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First total synthesis of valerianananoid A

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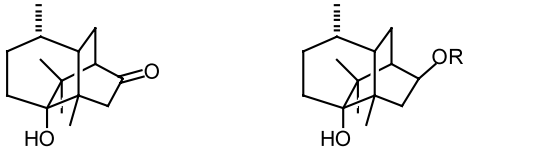
Abstract—A tricyclic sesquiterpenoid, valerianananoid A **1**, has been synthesized via domino Michael reaction of oxophorone **4** and subsequent 6-*endo*-trig cyclization of a ketyl radical as key steps.

Valeriana jatamansii Jones widely distributes in southwestern China and the roots of this plant have been utilized as a Chinese folk medicine which has hypnotic, tranquilizing and antiviral activities. In 1997, De Quan Yu and co-workers reported the isolation from ethyl acetate extracts of the roots and the structure determination of three new sesquiterpenoids, valerianananoids A **1**, B **2** and C **3** having a unique tricyclic carbon framework (Fig. 1).[1] The structure of valerianananoid A **1** was established by single crystal X-ray analysis and was revealed to be the same carbon framework as that of seychellene[2] or patchouli alcohol.[3]

Our ongoing interest toward the total synthesis of natural products via the domino Michael process[4] prompted us to investigate the synthesis of this unique sesquiterpenoid **1**.

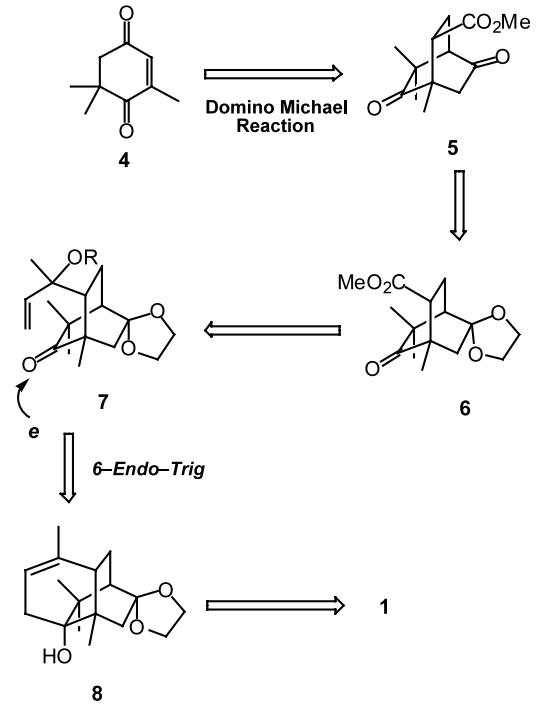
The synthetic design is outlined in Scheme 1. The bicyclic domino Michael product **5**, prepared according to our previous procedure[5] from oxophorone **4**, would enable mono-protection of the less hindered carbonyl group to give a mono-ketal whose ester group would be equilibrated to the same side as the carbonyl group to provide keto-ester **6**. After introduction of an allyl-alkoxy unit and subsequent ring closure by electron transfer reaction by the 6-*endo*-trig mode, the tricyclic valerianananoid framework would be obtained.



valerianananoid A **1**

valerianananoid B (R = H) **2**
valerianananoid C (R = Ac) **3**

Figure 1.



Scheme 1.

Keywords: bicyclic aliphatic compounds; domino Michael reactions; sesquiterpenenoid; valerianananoid.

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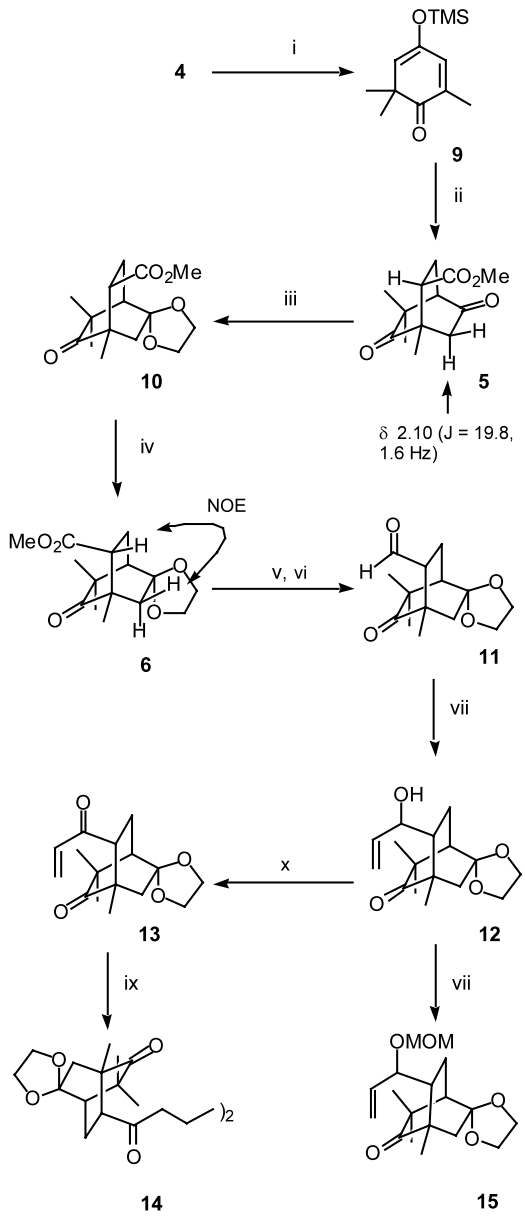
Trimethylsilylenol ether **9** prepared under specific reaction conditions was treated with methyl acrylate in the presence of diethylaluminum chloride to provide bicyclic compound **5**[5] (Scheme 2). The orientation of the ester group was determined by the observed W-type long-range coupling of the proton indicated. Conventional ketalization allowed selective protection of the less hindered ketone to provide ketal **10**. The overall yield in three steps from oxophorone **4** was 79%. Preliminary MM2 and PM3 calculations revealed a subtle difference in thermodynamic stability between keto-esters **6** and **10**. Fortunately, treatment of the keto-ester **10** with sodium methoxide in methanol resulted in complete isomerization of the ester group into the same side as the carbonyl group in 96% yield. The relative stereochemistry of the keto-ester **6** was confirmed by NOE enhancement between the two protons as depicted in Scheme 2, as well as disappearance of the W-type long-range coupling of the proton *endo* to the carbonyl group.



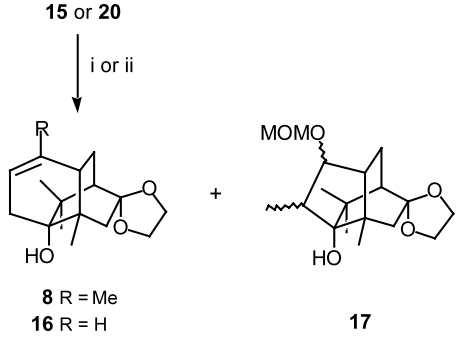
Scheme 2. *Reagents conditions and yields*: (i) $(TMS)_2NH$/TMSI/$(CH_2Cl)_2$; (ii) methyl acrylate, Et_2AlCl/CH_2Cl_2, rt; (iii) $(CH_2OH)_2$/PTSA, benzene, 79% (three steps); (iv) MeONa/MeOH, reflux, 96%; (v) LAH/Et_2O, 95%; (vi) PCC/AcONa/4 Å MS, 95%; (vii) vinylmagnesium bromide, 0°C, THF, 85%; (viii) Jones reagent, 98%; (ix) SmI_2 (3 equiv.)/*t*-BuOH (1.5 equiv.), HMPA/THF, −78°C, 73%; (x) NaH (2 equiv.), MOMBr (1.5 equiv.), THF, 0°C, 75%.

In order to construct the tricyclic carbon framework, a two-carbon unit must be introduced. Reduction of the keto-ester **6** followed by PCC oxidation provided keto-aldehyde **11** in 90% overall yield (two steps). Addition of vinylmagnesium bromide gave in 85% yield allyl-alcohol **12** which was oxidized by Jones reagent to furnish vinyl-ketone **13** in 98% yield.

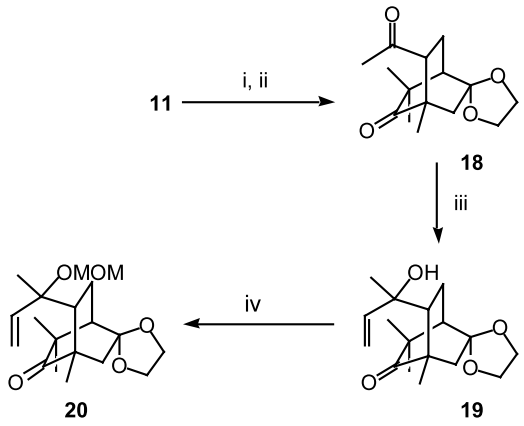
When vinyl-ketone **13** was treated with samarium diiodide in the presence of *t*-BuOH and HMPA, the desired ring closure did not proceed. Instead, intermolecular coupling of the vinyl moiety proceeded to give dimeric compound **14** in 73% yield. This result is understood by the preferential reduction of the unsaturated carbonyl moiety due to lower reduction potential and intermolecular C–C bond coupling reaction due to steric reason. Actually, MM2 calculation of **13** revealed that *s-cis* conformation of the vinyl-ketone moiety is thermodynamically more stable than *s-trans* conformation.

One solution to solve this problem is to prevent reduction of the side chain by raising the reduction potential and to facilitate preferential formation of the ketyl radical in the bicyclic framework. To this end, electron transfer cyclization of the substrate having an alkoxyallyl unit was investigated. Thus, allyl-alcohol **12** was protected as an MOM ether in 75% yield. Treatment of ether **15** with sodium[6] in refluxing THF closed the third ring to give tricyclic compound **16** in 61% yield having the valerianannoid carbon framework (Scheme 3). It is worthy of note that 6-*endo*-trig cyclization predominated rather than 5-*exo*-trig cyclization in this radical process, different from the common mode of radical cyclization.[7]

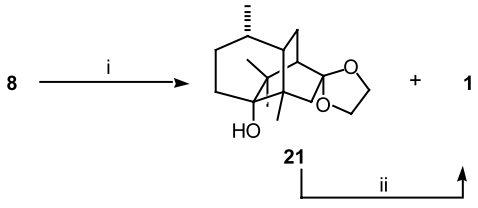
Encouraged by this result, a precursor having the requisite methyl group was prepared (Scheme 4). Addition of



Scheme 3. *Reagents conditions and yields*: (i) Na/THF, reflux, **16** 61%, **17** 35%; (ii) Na/HMPA/THF, reflux, **8** 44%.



Scheme 4. *Reagents conditions and yields*: (i) MeLi (2 equiv.), Et_2O, −78°C, 72%; (ii) PDC/AcONa/4 Å MS, 93%; (iii) vinylmagnesium bromide (5 equiv.), THF, rt, 99%; (iv) MOMBr (10 equiv.), t-C_4H_9OK (10 equiv.), THF, 0°C, 75%.



Scheme 5. *Reagents conditions and yields*: (i) H_2/Pd–C, MeOH, rt, 69%, valerianannoid A **1**, 15%; (ii) PTSA/H_2O/THF, rt, 99%

MeLi to keto-aldehyde **11** in 72% yield followed by PDC oxidation provided methyl-ketone **18** in 93% yield. Addition of vinylmagnesium bromide provided allyl-alcohol **19** as a separable mixture of diastereomers in 99% combined yield. Though protection of the tertiary allyl-alcohol **19** was difficult, a successful result was obtained in 75% yield by employing excess potassium t-butoxide.

After several attempts, the desired cyclization product **8** was obtained in 44% yield. The presence of HMPA was crucial to the present cyclization (Scheme 3).

Catalytic hydrogenation of olefin **8** proceeded selectively from the less hindered outer face of **8** to give in 65% yield **21** which was deprotected in 99% yield to furnish valerianannoid A **1** (Scheme 5). The spectral data were identical with those kindly provided by Professor Yu.

In summary, we have completed the first total synthesis of valerianannoid A **1** via domino Michael reaction of oxophorone **4** to construct the bicyclic framework and subsequent ketyl radical cyclization to close the tricyclic ring. Synthetic study toward optically active valerianannoids is now in progress and will be reported in due course.

Acknowledgements

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References

1. Ming, D. S.; Yu, D. Q.; Yang, Y. Y.; He, C. H. *Tetrahedron Lett*. **1997**, *38*, 5205.
2. Hikino, H.; Aota, K.; Takemoto, T. *Chem. Pharm. Bull. (Japan)* **1966**, *14*, 890.
3. Dobler, M.; Dunitz, J. D.; Gubler, B.; Weber, H. P.; Buchi, G.; Padilla, J. *Proc. Chem. Soc*. **1963**, 383.
4. Hagiwara, H.; Kobayashi, K.; Miya, S.; Hoshi, T.; Suzuki, T.; Ando, M.; Okamoto, T.; Kobayashi, M.; Yamamoto, I.; Ohtsubo, S.; Kato, M.; Uda, H. *J. Org. Chem*. **2002**, *67*, 5969.
5. Hagiwara, H.; Yamada, Y.; Sakai, H.; Suzuki, T.; Ando, M. *Tetrahedron* **1998**, *54*, 10999.
6. (a) Bertrand, M.; Teisseire, P.; Perelin, G. *Nouv. J. de Chim*. **1983**, *7*, 61; (b) Spreitzer, H.; Kalchhauser, H. *Liebigs Ann. Chem*. **1990**, 709 and references cited therein.
7. Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p. 715.