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Enantioselective Total Synthesis of Valerianannoids A–C†

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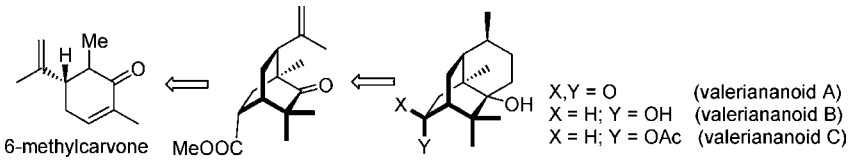
ABSTRACT



The first enantioselective total synthesis of valerianannoids A–C (–)-1–3 is reported starting from the readily available monoterpene (*R*)-carvone, employing a tandem intermolecular Michael addition–intramolecular Michael addition–alkylation sequence and an electron-transfer-mediated 6-endo-trig cyclization as key steps.

Valeriana jatamansi Jones, distributed widely in southwestern areas of China, has been used as a traditional Chinese medicine due to its hypnotic, tranquilizing and antiviral activities. In 1997, Yu and co-workers reported[1] the isolation and structure elucidation of three sesquiterpenoids, valerianannoids A−C **1**−**3** (Figure 1), from the ethyl acetate extract of the roots and rhizomes of *V. jatamansi Jones*. The structures of **1**−**3** were assigned on the basis of the spectral data in combination with chemical transformations and X-ray crystal structure of **1**. However, the stereochemistry of the secondary hydroxy and acetoxy groups in **2** and **3** were not clearly assigned. Interestingly, in 1995, the research groups of Takeya and Itokawa reported[2] the isolation and structure elucidation (including the stereochemistry of the hydroxy and acetoxy groups) of sesquiterpenoids **2** and **3** along with the parent member of the series patchouli alcohol **4** from the methanolic extract of the rhizomes and roots of *Valeriana fauriei*, which has been used in the preparation of a crude drug for sedative and antispasmodic purposes. Subsequently, in 1999 Collado and co-workers reported the formation of the diol **2** as a minor metabolite in the biotransformation of patchoulol **4** by the fungus *Botrytis cinerea* along with various other isomers.[3] The presence of an interesting tricyclic carbon framework, incorporating three contiguous quaternary carbon atoms coupled with potential biological properties associated with patchouli alcohols, made valerianannoids **1**−**3** challenging synthetic targets. Recently, Hagiwara and co-workers reported[4] the first racemic synthesis of valerianannoid A (±)-**1**. Herein we report the first enantioselective total synthesis of all three valerianannoids A−C **1**−**3**, starting from the readily and abundantly available monoterpene (*R*)-carvone **5**, which in addition to establishing the stereostructures also established the absolute configuration.

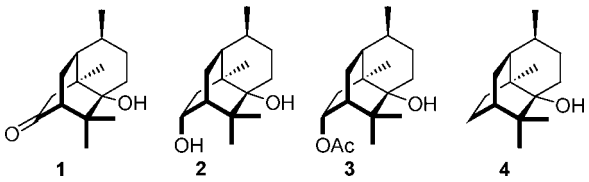


Figure 1.

It was contemplated (Scheme 1) that tandem intermolecular Michael addition−intramolecular Michael addition−alkylation sequence[5] on 6-methylcarvone **6** would generate

† Chiral Synthons From Carvone. 64. For part 63, see: Srikrishna, A.; Dethe, D. H.; Kumar, P. R. *Tetrahedron Lett.* **2004**, *45*, 2939−2942.

(1) Ming, D. S.; Yu, D. Q.; Yang, Y. Y.; He, C. H. *Tetrahedron Lett.* **1997**, *38*, 5205−5208.

(2) Nishiya, K.; Tsujiyama, T.; Kimura, T.; Takeya, K.; Itokawa, H.; Iitaka, Y. *Phytochemistry* **1995**, *39*, 713−714.

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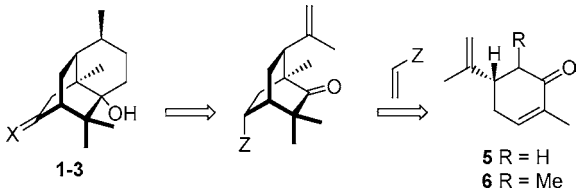
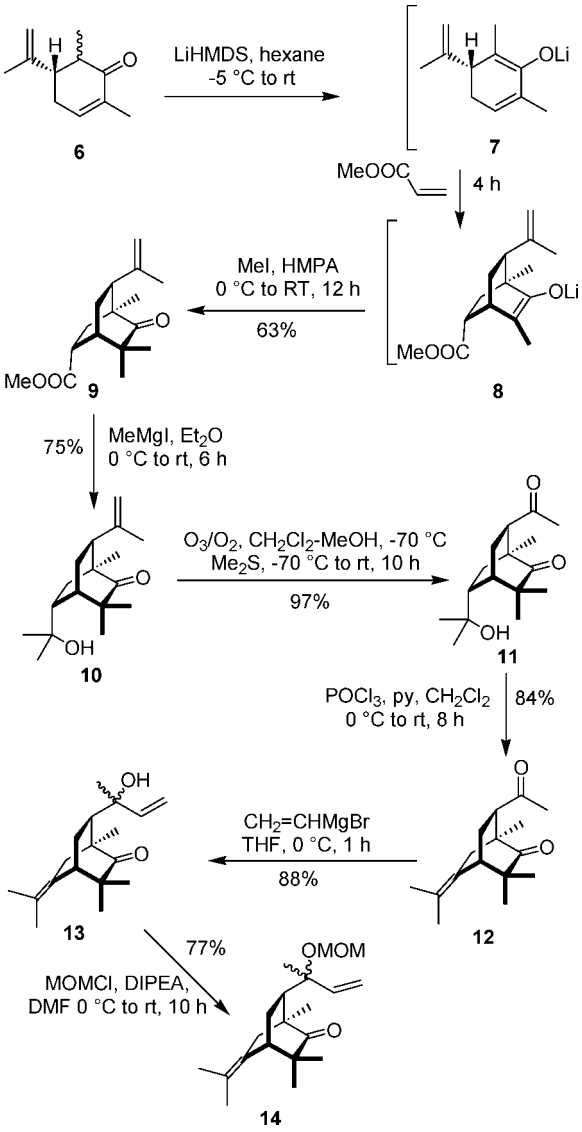
Scheme 1

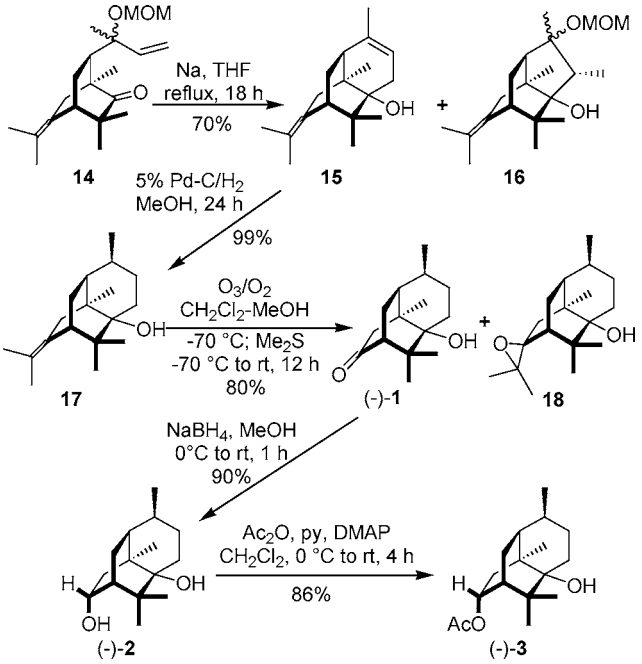


an ideal starting material, containing two of the three requisite quaternary carbon atoms and an isopropenyl group (equivalent to acetyl group) with correct stereochemistry for constructing the third ring, for the synthesis of valerianannoids A−C **1**−**3**. The synthetic sequence is depicted in Schemes 2 and 3 starting from 6-methylcarvone **6**, which was obtained by kinetic alkylation of (*R*)-carvone **5** with LDA and methyl iodide.[6] Generation of the kinetic enolate **7** of 6-methylcarvone **6** with lithium hexamethyldisilazide (LiHMDS) in

Scheme 2



Scheme 3



hexane followed by treatment with 1.1 equiv of methyl acrylate and finally quenching the enolate **8** with methyl iodide furnished the key intermediate of the sequence, the bicyclic ketoester **9** in 63% yield, whose structure was established from the spectral data. Before addressing the construction of the third ring, the ester group in **9** was modified into a masked ketone group. Thus, reaction of the ketoester **9** with an excess of methylmagnesium iodide furnished the tertiary alcohol **10** in a highly chemoselective manner,[7] obviously due to the steric crowding of the ketone group in **9**. Ozonolysis of the isopropenyl group in **10** followed by reductive workup generated the hydroxydione **11**, which on dehydration with phosphorus oxychloride in pyridine furnished the dione **12**. For the construction of the third ring, a well established[4] 6-endo-trig cyclization via electron-transfer methodology was chosen. Grignard reaction of the dione **12** with vinylmagnesium bromide introduced the requisite two carbons and generated a 1:2 epimeric

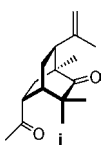
(3) Aleu, J.; Hanson, J. R.; Galan, R. H.; Collado, I. G. *J. Nat. Prod.* **1999**, *62*, 437−440.

(4) Hagiwara, H.; Morii, A.; Yamada, Y.; Hoshi, T.; Suzuki, T. *Tetrahedron Lett.* **2003**, *44*, 1595−1597.

(5) For a tandem intermolecular Michael addition−intramolecular Michael addition sequence, see: Zhao, R.-B.; Zhao, Y.-F.; Song, G.-Q.; Wu, Y.-L. *Tetrahedron Lett.* **1990**, *31*, 3559−3562. Srikrishna, A.; Gharpure, S. J. *Chem. Commun.* **1998**, 1589−1590.

(6) Gesson, J.-P.; Jacquesy, J.-C.; Renoux, B. *Tetrahedron* **1989**, *45*, 5863.

(7) In addition to the hydroxyketone **10**, varying amounts (8−15%) of the diketone **i** were also obtained.



mixture of the tertiary alcohol **13** in a highly chemoselective manner. Reaction of the keto alcohol **13** with methoxymethyl chloride and diisopropylethylamine (DIPEA) in methylene chloride furnished a 1:2 epimeric mixture of the MOM ether **14**. Electron-transfer-mediated cyclization of the MOM ether **14** with sodium in THF furnished a ~1:1:1 mixture of the requisite 6-endo-trig cyclized compound **15** and the two isomers of 5-exo-trig cyclized product **16** in 70% yield. The compounds **15**, **16a**, and **16b** were separated by silica gel column chromatography. Contrary to our expectation,[4] the reaction was found to be cleaner in THF than in a mixture of THF and HMPA. Regiocontrolled hydrogenation of the trisubstituted olefin in **15** with 5% palladium on carbon in methanol, as expected, furnished exclusively the dihydro compound **17** in quantitative yield, in a highly stereoselective manner via addition of hydrogen from the less hindered exo face of the molecule. Ozonolytic cleavage of the isopropylidene moiety in **17** followed by reductive workup with dimethyl sulfide furnished valerianananoid A **1** in 66% yield, mp 117−118 °C (lit.[1] 122−124 °C); $[\alpha]_D^{24}$ −33.3 (*c* 0.3, $CHCl_3$) {lit.[1] −34.6 (*c* 0.231, $CHCl_3$)}, along with varying amounts (7−15%) of the epoxide **18**. Stereoselective reduction of valerianananoid A **1** with sodium borohydride in methanol furnished valerianananoid B **2**, mp 185−187 °C, $[\alpha]_D^{24}$ −90.0 (*c* 1.0, $CHCl_3$), in 90% yield. Formation of a single stereoisomer in the reduction clearly indicated that the steric bias is significant and that the hydride approached only from the less crowded (anti to the *gem*-dimethyl group) face of the molecule. Finally, treatment of the alcohol **2** with acetic anhydride in pyridine and dichloromethane in the presence of a catalytic amount of DMAP gave valerianananoid C **3**, mp 74−76 °C, $[\alpha]_D^{22}$ −116.0 (*c* 1.0, $CHCl_3$), in 86% yield. The synthetic samples **1**−**3** exhibited the identical value and sign of the optical rotation and ^{1}H and ^{13}C NMR spectral data to the natural products,[8] thus establishing the stereostructures as well as the absolute configuration of the natural valerianananoids A−C **1**−**3**.

In conclusion, we have accomplished the first enantiospecific total synthesis of natural valerianananoids A−C **1**−**3** starting from the readily and abundantly available monoterpene (*R*)-carvone employing a tandem intermolecular Michael addtion−intramolecular Michael addition−alkylation sequence and an electron-transfer-mediated 6-endo-trig cyclization as key steps.

Acknowledgment. We thank Dr. Koichi Nishiya, Aventis Pharma Limited, for sending the copies of the IR, ^{1}H and ^{13}C NMR, and mass spectra of the natural compounds **2** and **3** and the Council of Scientific and Industrial Research, New Delhi, for the award of a research fellowship to G.S.

Supporting Information Available: Characterization data for all the compounds and ^{13}C NMR spectra of the compounds **9**−**18** and **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) It is worth noting that the ^{1}H and ^{13}C NMR spectra of the natural compound **2** obtained by the research groups of Takeya and Itokawa were recorded in CD_3OD (not in $CDCl_3$ as mentioned in ref 2).