Natural Product Synthesis

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A Telescoped Route to 2,6-Disubstituted 2,3,4,5-Tetrahydropyridines and 2,6-*syn*-Disubstituted Piperidines: Total Synthesis of (−)-Grandisine G**

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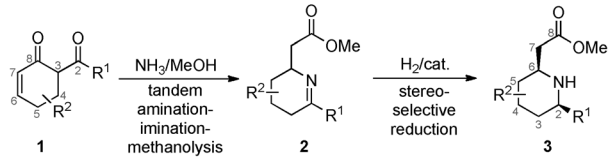
Nitrogen heterocycles constitute one of the most important classes of lead compounds in the pharmaceutical and agrochemical industries, with pyridines and their reduced analogues occupying a prominent position,[1] particularly in the case of piperidines.[2] New and efficient routes to such compounds are always valuable and herein we describe a remarkable one-pot rearrangement for the conversion of readily available 6-acyl cyclohexenones **1** into 2,6-disubstituted 2,3,4,5-tetrahydropyridines **2** and then into 2,6-*syn*-disubstituted piperidines **3** after diastereoselective reduction (Scheme 1). The conceptual novelty of such a telescoped



Scheme 1. Novel route to *syn*-2,6-disubstituted piperidines.

approach to reduced pyridines becomes apparent from an atom mapping analysis: the five carbon atoms in the heterocyclic rings originate from the cyclohexenone ring (4 carbons) with the 6-acyl carbonyl group providing the fifth carbon atom.

The sequence shown in Scheme 1 was inspired by biosynthetic speculation concerning the grandisine alkaloids,[3] and synthetic studies by our group in the same area.[4] However, this approach to piperidines has not been explored, and given the widespread distribution of bioactive piperidines in nature (from amphibians, insects, plants, and others), and their importance in pharmaceuticals and agrochemicals,[1,2] we decided to explore its potential.

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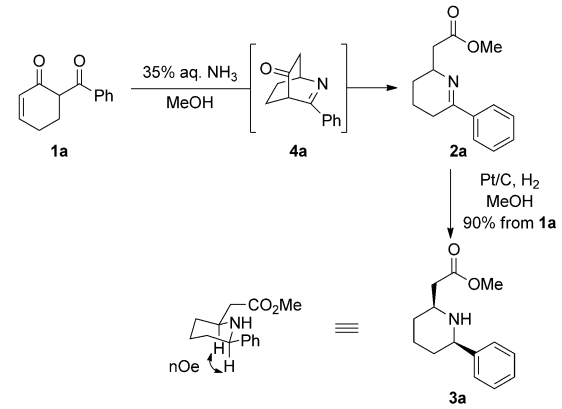
Initial studies (Scheme 2) were based on the cyclization/ring-opening of the known diketone **1a**,[5] which was readily prepared from cyclohexenone. The grandisine synthetic

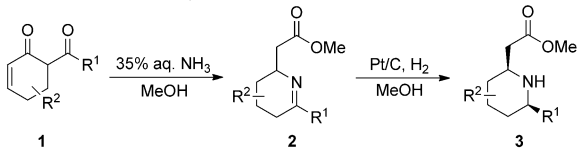


Scheme 2. Initial studies on the rearrangement-hydrogenation sequence.

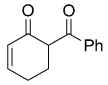
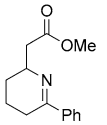
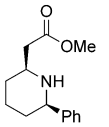
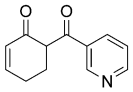
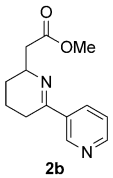
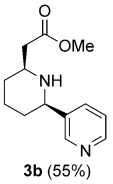
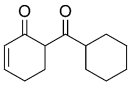
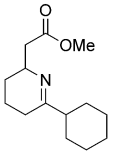
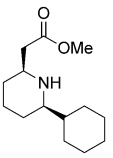
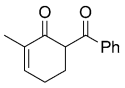
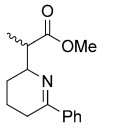
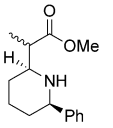
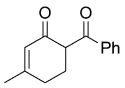
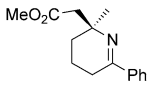
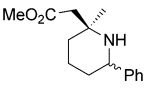
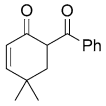
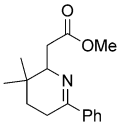
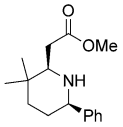
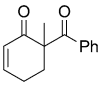
studies had demonstrated that treatment of such diketones with ammonia resulted in a tandem amination–imination sequence to generate 5-oxo-2-aza-bicyclo[2.2.2]oct-2-enes such as **4a**.[4,6] However, biosynthetic speculation[3] (and limited experimental evidence[4b]) indicated that such bicyclic systems should be susceptible to retro-Dieckmann-like ring-opening by methanol. Upon treatment with excess 35% aqueous ammonia in methanol,[4b] rapid consumption of the starting material was observed giving rise directly to the imine **2a**, presumably through the intermediacy of bicycle **4a**, in 96% yield (>90% purity by NMR spectroscopy). Imine **2a** underwent significant decomposition upon chromatography and was therefore immediately reduced: treatment with Pt/C, H_2 (1 h, RT) gave rise to a single diastereomer **3a**, which was isolated in 90% yield over two steps.[7] Analysis by ^{1}H/^{13}C NMR spectroscopy, following Lhommet's guidelines,[8] revealed the product to be *syn*-2,6-disubstituted piperidine **3a**. This stereochemical assignment was subsequently confirmed by X-ray analysis on a related compound.[9]

Having confirmed the viability of the proposed sequence for the preparation of heterocycles **2** and **3**, the scope of the reaction was investigated using a range of readily available 1,3-diketones **1**. As can be seen from Table 1 (entries 1–3), unsubstituted cyclohexenone substrates bearing phenyl, heterocyclic and aliphatic ketones **1a–c** gave the corresponding piperidines **3a–c** in good to excellent yield over the two step

Table 1: Conversion of cyclohexenones **1**.[a]



1 **2** **3**

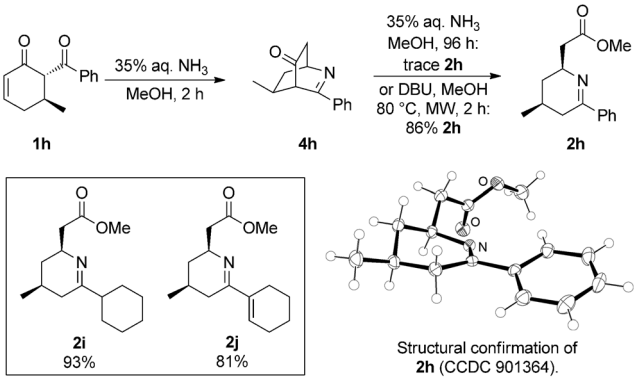
Entry	Cyclohexenone	2,3,4,5-Tetrahydropyridine[b]	Piperidine[c]
1	 **1a**	 **2a** (97%)	 **3a** (90%)
2	 **1b**	 **2b**	 **3b** (55%)
3	 **1c**	 **2c** (97%)	 **3c** (92%)[g]
4	 **1d**	 **2d** (95%)[d]	 **3d** (69%, 1:1)
5	 **1e**	 **2e** (94%)[d]	 **3e** (77%, 1:1)
6	 **1f**	 **2f** (97%)[d]	 **3f** (68%)
7	 **1g**	no reaction	no reaction

[a] Reaction conditions: Unless otherwise stated, all reactions were performed on a 0.500 mmol scale with 1) MeOH (4 mL), 35% aq. NH_3 (2 mL), 0°C for 30 min, then RT for 3 h; 2) MeOH (5 mL), Pt/C (2.5 mol%), H_2, RT for 1 h. Chromatographic purification was used for all products except **3a** and **3c**. [b] The identity of imines **2** was confirmed by NMR analysis of the unpurified product and the crude material was then reduced before chromatographic purification. [c] Yield of isolated product over 2 steps; in all cases, apart from **3e**, only the *cis* diastereoisomer of the piperidine was observed, according to the ^{1}H NMR spectrum of the unpurified product. [d] Standard conditions, but a longer reaction time was required for the ammonolysis/rearrangement (**2d**, 36 h; **2e**, 16 h; **2f**, 8 h).

process. In all cases, the identity of imines **2** was confirmed by NMR analysis of the unpurified products and the crude material was then reduced to give piperidines **3**. The HCl salt of cyclohexyl piperidine **3c** proved to be crystalline, and single crystal X-ray analysis confirmed the *syn*-stereochemistry of the side chains.[9]

We next moved on to examine the effect of substituents on the cyclohexenone ring (entries 4–7). In the case of 2-methylcyclohexenone **1d**, 3-methyl- **1e**, and 4,4-dimethylcyclohexenone **1f** the expected 2,3,4,5-tetrahydropyridines **2d**,**e**,**f** and 2,6-disubstituted piperidines **3d**,**e**,**f** were formed, but extended reaction times were required for the ammonolysis/ring-opening sequence (8–36 h as opposed to 3 h for the unsubstituted examples). With 6-methylcyclohexenone **1g** (entry 7), the ammonia addition reaction was unsuccessful, presumably because of the fact that epimerization at the C6 center is now precluded.

Much more surprising, however, was the observation that the bicyclo[2.2.2]oct-2-enes derived from 5-methyl-substituted cyclohexenones were completely stable to methanolic ring-opening (Scheme 3). So, when cyclohexenone **1h** was



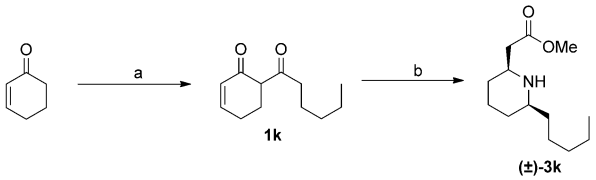
Scheme 3. Conditions for 5-methylcyclohexenones.

treated with methanolic ammonia under the normal conditions for 3 h only the bicycle **4h** was isolated, and even after 96 h only a trace of the ring-opened tetrahydropyridine **2h** was observed. Other 5-methyl-substituted cyclohexenones behaved in a similar manner. It would therefore appear that it is the presence of the 5-methyl substituent that dramatically inhibits the ring-opening of 5-oxo-2-aza-bicyclo[2.2.2]oct-2-enes such as **4h**. There are a number of possible rationales for this observation, but further studies are needed to provide a definitive explanation. However, with bicycle **4h** in hand, more forcing conditions for the base-induced methanolic ring-opening process to give 2,3,4,5-tetrahydropyridine **2h** were examined. Eventually, it was found that the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methanol at reflux resulted in complete conversion into methyl ester **2h** after 6 h; when the reaction was repeated in the microwave at 80°C, the reaction time could be reduced to 2 h. X-ray crystallography confirmed the structure of compound **2h**[9] (Scheme 3).

Using the same two-step procedure, the corresponding 5-methyl-substituted cyclohexenone compounds were converted into cyclohexyl- and cyclohexenyl-substituted tetrahydropyridines **2i** and **2j**, respectively. So either directly, or by

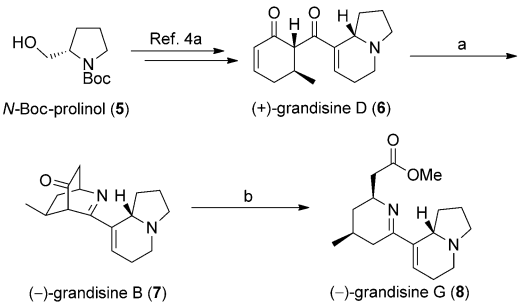
a two-step procedure, a new route for the preparation of tetrahydropyridines **2** and piperidines **3** had been developed.

To demonstrate the utility of this novel sequence, the conversion of cyclohexenone into *cis*-2-methoxycarbonyl-(methyl)-6-pentylpiperidine (**3k**), a natural product isolated from ladybirds of the species *Calvia guttata*,[10] was investigated (Scheme 4). The readily obtained diketone **1k** underwent ammonia addition/imine formation/methanolysis under standard conditions and then *syn*-hydrogenation to give the natural product **3k** in 90% yield from compound **1k** (68% from cyclohexenone).



Scheme 4. Reagents and conditions: a) 1) LDA, −78 °C, THF then RCHO, THF, −78 °C; 2) TFAA, DMSO, Et_3N, CH_2Cl_2, −78 °C, 76% yield over 2 steps; b) 1) 35% aq. NH_3, MeOH, 0 °C→RT; 2) Pt/C, H_2, MeOH, RT, 90% yield over 2 steps. LDA = lithium diisopropylamine, TFAA = trifluoroacetic anhydride.

Finally, the value of this new procedure as a means of preparing 2,3,4,5-tetrahydropyridines was exemplified by application to the first total synthesis of (−)-grandisine G (**8**), a compound isolated by Carroll et al. from an extract obtained from the Australian rainforest tree *Elaeocarpus grandis* and shown to display human δ-opioid receptor binding affinity.[3b] Thus (Scheme 5), (+)-grandisine D (**6**)



Scheme 5. Reagents and conditions: a) 35% aq. NH_3, 1 M aq. HCl, 0 °C→RT, 72%; b) DBU, MeOH, 80 °C (microwave), 63%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

was prepared from a commercially-available L-proline derivative **5** using the procedure previously reported by our group,[4a] and then subjected to the tandem amination-imination conditions to generate (−)-grandisine B (**7**).[4a,6] We were now in a position to test the base-induced methanolysis of compound **7**; given the presence of the 5-methyl substituent it was not surprising to find that no ring-opening was observed at room temperature under the original conditions. However, we were delighted to observe that the use of the DBU/MeOH microwave reaction for 7 h gave the ring-opened product (−)-grandisine G (**8**) in 63% yield after column chromatography.

This is the first reported total synthesis of grandisine G (**8**) and the characterization data was fully consistent with the assigned structure: for example, ^{13}C NMR ($CDCl_3$, 100 MHz) 173.1 (ester), 164.0 (imine). Although no optical rotation data was reported for grandisine G (**8**),[3b] the synthetic material gave $[\alpha]_D = -82.2$ ($c = 0.60$, $CHCl_3$). Treatment of the free base **8** with trifluoroacetic acid (TFA) allowed comparison with the NMR spectroscopic data reported by Carroll and coworkers.[3b] Full details are given in the Supporting Information, but an excellent agreement was observed between the NMR spectroscopic data for $(\mathbf{8})_2$·TFA and the published values: for example, ^{13}C NMR ([D_6]DMSO, 100 MHz): $\delta =$ 172.0, 162.9, 135.7, and 127.1 ppm; published values:[3b] ^{13}C NMR ([D_6]DMSO, 125 MHz): $\delta = 172.0$, 163.0, 135.2, and 127.0 ppm.

In summary, we have developed and evaluated the scope of a novel, bio-inspired method for the conversion of 6-acyl cyclohexenones into 2,6-disubstituted 2,3,4,5-tetrahydropyridines and, after diastereoselective reduction, 2,6-*syn*-disubstituted piperidines. The potential of the piperidine synthesis has been demonstrated by a short synthesis of *cis*-2-methoxycarbonylmethyl-6-pentylpiperidine (**3k**, isolated from ladybirds of the species *Calvia guttata*). Furthermore, the first total synthesis of (−)-grandisine G (**8**) has been accomplished. Applications of this new method for the synthesis of more complex piperidine alkaloids are the subject of current investigations.

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[7] Reduction using sodium borohydride in methanol gave a mixture (ca. 3:1) of the *cis*/*trans*-isomers of the disubstituted piperidine **3a**.
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[9] CCDC 899115 (**3c**) and 901364 (**2h**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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