Natural Products

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Conformational Locking through Allylic Strain as a Device for Stereocontrol—Total Synthesis of Grandisine A**

*David J. Maloney and Samuel J. Danishefsky**

Carroll et al. have described the isolation and structural assignment of a family of indolizidine alkaloids known as grandisines from *Elaeocarpus grandis*.[1] From a biological perspective, these small-molecule natural products (SMNP) are of interest since they bind to the opioid receptors with apparent selectivity.[2] On the basis of earlier studies that addressed the consequences of binding to opioid receptors, it is thought that agents with specific affinity for the δ receptor may well bring about modulation and reduction of pain while minimizing common side effects such as nausea and hypertension.[3] Although the binding affinity of various grandisines to the δ-opioid receptor does not yet warrant their development as pharmaceuticals, their receptor selectivity is encouraging. To pursue such potentialities in the context of a medicinal chemistry effort would require the development of a reasonably concise and efficient total synthesis of a particular grandisine, which would provide adequate material for a collaborative exploratory program with specialist laboratories. In this connection, we identified grandisine A (**1**)[1a] as our target molecule.

This selection was influenced, to no small extent, by a perception that it would be the most challenging of the grandisines from the perspective of a stereoselective total synthesis. It seemed that if a successful program to reach **1** could be realized, there would be a broader menu of options for gaining access to other members of the grandisine family. What makes the grandisine A congener unique is its backbone stereoconnectivity at carbon atoms 7, 8, and 9. The *syn-syn* relationship of the protons at these stereogenic centers enforces a hemisphere-like presentation of rings B, C, and D, thus resulting in a significant abutment of loci in rings B and D (Scheme 1). Furthermore, if pyramidalization of the lone pair of electrons on the bridgehead indolizidine nitrogen atom tended to occur in the direction of a cisoid C:D bridgehead junction, as expected, the B:D abutment could be even more severe. Hence, stereocontrol would have to be manifested at the kinetic level. Thermodynamic equilibration of a tricyclic intermediate through a C10 ketone or vinylogously through the C14 ketone of the fully mature grandisine would most likely lead to an undesired B:C *trans* fusion.

From the outset, our retrosynthetic analysis favored introducing the A ring of grandisine A by merging, in some fashion, a single antipode of a 3-hydroxy-butyrate moiety **5** (X is undefined) with a suitable tetrahydro-*cis*-fused pyranone, which we represent for discussion purposes as **4** (Scheme 1). It goes without saying that, in the merger of **4** and **5**, the resident sites of stereogenicity would be matched appropriately for progression to **1**. In the light of our concerns discussed above, we are deliberately vague as to the form in which the future D ring is presented in the step in which **4** and **5** merge. Indeed, as will be seen, the proper timing in the fashioning of the D ring is critical.

Aside from the uncertainties surrounding the D ring, there was concern about the viability of the coupling step itself. Insofar as it would involve the use of a C11-based carbanion, there was a possibility of β elimination of the oxygen atom of the ether-like ring, thus potentially compromising the configurational robustness at C12 and even threatening the feasibility of the central idea. Moreover, there was concern that a base-induced merger of **4** and **5** might serve to equilibrate C8, which could undermine the viability of a B:C *cis* fusion (see above).

Recognizing the B ring tetrahydropyranone substructural motif in **4**, we sought to exploit a Lewis acid catalyzed diene–aldehyde cyclocondensation (LACDAC)[4] of an unusual sort. Thus, one of the double bonds in the diene would be contained in a suitably substituted $\Delta 3^{(4)}$ tetrahydropyridine ring, the C3 atom of the piperidine ring would be joined to an α-oxygenated vinyl group (see diene **2**), and the heterodienophile would be acetaldehyde. Somehow, kinetic protonation of the enol derivative in cycloadduct **3** would have to occur from the β face to afford the *cis* B:C junction (see **4**).

The results from some initial experiments are important in appreciating the strategy that was adopted and implemented. First, as has been reported, the LACDAC reaction of **6** and acetaldehyde yielded **7**, in which cycloaddition of the acetaldehyde had occurred in an *anti* fashion to the existing

[*] Prof. S. J. Danishefsky
Laboratory of Bioorganic Chemistry
Memorial Sloan-Kettering Cancer Center
1275 York Avenue, Box 106
New York, NY 10021 (USA)
Fax: (+1) 212-772-8691
E-mail: danishes@mskcc.org
and
Department of Chemistry
Columbia University
3000 Broadway
New York, NY 10027 (USA)
Dr. D. J. Maloney
Laboratory of Bioorganic Chemistry
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10021 (USA)

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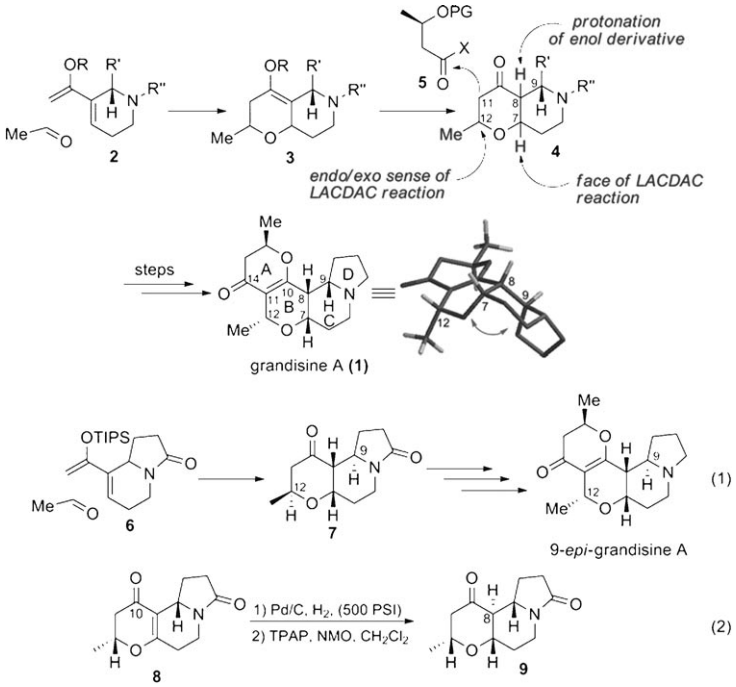


Scheme 1. Strategy toward grandisine A. PG = protecting group, TIPS = triisopropylsilyl, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine-*N*-oxide.

five-membered precursor to the D ring.[5] While stereomodification at C12 proved to be possible, we were never able to achieve the required correction of the configuration at C9 [Scheme 1, Eq. (1)].

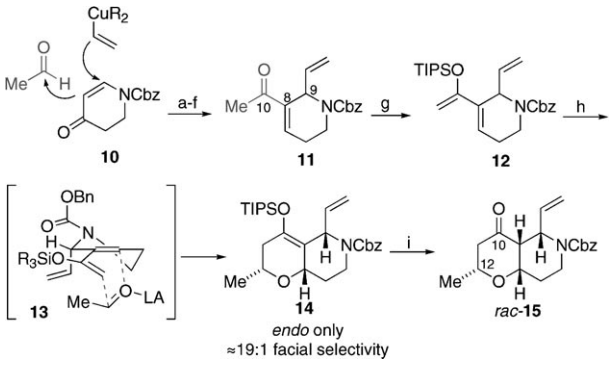
Another influential finding resulted from hydrogenation of **8**. Oxidation of the C10 alcohol of the resultant crude tetrahydroproduct afforded only a *trans*-fused B:C product (**9**) [Scheme 1, Eq. (2)]. This result again demonstrates the difficulties of generating the required B:C *cis* fusion with an intact five-membered D ring.

From these hard-won lessons, an exciting idea for reaching grandisine A presented itself. The cyclocondensation reaction with acetaldehyde would be conducted on a seco version of the D ring; that is, on **12** (Scheme 2). We envisioned that the planar Cbz group on the nitrogen atom as well as the siloxyvinyl group at C8 would tend to impose a strong pseudoaxial bias upon the vinyl function at C9 (to minimize $A^{(1,3)}$- and $A^{(1,2)}$-type abutments (see **13** in Scheme 2).[6] It was also anticipated that, even with the vinyl group in an axial-like orientation, the LACDAC reaction would occur from the α face, with formation of the incipient C7–O bond in an axial sense with respect to the B ring.

A straightforward synthesis of **12**, as shown in Scheme 2, enabled the experimental evaluation of these concepts. The route started from the readily available dihydropyridone **10**.[7] Nucleophilic vinylation followed by trapping with acetaldehyde led to diastereomeric aldol products. Progression from the aldol adducts involved protection of the epimeric alcohols as silyl ethers, reduction of the keto moiety, and activation of the resultant alcohols as their mesylates.[8] Deprotection of the side-chain alcohols and oxidation to the corresponding ketone set the stage for β elimination of the mesyloxy group to provide ketone **11**. Finally, silylation of the methyl ketone gave the required enol **12**. The setting for studying the fateful LACDAC reaction was now in place.

Cyclocondensation of diene **12** with acetaldehyde was conducted as shown. Under the conditions of our experiment (Scheme 2), we were unable to detect any reaction intermediates en route to **14**. On the basis of our observations, we would tend to characterize the mechanism of this particular LACDAC reaction as a cycloaddition rather than the other extreme possibility described many years ago: that is, aldolization followed by heterocyclization.[9] Deprotection of the silyl enol ether of crude **14** gave rise to the desired **15**, as essentially the only product (in 74% yield over two steps). In addition to achieving the desired face selectivity corresponding to axial addition during the formation of the C7–O bond of **14**, the configuration at C12 was seen to be under tight kinetic control—corresponding formally to *endo* addition with respect to the methyl group, as proposed in our early investigation two decades ago.[9] We attribute this high selectivity to the more concerted-like cycloaddition mechanism in which the *endo* preference for disposition of the methyl group in alignment **13** may well reflect an *exo* preference for the catalytic system activating the carbonyl group of the acetaldehyde.

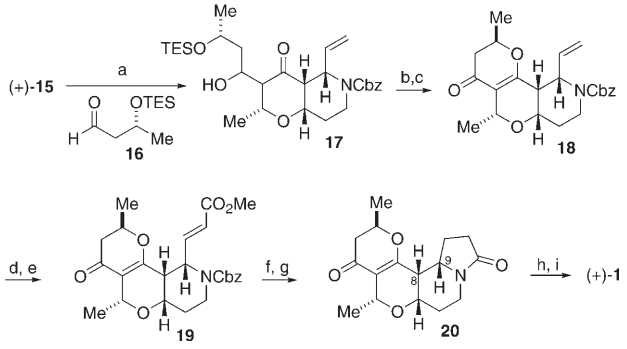
The combination of $BF_3{\cdot}OEt_2$ with the aldehydocarbonyl group could well be quite sterically demanding and might, therefore, preferentially be integrated into ensemble **13** in an *exo* sense. This would direct the methyl group to be incorporated in an *endo* manner. Moreover, the imposed conformational lock occasioned by the NCbz group readily accounts for the β-face protonation in the conversion of **14** into **15**. This arrangement corresponds to a stereo-electroni-



Scheme 2. Synthesis of **15**. Reagents and conditions: a) CuI (20 mol%), Me_2S (10% v/v), vinyl-MgBr (1.0 M THF), THF, −20°C, then acetaldehyde; b) TESCl, imidazole, CH_2Cl_2, 76% over 2 steps; c) $NaBH_4$, MeOH, 0°C, 100%; d) MsCl, NEt_3, CH_2Cl_2, 0°C; e) cat. 10-CSA, MeOH, 25°C; f) oxalyl chloride, DMSO, $(iPr)_2NEt$, CH_2Cl_2, −78°C, then DBU, reflux, 4 h, 66% over 4 steps; g) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C→25°C, 97%; h) $BF_3{\cdot}OEt_2$, acetaldehyde, Et_2O, −78°C; i) TBAF, AcOH, THF, 25°C, 74% over 2-steps. Cbz = benzyloxycarbonyl, TES = triethylsilyl, Ms = methanesulfonyl, CSA = camphorsulfonic acid, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Tf = trifluoromethanesulfonyl, TBAF = tetrabutylammonium fluoride, Bn = benzyl, LA = Lewis acid.

cally preferred axial attack. In any case, the required array of stereogenic centers encompassing carbon atoms 12, 7, 8, and 9 had been installed in **15**.

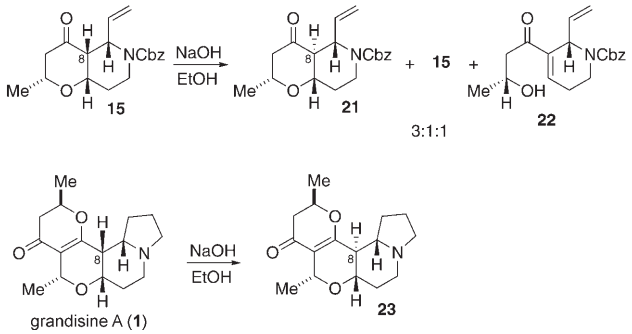
With the desired *rac*-**15** in hand, we addressed the concluding phases of the synthesis. The next stage would require annealing the A ring onto the pyranone. To avoid issues associated with the coupling of a racemic material with an enantiomerically defined entity, we readily obtained enantiopure (+)-**15** by resolution of its racemic precursor by HPLC on a chiral support.[10] Next, the lithium enolate of **15** was coupled to (*R*)-3-(triethylsilyloxy)butanal (**16**)[11] mediated by anhydrous zinc chloride (Scheme 3). The resultant β-hydroxyketone **17** was oxidized, and subsequent acid-catalyzed deprotection of the silyl group led to dehydrative cyclization, thereby providing **18** as a single antipode. Thus, in practice, reaching ring A by annulation of an appropriately matched β-hydroxybutyrate derivative could be realized in spite of the potential difficulties discussed previously (see **22** below).



Scheme 3. Synthesis of grandisine A (**1**). Reagents and conditions: a) LiHMDS, $ZnCl_2$, THF, −78 °C, then **16**, −78 °C→−50 °C, 3.5 h; b) Dess–Martin periodinane, CH_2Cl_2; c) TFA, CH_2Cl_2, 73% over 3 steps; d) O_3, MeOH, Sudan III (indicator), −78 °C, then Me_2S, −78 °C→25 °C; e) methyl (triphenylphosphoranylidene)acetate, benzene, 60 °C→40 °C, 9.5 h, 80% over 2 steps; f) 10% Pd/C, H_2 (1 atm), MeOH; g) PhMe, reflux, 24 h, 98% over 2 steps; h) Lawesson's reagent, PhMe, 65 °C, 98%; i) Raney nickel (washed), THF, 25 °C, 94%. HMDS = hexamethyldisilazide, TFA = trifluoroacetic acid.

There now remained the requirement of installing the D ring from its seco precursor. Clearly, we would be exploiting the vinyl group in this regard. In practice, the vinyl group was cleaved by ozonolysis and the resultant aldehyde was homologated through a Wittig-type condensation with methyl (triphenylphosphoranylidene)acetate to afford the α,β-unsaturated ester **19**.[12] Concurrent reduction of the disubstituted double bond and cleavage of the Cbz group followed by heating led to lactamization, resulting in formation of **20**. In the last stage of the synthesis, Lawesson's reagent served to convert **20** into the requisite thiolactam. Following reduction with Raney nickel under carefully defined conditions, this intermediate was converted into grandisine A (**1**). The spectroscopic properties of fully synthetic **1** were identical to those previously reported and, in any case, are independently conclusive. We attribute the significant difference in the magnitude of the optical rotation data [found: $[\alpha]_D^{26} = +180.1\ cm^3 g^{-1} dm^{-1}$ ($c = 0.1\ g cm^{-3}$ in CH_2Cl_2), previously reported: $[\alpha]_D^{23} = +38.5\ cm^3 g^{-1} dm^{-1}$ ($c = 0.1\ g cm^{-3}$ in CH_2Cl_2)] to the synthetic material having a much higher level of purity.[13,14] It is clear that the stereostructure of grandisine A had been properly assigned and that its inaugural total synthesis was now complete.

With the total synthesis of grandisine A accomplished, and with intermediates en route to the natural products in hand, we were in a position to evaluate some key thermodynamic relationships. In this connection, we examined **15**. Equilibration of this compound with a base led to a 1:3 ratio of the starting *cis*-fused **15** and *trans*-fused **21** (Scheme 4).



Scheme 4. Epimerization of grandisine A.

This ratio corresponds at least roughly to the thermodynamic equilibrium under these conditions. This was established by re-equilibration of the purified major compound **21**, where a 3:1 ratio of **21**:**15** was again obtained. Hence, it does seem that, at the bicyclic level, the *trans*-fused epimer is more stable than the *cis*, although by only a relatively small differential (approximately 1 kcal mol^{-1}). In addition to equilibrating **15** to **21**, under these conditions, a minor amount of **22** (**21**:**15**:**22** ca. 3:1:1) was also observed. It is interesting to note that **22** formally corresponds to β elimination of the C7–O bond via the C8 enolate of **15** or **21**. This possibility had been raised above in connection with the proposed generalized condensation of **4** and **5**, but, in fact, does not occur under the very mild conditions used in the coupling of **15** and **16**.

In addition, we also treated grandisine A (**1**) under equilibrating conditions. Here, there was a clean conversion into 8-*epi*-grandisine (**23**). As such, our early conjecture that 8-*epi*-grandisine is likely to be far more stable than **1** turned out to be correct. Thus, it is clear that the total synthesis of grandisine had been accomplished through kinetic control to maintain the *cis* B:C ring fusion in its less stable form.

In summary, the total synthesis of grandisine A has been accomplished. The defining step in the total synthesis was a LACDAC reaction which exhibited stereo-electronic control that favored axial addition in the formation of the C7–O bond. Under these circumstances, *endo* addition was controlled through preferential presentation of the catalytic domain of ensemble **13** to the less hindered *exo* face.[15] It appears that the course of this reaction was governed by a conformational lock imposed on the bicyclic **13**, wherein the

vinyl group was coaxed into a strongly preferred pseudoaxial orientation. We believe that there are significant take-home lessons to be garnered from this now straightforward route to grandisine A. Moreover, the newfound accessibility of the natural product in its appropriate enantiomeric form enables a medicinal chemistry program to probe structure–activity relationships in an attempt to upgrade its binding affinity to the δ-opioid receptor.

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[10] The relative stereochemistry was determined by extensive 2D NMR analysis; see the Supporting Information for a detailed procedure of the HPLC (chiral support) separation of the enantiomers.

[11] Prepared in two steps from commercially available ethyl *(R)*-3-hydroxy butyrate: 1) TESCl, imidazole, CH_2Cl_2; 2) diisobutylaluminum hydride, CH_2Cl_2, −78 °C.

[12] A more direct route that involved a cross-metathesis of **18** with methyl or ethyl acrylate was attempted; however, despite a number of different catalysts and reaction conditions being used, only starting material was recovered. Presumably this result is due to the hindered nature of the vinyl group.

[13] See the Supporting Information for the ^1H and ^{13}C spectra of the authentic and synthetic natural products. The accuracy of our polarimeter was verified with commercially available optically pure compounds (*R*)-(+)-1,1′-bi-2-naphthol and (*S*)-(−)-4-benzyl-2-oxazolidinone.

[14] At the time that we were planning the closing phases of the total synthesis, the absolute configuration of naturally occurring grandisine A was not known. By happenstance, we first used the *R* form of 3-hydroxybutyrate, which in turn led to the *R* aldehyde **16**. Ultimately, this was coupled to both (+)-**15** and (−)-**15**. At that stage we had no way of knowing which one would be opportune for merger with (*R*)-**16** to attain the relative configuration of grandisine A. As shown above, coupling with (+)-**15** led eventually to grandisine A (**1**). The same sequence of steps starting with (−)-**15** led to a final product whose ^1H NMR spectrum is similar, but clearly different from that of grandisine A. This product is thus assigned the structure, 16-*epi*-*ent*-grandisine A, the ^1H and ^{13}C spectra of which are provided in the Supporting Information. Hence there can be no doubt that the relative configuration of synthetic **1** corresponds to that of natural grandisine A. It also seems likely (discrepancies in the magnitude of dextrarotation notwithstanding) that the absolute configuration of synthetic **1** also corresponds to that of natural grandisine A.

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