, *23*, 3215.
(12) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(13) Lee, H. W.; Ji, S. K.; Lee, I.-Y. C.; Lee, J. H. *J. Org. Chem.* **1996**, *61*, 2542.
(14) The pulegone used in our experiments was purchased from ACROS ORGANICS and was 92% pure (pract. grade) according to the supplier.
(15) Chiral auxiliary: Drewes, S. E.; Malissar, D. G. S.; Roos, G. H. P. *Chem. Ber.* **1993**, *126*, 2663; details for the synthesis of **10** will be published elsewhere.
(16) (a) de Fátima, A. *Synlett* **2005**, 1805. (b) Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1988**, *29*, 3749.
(17) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.
(18) Racemic aldehyde **13** has been prepared previously by Bohlmann and Lonitz and found to be highly prone to epimerization on silica gel.[10]
(19) **Preparation and Analytical Data of Compound 1**
To a solution of ethyl ester **14** (32 mg, 0.12 mmol) in 2-PrOH–H_2O (5:1, 0.6 mL) was added LiOH (6 mg, 0.24 mmol), and the mixture was heated to 40 °C for 10 h. The solution was concentrated and the residue directly purified by FC (hexane–EtOAc = 5:1, 1% formic acid) to give 29 mg (97%) of valerenic acid (**1**) as a white solid. Crystals suitable for X-ray crystallography were obtained from hexane–MeOH–Et_2O.
Mp 138.5–139.5 °C (lit.: 140–142 °C).[10] $[\alpha]_D^{25}$ –13.0 (*c* 2.15, $CHCl_3$); $[\alpha]_D^{20}$ –119.8 (*c* 2.50, EtOH). {lit.: $[\alpha]_D^{20}$ –120.0, EtOH}.[10] HRMS (EI): *m/z* calcd for $C_{15}H_{22}O_2$: 234.1614; found $[M]^+$: 234.1616. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.16 (d, *J* = 9.8 Hz, 1 H), 3.58–3.52 (m, 1 H), 3.00–2.92 (m, 1 H), 2.21 (br t, *J* = 7.5 Hz, 2 H), 2.05–1.96 (m, 1 H), 1.90 (s, 3 H), 1.89–1.73 (m, 3 H), 1.65 (br s, 3 H), 1.61–1.51 (m, 1 H), 1.47–1.39 (m, 2 H), 0.79 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.7, 146.2, 133.1, 131.2, 125.0, 47.4, 37.5, 34.6, 33.0, 28.8, 25.4, 24.5, 13.5, 12.1, 12.1. IR (neat): ν = 2932, 2856, 2834, 1675, 1632, 1422, 1299, 1255, 901 cm^{-1}.
(20) Natural valerenic acid was purchased from *extrasynthèse* (France).
(21) The structural data have been deposited with the Cambridge Crystallographic Data Centre. Deposition No. CCDC 719101.
(22) Bal, B. S.; Childers, W. E. Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.