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The Preparation of (−)-Grandisine B from (+)-Grandisine D; A Biomimetic Total Synthesis or Formation of an Isolation Artefact?

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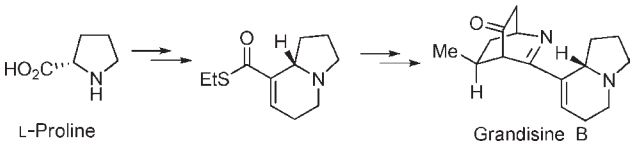
ABSTRACT



An efficient new alkyne-acetal cyclization procedure has been developed to prepare enantiopure indolizidine building blocks from L-proline and then applied to prepare the *Elaeocarpus*-derived alkaloids grandisine B and grandisine D in an efficient manner. However, evidence is presented which indicates that grandisine B does not occur naturally but is formed by reaction of grandisine D with ammonia during the extraction/purification process.

The *Elaeocarpaceae* plant family has been the source of numerous, structurally diverse alkaloids over the years.[1] Carroll and co-workers recently reported the isolation of the *Elaeocarpus*-derived indolizine alkaloids grandisines A **1** and B **2** (Figure 1) from the Australian rainforest tree *Elaeocarpus grandis* as part of a high throughput drug discovery program.[2a] Subsequently, further studies revealed the presence of five additional members of this family, grandisines C−G (**3**−**7**).[2b] These indolizidine alkaloids have attracted considerable attention as they display human δ-opioid receptor affinity.[2] First, Danishefsky and Maloney reported a total synthesis of (+)-grandisine A **1**,[3] and then Tamura's group published a total synthesis of (+)-grandisine D **4** (as its TFA salt).[4] Most recently, the latter group reported the conversion of grandisine B **2** into grandisine D **4** by the double addition of ammonia[5] (following the biosynthetic proposal by Carroll[2]).

Our interest also focused on grandisine B **2**, particularly in view of its structural novelty; it contains an unprecedented combination of both indolizidine and isoquinuclidinone units linked by a C_{sp^2}−C_{sp^2} bond. Although many indolizidine alkaloids have been isolated,[6] isoquinuclidinone alkaloids are very rare indeed. In fact, mearsine **8**,[7,8] isolated from another member of the *Elaeocarpaceae* family, *Peripentadenia mearsii*, appears to be the only other published example. We recently reported a facile route to a range of isoquinuclidinones from 6-acyl-cyclohex-2-enones, employing aqueous ammonia in a one-pot tandem amination/imination procedure, and applied this

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(1) Johns, S. R.; Lamberton, J. A. *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1993; Vol. 14, p 324.
(2) (a) Carroll, A. R.; Arumugan, G.; Quinn, R. J.; Redburn, J.; Guymer, G.; Grimshaw, P. *J. Org. Chem.* **2005**, *70*, 1889. (b) Katavic, P. L.; Venables, D. A.; Forster, P. I.; Guymer, G.; Carroll, A. R. *J. Nat. Prod.* **2006**, *69*, 1295.
(3) Maloney, D. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7789.
(4) Kurasaki, H.; Okamoto, I.; Morita, N.; Tamura, O. *Org. Lett.* **2009**, *11*, 1179.
(5) Kurasaki, H.; Okamoto, I.; Morita, N.; Tamura, O. *Chem.—Eur. J.* **2009**, *15*, 12754.
(6) For a recent review, see: Michael, J. P. *Beilstein J. Org. Chem.* **2007**, *3*, 27.
(7) Robertson, G. B.; Tooptakong, U.; Lamberton, J. A.; Geewananda, Y. A.; Gunawardana, P.; Bick, I. R. C. *Tetrahedron Lett.* **1984**, *25*, 2695.
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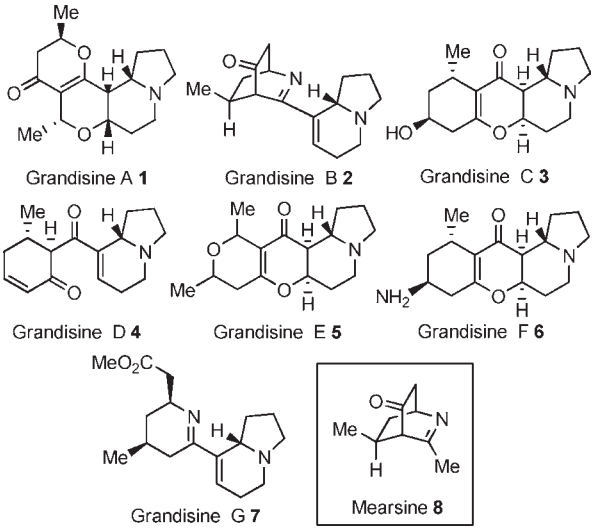


Figure 1. Structure of grandisines and mearsine.

methodology as part of an efficient synthesis of (−)-mearsine **8**.[9] Herein, we report an efficient new route to grandisine D **4** and its conversion into grandisine B **2** (with confirmation by X-ray crystallography); we also discuss the likely nonbiological origin of grandisine B **2**.

Our retrosynthetic approach is illustrated in Figure 2. Disconnection of the isoquinuclidinone moiety of grandisine B **2** by an imination/amination sequence *via* amine **9** leads back to grandisine D **4**. The use of an aldol/oxidation sequence involving enolate **10** derived from (*S*)-5-methylcyclohexenone[10] then leads to the requirement for indolizidine **11**.

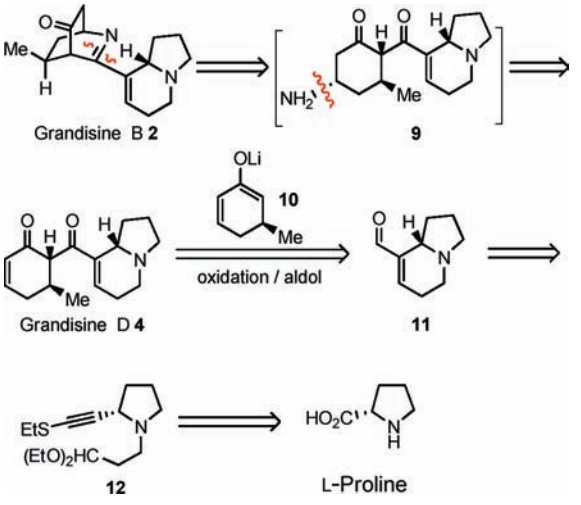
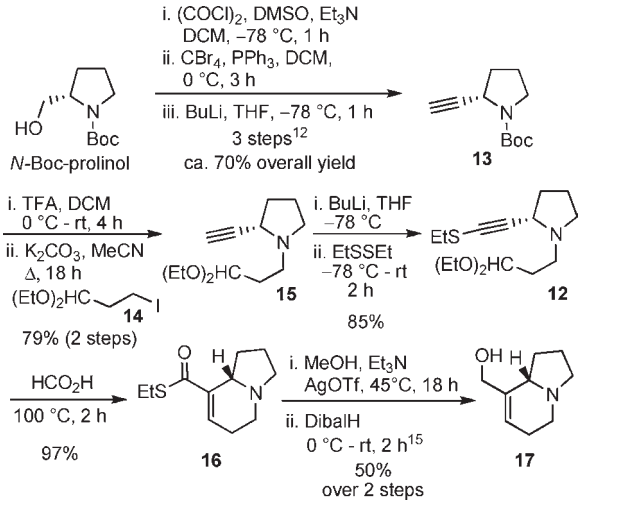


Figure 2. Retrosynthetic analysis of grandisine B **2**.

Given the recent interest in the cyclization reactions of alkynyl aldehydes/acetals,[11] we envisaged preparing **11** utimately from alkyne **12** which we felt would be readily accessible from L-proline.

Scheme 1. Synthesis of Indolizidine Alcohol **17**



The preparation of the key indolizidine building block is shown in Scheme 1. Thus, alkyne **13** was readily accessed on a multigram scale from commercially available *N*-Boc-prolinol in *ca.* 70% overall yield (3 steps) using known procedures.[12] Boc deprotection followed by *N*-alkylation with iodo-acetal **14** proceeded readily to afford acetal **15** in 79% yield over the two steps. Thioalkynes are known to undergo hydration in acidic media to afford the corresponding thioester,[13] and therefore, deprotonation of alkyne **15** with *n*-butyllithium and trapping with ethyl disulfide afforded the cyclization precursor **12** in 85% yield. Pleasingly, on heating a solution of thioalkyne **12** in formic acid,[14] clean cyclization was observed giving thioester **16** as the sole product and as a single enantiomer {$[\alpha]_D$ −87 (*c* 0.97, $CHCl_3$)}. This is an extremely efficient route (7 steps from *N*-Boc-prolinol, *ca.* 50% overall, unoptimised yield) which appears to be simple, robust, and scaleable. In order to prepare the desired allylic alcohol **17**, thioester **16** was converted into the corresponding methyl ester and then reduced using DibalH[15] (direct reduction of the thioester proved problematic).

(9) Cuthbertson, J. D.; Godfrey, A. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2011**, *52*, 2024. See also: Cuthbertson, J. D.; Godfrey, A. A.; Taylor, R. J. K. *Synlett* **2010**, 2805.

(10) (a) (*S*)-5-Methylcyclohexenone is available via a number of procedures; see: Carpenter, R. D.; Fettinger, J. C.; Lam, K. S.; Kurth, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6407 and ref 10b for lead references. (b) Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jorgensen, K. A. *Chem. Commun.* **2006**, 4928.

(11) (a) Gonzalez-Rodriguez, C.; Escalante, L.; Varela, J. A.; Castedo, L.; Saa, C. *Org. Lett.* **2009**, *11*, 1531. (b) Xu, T.; Yang, Q.; Yu, Z.; Li, D.; Dong, J.; Li, Y. *Chem.—Eur. J.* **2010**, *16*, 9264 and references therein.

(12) Paul, A.; Bitterman, H.; Gmeiner, P. *Tetrahedron* **2006**, *62*, 8919 and references therein.

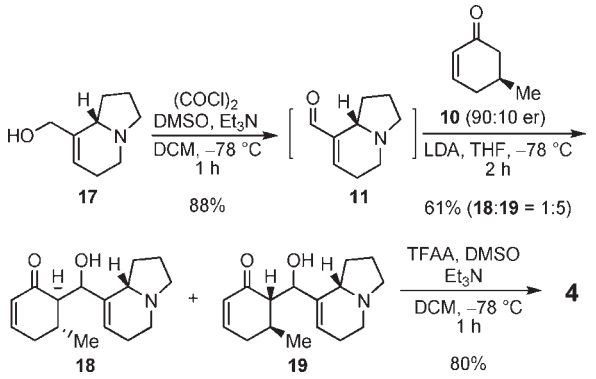
(13) Maruyama, H.; Shiozaki, M.; Oida, S. *Tetrahedron Lett.* **1985**, *26*, 4521.

(14) Menashe, N.; Shvo, Y. *J. Org. Chem.* **1993**, *58*, 7434.

(15) Cordero, F. M.; Anichini, B.; Goti, A.; Brandi, A. *Tetrahedron* **1993**, *49*, 9867.

We were now in a position to explore the final steps of the grandisine synthesis (Scheme 2). Swern oxidation of alcohol **17** gave aldehyde **11** which was reacted with the lithium enolate derived from (*S*)-5-methyl-cyclohexenone **10** (90:10 er; obtained from *tert*-butyl acetoacetate and crotonaldehyde by an organocatalytic procedure).[10b] This aldol reaction produced allylic alcohol **19** along with the diastereoisomer **18** derived from (*R*)-5-methyl-cyclohexenone, which was readily removed by chromatography. Alcohol **19** was obtained as a single diastereomer, tentatively assigned as the *trans*-isomer about the ring. Oxidation using Swern conditions gave grandisine D **4** in 80% yield {$[\alpha]_D$ +73.7 (*c* 0.1, MeOH); published values: $[\alpha]_D^2$ +34.6 (*c* 0.09, MeOH); $[\alpha]_D^{4,5}$ +65.7 (*c* 0.09, MeOH)}. Compound **4** was assigned as the *trans*-isomer, as evidenced by the large coupling constant (11.5 Hz) although minor traces of the enol tautomer/*cis*-isomer were also observed in the ^{1}H NMR spectrum.

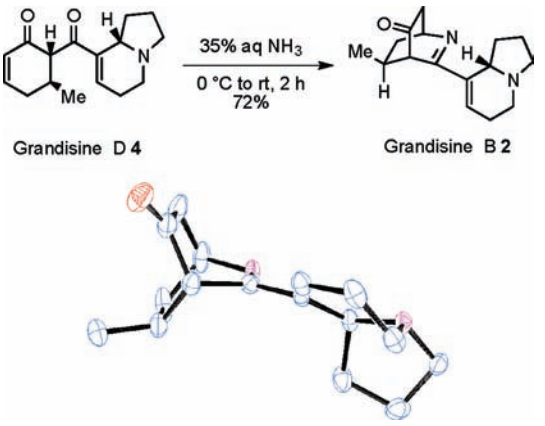
Scheme 2. Synthesis of Grandisine D **4**



With grandisine D **4** in hand, we were in a position to investigate the one-pot tandem amination/imination sequence to generate grandisine B **2** (Scheme 3). This reaction had also been utilized by Tamura's group in their studies.[5] Upon treatment of diketone **4** with 35% aq ammonia, the target compound **2** was obtained stereoselectively in 72% yield; key spectroscopic data were consistent with those published (see Supporting Information). The isolation paper[2] and the publication by Tamura et al.[5] were inconsistent concerning the optical rotation data {$[\alpha]_D$ +11 (*c* 0.1, CH_2Cl_2)[2]; $[\alpha]_D$ −159 (*c* 0.08, CH_2Cl_2)[5]}. Our sample had $[\alpha]_D$ −177.5 (*c* 0.08, CH_2Cl_2), which agreed well with Tamura's value. A further indication of the purity was that compound **2**, as its dipicrate salt, was readily crystallized and, for the first time, an X-ray crystal structure was obtained which fully confirmed the published structure (Scheme 3).

On close reading of the original publications describing the isolation of grandisine B, our attention was drawn to the extraction conditions: "The aqueous layer (400 mL) was basified with 27% NH_4OH (2 × 200 mL) and

Scheme 3. Synthesis of Grandisine B **2**[a]



[a] X-ray structure of compound **2**·(picric acid)$_2$ depicted using ORTPE-3 (CCDC 815228); picrate anions omitted for clarity.

partitioned with CH_2Cl_2."[2] These conditions were extremely close to the ones we had employed for the conversion of grandisine D **4** into grandisine B **2**; we therefore conjectured about the origin of grandisine B **2**. One distinct possibility appeared to be that grandisine D **4** is a true natural product but that on extraction using ammonia it is converted into grandisine B **2**. If true, then grandisine B **2** is not a natural product and is actually an artefact of the extraction procedure.[16] To gain greater understanding, we contacted Professor Carroll who replied stating "Yes, we have certainly speculated about whether some of these compounds might be artefacts of the extraction and purification process. Grandisines B, F, and G in particular are not observed by (+) ESI MS in crude methanol extracts of the leaves suggesting that these compounds at least are artefacts formed on treatment with ammonia." It would therefore appear that grandisine B **2** is not naturally occurring but is formed by reaction of grandisine D **4** with ammonia during the extraction/purification process.

In summary, an efficient new alkyne cyclization procedure has been developed to prepare enantiopure indolizidine building blocks from L-proline. Using this methodology, the natural product grandisine D **4** has been prepared in an efficient manner (9 steps, 14% overall yield from the known alkynyl-pyrrolidine **13**; 13 steps, 10% overall yield from prolinol); this route compares well with the procedure recently published by Tamura et al. (15 steps, 12% overall yield from (*S*)-malic acid).[4]

In addition, a tandem imination/amination sequence has been employed for the assembly of the isoquinuclidinone moiety in the conversion of grandisine D **4** into grandisine B **2** (and the first X-ray of grandisine B as its dipicrate salt has been obtained). Perhaps most

(16) For other examples of ammonia-induced artefact formation during the isolation of natural products, see: (a) Wenkert, E.; Fuchs, A.; McChesney, J. D *J. Org. Chem.* **1965**, *30*, 2931 (rosmaricine). (b) Suliman, M.; Martin, M. -T.; Pais, M.; Hadi, H. A.; Awang, K. *Phytochem.* **1998**, *49*, 2192 (desmosine).

significantly, evidence is presented which indicates that grandisine B **2** does not occur naturally but is formed by reaction of grandisine D **4** with ammonia during the extraction/purification process.

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Supporting Information Available. Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all novel compounds. Crystallographic data for **2** (CCDC815228). This material is available free of charge via the Internet at http://pubs.acs.org.