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Total Synthesis of Grandisine D

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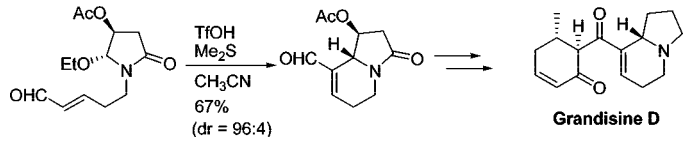
ABSTRACT



Total synthesis of grandisine D (5) was achieved by a Brønsted acid mediated Morita−Baylis−Hillman (MBH) ring-closure reaction and stereoselective aldol condensation with (*S*)-5-methylcyclohexenone (9) as key steps. The MBH approach was also applicable for the construction of the aza-fused bicyclic systems of pyrrolizidine and stemona alkaloids.

Opioid receptors have been classified into three subtypes, μ, κ, and δ, and activation of μ-opioid receptor is known to cause dependence, respiratory depression, and muscle rigidity. Therefore, a selective agonist of δ-opioid receptor is a promising lead for development of new analgetics with few side effects. Grandisines A−G (**1**−**7**) are indolizidine alkaloids isolated by Carroll and co-workers from the leaves of the Australian rain forest tree *Elaeocarpus grandis*, and these alkaloids display selective human δ-opioid receptor affinity (Figure 1).[1,2] Despite their attractive biological profiles, only grandisine A (**1**) has been synthesized so far.[3] In this paper, we describe the first total synthesis of grandisine D (**5**), which was proposed to be a biogenetic precursor of grandisines B (**2**) and F (**4**) and (−)-isoelaeocarpiline,[1,2] by means of a Brønsted acid mediated Morita−Baylis−Hillman (MBH) reaction[4] and a stereoselective aldol reaction with (*S*)-5-methylcyclohexenone (**9**).

The retrosynthetic analysis is as follows (Scheme 1). Grandisine D (**5**) would be obtained by an aldol reaction of 8-formylindolizidine **10** with (*S*)-5-methylcyclohexenone (**9**), readily prepared from (*S*)-pulegone,[5] followed by reduction of amide **8**. 8-Formylindolizidine **10** would be synthesized by an MBH ring-closure reaction via acyl iminium ion[6] generated from aminal **11**, which can be derived from (*S*)-malic acid.

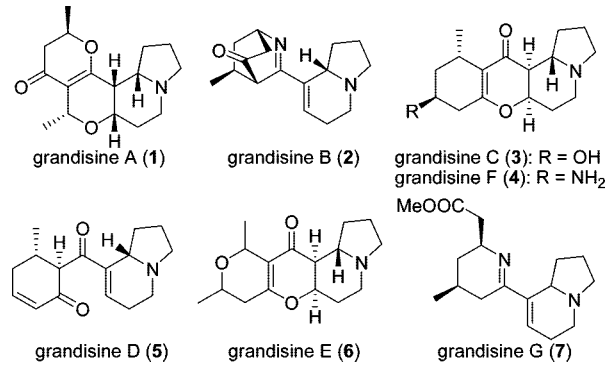


Figure 1. Structure of grandisines.

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(1) Carroll, A. R.; Arumugan, G.; Quinn, R. J.; Redburn, J.; Guymer, G.; Grimshaw, P. *J. Org. Chem.* **2005**, *70*, 1889–1892.
(2) Katavic, P. L.; Venables, D. A.; Forster, P. I.; Guymer, G.; Carroll, A. R. *J. Nat. Prod.* **2006**, *69*, 1295–1299.
(3) Maloney, D. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7789–7792.
(4) For reviews on MBH reaction, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891. (b) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581–1588.
(5) (a) Katsuhara, J. *J. Org. Chem.* **1967**, *32*, 797–799. (b) Mutti, S.; Daubié, C.; Decalogne, F.; Fournier, R.; Rossi, P. *Tetrahedron Lett.* **1996**, *37*, 3125–3128. (c) Caine, D.; Procter, K.; Cassell, R. A. *J. Org. Chem.* **1984**, *49*, 2647–2648. (d) Oppolzer, W.; Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 2755–2762.

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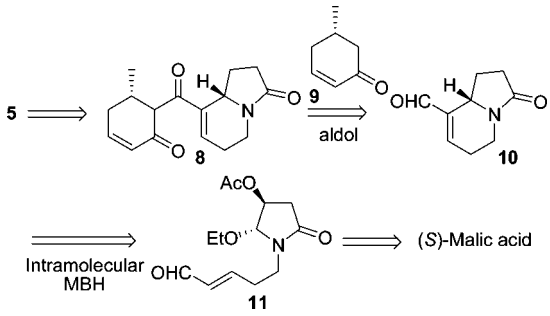
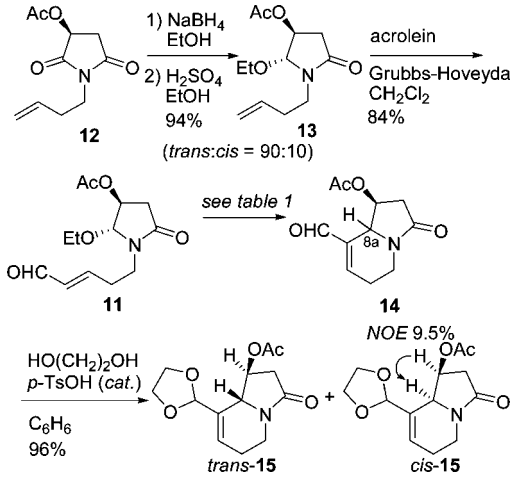
Scheme 1



Our synthetic study was initiated by synthesis of aminal **11** from imide **12** prepared by Lee's method[7] from (*S*)-malic acid (Scheme 2). Regioselective reduction of **12** with $NaBH_4$, immediately followed by ethanolysis, produced ethoxy lactam **13**.[8] Cross-metathesis of **13** with acrolein was achieved using the Grubbs−Hoveyda catalyst to give the MBH-precursor **11**.[9]

Scheme 2



We next examined the MBH ring-closure reaction of **11**. Initial investigations were focused on the solvent effect using TMSOTf and Me_2S.[9] Although the stereoselectivities were high, the chemical yield was fairly low in CH_2Cl_2, CH_3NO_2, or toluene (Table 1, entries 1−3). When acetonitrile was used as the solvent, the desired indolizidine **14** was obtained in the best yield (entry 4). The effects of Lewis and Brønsted acids were next examined. When $BF_3{\cdot}OEt_2$ instead of TMSOTf was used, the stereoselectivity was slightly decreased (entry 5). After experimentation, the use of a Brønsted acid such as Tf_2NH or TfOH was found to give good yield with high stereoselectivity (entries 6−8).[10] The configuration of the resulting stereocenter C-8a of MBH product **14** was confirmed, after conversion into **15**, by the observation of convincing differences in NOE effects between *trans*-**15** and *cis*-**15**.

Table 1. Morita−Baylis−Hillman Reaction of **11**

entry	reagents[a]	solvent	temp	yield (%) (*trans*-**14**:*cis*-**14**)[b]
1	TMSOTf, Me_2S	CH_2Cl_2	−78 °C to rt	32 (96:4)
2	TMSOTf, Me_2S	CH_3NO_2	−15 °C to rt	26 (97:3)
3	TMSOTf, Me_2S	toluene	−60 °C to rt	28 (92:8)
4	TMSOTf, Me_2S	CH_3CN	−35 °C to rt	56 (94:6)
5	$BF_3{\cdot}OEt_2$, Me_2S	CH_3CN	−35 °C to rt	61 (81:19)
6	Tf_2NH, Me_2S	CH_3CN	−35 °C to rt	64 (95:5)
7	TfOH, tetrahydrothiophene	CH_3CN	−35 °C to rt	65 (94:6)
8	TfOH, Me_2S	CH_3CN	−35 °C to rt	67 (96:4)

[a] Aminal **11** (1.0 equiv), Lewis acid or Brønsted acid (2.5 equiv), and sulfide (1.5 equiv) were used. [b] The ratios of products *trans*-**14** and *cis*-**14** were estimated by the ^1H NMR spectra.

We have also partially examined the scope of the Brønsted acid mediated MBH ring-closure reaction, particularly with respect to ring size, because aza-fused bicyclic systems, such as those of the pyrrolizidine, indolizidine, and stemona alkaloids, possess biological activities and have attracted considerable attention in organic synthesis.[11] Aminals **16** and **17**, obtained from (*S*)-malic acid, smoothly cyclized to afford the 5/5-bicyclic lactam **18**[9] in 36% yield (*trans*:*cis* = 91:9) and the 5/7-bicyclic lactam **19** in 64% yield (*trans*:*cis* = 66:34), respectively (Scheme 3). The stereochemistry of the resulting stereocenter C-9a of the MBH product **19** was also confirmed, after conversion into **20**, by the observation of convincing differences in NOE effects between *trans*-**20** and *cis*-**20**.

Completion of the total synthesis of **5** is depicted in Scheme 4. Removal of the acetoxy group of *trans*-**15** was conducted by using the Barton−McCombie deoxygenation protocol.[12] Thus, lactam **21** obtained by deacetylation of *trans*-**15** was transformed to thionocarbonate, which was then

(6) For Brønsted acid catalyzed MBH reaction, see: (a) Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1981**, *22*, 5079–5082. (b) Melching, K. H.; Hiemstra, H.; Klaver, W. J.; Speckamp, W. N. *Tetrahedron Lett.* **1986**, *27*, 4799–4802. (c) Taber, D. F.; Hoerrner, R. S.; Hagen, M. D. *J. Org. Chem.* **1991**, *56*, 1287–1289. (d) Koseki, Y.; Fujino, K.; Takeshita, A.; Sato, H.; Nagasaka, T. *Tetrahedron: Asymmetry* **2007**, *18*, 1533–1539.

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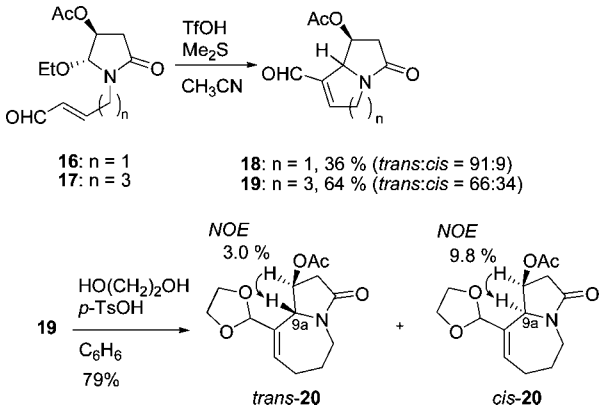
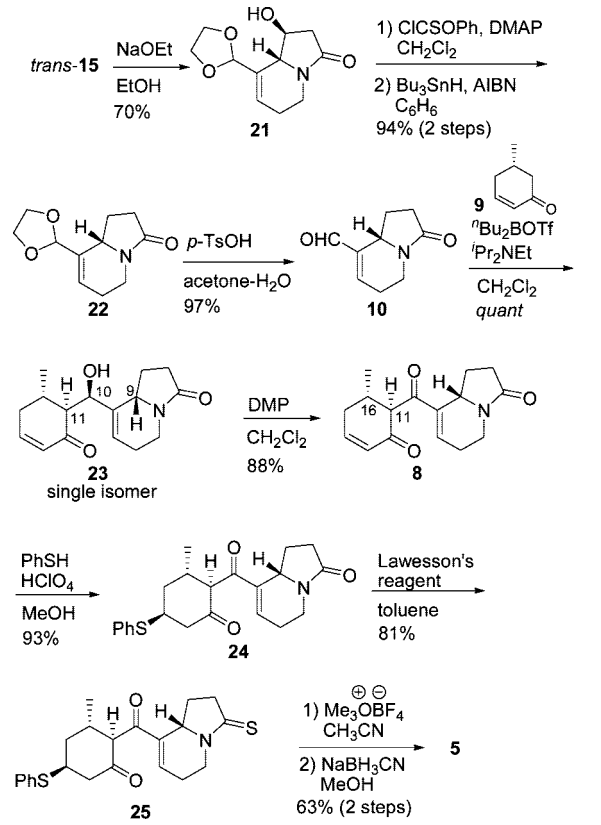
(12) Barton, D. H. R.; Dorchak, J.; Jaszberenyi, J. C. *Tetrahedron* **1992**, *48*, 7435–7446.

Scheme 3



Scheme 4



treated with tributyltin hydride and a catalytic amount of AIBN to afford deoxygenated lactam **22** in 94% yield from **21**. Deprotection of the acetal of **22** by acid hydrolysis gave aldehyde **10** in 97% yield. The crucial aldol reaction of enone **9**[5] with aldehyde **10** was accomplished by employing boron-enolate methodology to furnish **23** in quantitative yield as a single isomer. The stereochemistry at the C-10 position of **23** was confirmed by means of the modified Mosher's method (see Supporting Information).[13] Treatment of alcohol **23** with Dess−Martin periodinane gave **8**, in which the stereochemistry of C-11 was deduced from the large vicinal coupling constants ($J_{H11-H16}$ = 11.2 Hz) in the ^{1}H NMR spectrum. α,β-Unsaturated ketone of **8** was protected as the thiophenol adduct **24**,[14] which was converted into the corresponding thioamide **25** by treatment with Lawesson's reagent. Finally, synthesis of grandisine D (**5**) was accomplished by elimination of the phenylthio group[15] and reduction of thioamide to grandisine D (**5**) with Meerwein's salt and $NaBH_3CN$,[16] in 63% yield from **25**. The spectral data were identical in all respects with the literature data.[2]

In summary, we have successfully completed the total synthesis of grandisine D (**5**) from (*S*)-malic acid, featuring Brønsted acid mediated MBH ring-closure reaction of **11** and stereoselective aldol reaction with (*S*)-5-methylcyclohexenone (**9**). This compound **5** is thought to be a biogenetic precursor of grandisines B (**2**) and F (**4**) and (−)-isoelaeocarpiline.[1,2] This cyclization was also shown to be an efficient strategy for the construction of aza-fused bicyclic systems, such as those of pyrrolizidines and stemona alkaloids. Further application of this strategy to the synthesis of grandisines and other natural products is under investigation.

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Note Added after ASAP Publication. BF_3•OEt_2 was incorrectly shown as BF_3•Et_2 in the version published ASAP February 9, 2009; the corrected version was published on the Web February 12, 2009.

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

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