

Asymmetric Synthesis of the Core Structure of the Melodinus Alkaloids

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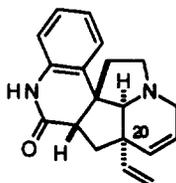
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Abstract: The strategy developed for an asymmetric synthesis of (+)-meloscine (**1**) features an early incorporation of the aromatic ring in **1** as the 5-benzyl substituent in **2**. The highly diastereoselective Birch reduction-alkylation **2** → **3**, the unraveling of **3** to the butyrolactone carboxylic acid **7**, and the Mannich cyclization **9c** → **10c** are the key steps in the synthesis of the core tricyclic unit in **1**. © 1999 Elsevier Science Ltd. All rights reserved.

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The *Melodinus* alkaloids, isolated from the New Caledonian plant *Melodinus Scandens* Forst., are structurally and biogenetically related to the *Aspidosperma* alkaloids. A proposed biosynthetic pathway to (+)-meloscine (**1**) involves an oxidative rearrangement of the *Aspidosperma* alkaloid 18,19-dehydrotabersonine; a laboratory conversion of 18,19-dehydrotabersonine to (+)-meloscine (~2% yield) has been reported.¹⁻³ The only total synthesis of **1** (as the racemate) was reported by Overman and co-workers in 1991.⁴ This landmark in *Melodinus* alkaloid synthesis featured an aza-Cope rearrangement-Mannich cyclization to provide (±)-meloscine in 24 steps and 3-4% overall yield from ethyl 2-oxocyclopentane acetate.

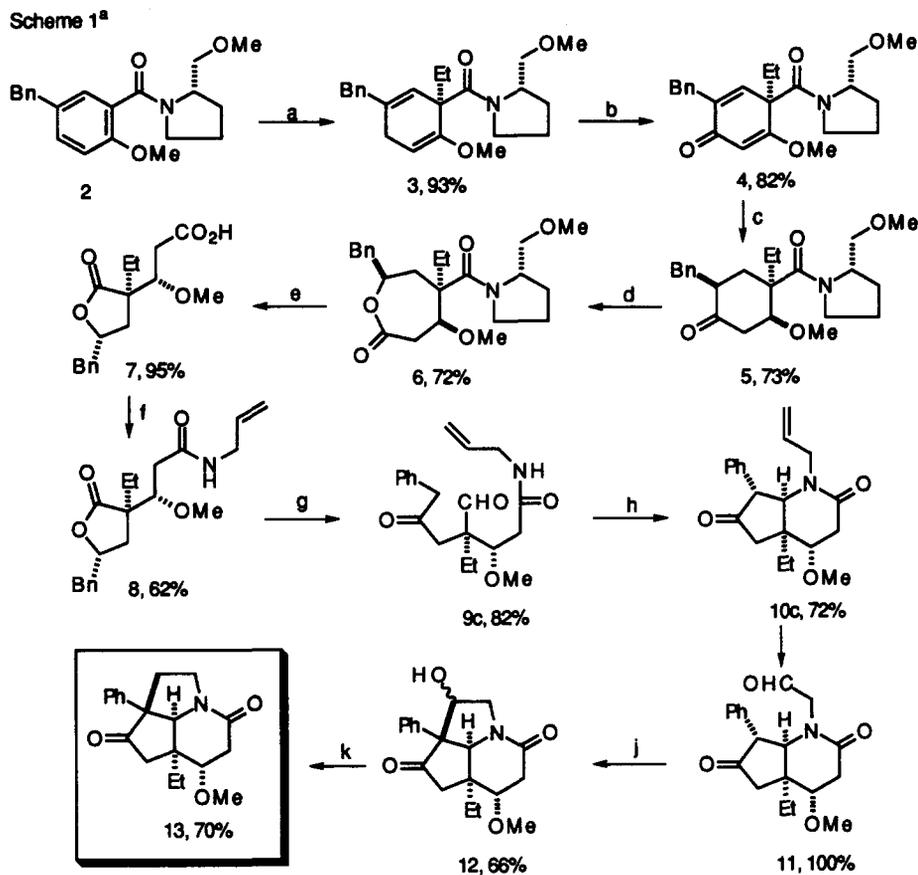


1, (+)-meloscine

In this note we describe an asymmetric synthesis of the meloscine core structure **13** by utilization of the asymmetric Birch reduction-alkylation **2** → **3** to establish absolute configuration at C(20) of the alkaloid and the Mannich cyclization **9c** → **10c** to provide the *cis*-pyrindin-6-one ring system.⁵ An important strategic element of the approach is an early incorporation of the aromatic ring in **1** as the 5-benzyl substituent in **2**.

Reduction of the chiral benzamide **2**⁶ with potassium in NH₃, THF and *tert*-butyl alcohol (1 equiv) at -78 °C, followed by consumption of excess metal by the addition of piperylene, and then alkylation of the intermediate amide enolate with EtI gave the 1,4-cyclohexadiene **3** in 93% yield (Scheme 1). Bis-allylic oxidation of **3** provided the 2-benzyl-5-methoxy-2,5-cyclohexadien-1-one **4**, which was efficiently converted to butyrolactone **7** as shown in Scheme 1.⁷ Conversion of the carboxylic acid group in **7** to the amide **8** by coupling with allyl amine was followed by reduction of the lactone in **8** to the corresponding diol with LiBH₄; Swern oxidation of the diol gave the key Mannich cyclization substrate **9c**.

After an intensive search for the optimum cyclization conditions (*vide infra*) it was found that **9c** could be converted to the *cis*-pyrindin-6-one **10c** in 72% yield on treatment with triflic acid in CH_2Cl_2 at 0°C .⁸ Oxidative cleavage of the *N*-allyl group in **10c** gave the keto aldehyde **11** and acid-catalyzed cyclization of **11** gave **12** as a mixture of alcohol diastereomers in 66% overall yield from **10c**. Deoxygenation of the hydroxyl group in **12** was accomplished by reduction of the intermediate (thiocarbonyl)imidazolidine (not

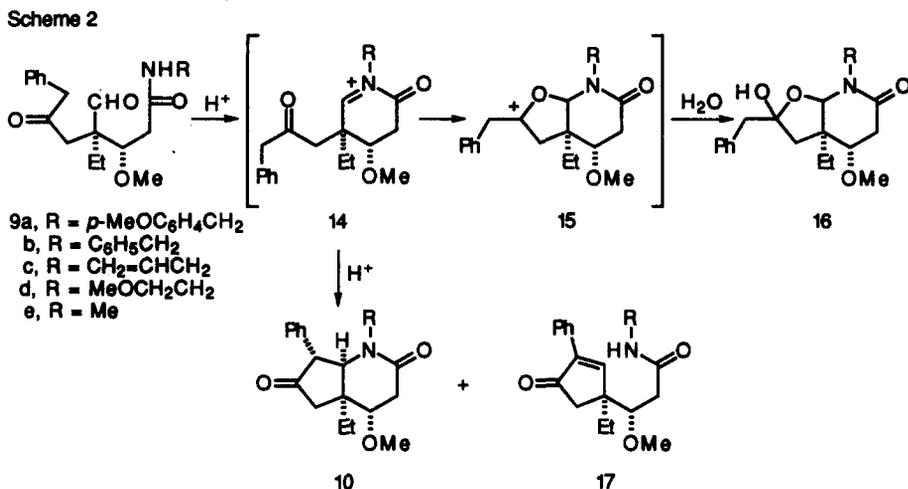


^aReaction conditions: (a) K, NH_3 , THF, *t*-BuOH (1 equiv), -78°C ; piperylene; EtI. (b) PDC (cat.), Celite, *t*-BuOOH, PhH. (c) H_2 , 5% Pd/C, THF (60 psi). Li, NH_3 , THF, *t*-BuOH, -78°C ; piperylene; NH_4Cl . (d) *m*-CPBA, CH_2Cl_2 . (e) TsOH, PhH/ H_2O , reflux. (f) allyl amine, CH_2Cl_2 , EDC, 0°C . (g) LiBH_4 , MeOH, THF. ClCOCOCl , DMSO, CH_2Cl_2 , -78°C ; Et_3N , -78°C to 25°C . (h) TfOH , CH_2Cl_2 , 0°C . (i) O_3 , CH_2Cl_2 ; Me_2S . (j) TsOH, CH_2Cl_2 , 25°C . (k) $\text{Im}_2\text{C}=\text{S}$; AIBN, Bu_3SnH , PhH, reflux.

shown)⁹ with *n*- Bu_3SnH in refluxing benzene to give the core structure of the *Melodinus* alkaloids **13**¹⁰ in 70% overall yield from **12**.

The acid-catalyzed Mannich cyclization **9c** \rightarrow **10c** required substantial development to obtain a reasonable level of efficiency.¹¹ Two critical parameters for the reaction proved to be acid strength and the

nature of the substituent on nitrogen. From a series of *N*-substituted amides **9a-9e**, it was discovered that treatment with $\text{CF}_3\text{CO}_2\text{H}$ in CH_2Cl_2 at 25°C or camphorsulfonic acid in refluxing benzene provided the bicyclic hemiketal **16** as mixtures of diastereomers, suggesting that under these reaction conditions the intermediate acyl iminium ion **14** was trapped by the ketone oxygen atom to give **15**.



A stronger acid was utilized in an attempt to induce enolization of the ketone in **14**. We were pleased to find that bicyclization to give **10** occurred with triflic acid in CH_2Cl_2 at 0°C , although significant quantities of the cyclopentenone **17** also were produced. Remarkably, the distribution of **10** and **17** was very strongly dependent on the substituent on the amide nitrogen atom as shown in Table 1. It is noteworthy that the mixtures of diastereomers **16a** and **16b** reacted with triflic acid in CH_2Cl_2 to give **10a** and **10b** as major reaction products. However, the two-step sequence involving either **16a** or **16b** provided the *cis*-pyrindin-6-one in poorer overall yield than the direct route, **9** → **10**. Treatment of **9** with KOH in refluxing MeOH also resulted in the formation of mixtures of **10** and **17** for the three cases studied (Table 1), but with these basic reaction conditions the distribution of **10** and **17** was only weakly dependent on the *N*-substituent.

Table 1. Distribution of *cis*-Pyrindin-6-one **10** and Cyclopentenone **17** from Cyclizations of **9**

Substrate 9	Acidic Conditions ^a Ratio of 10 to 17 ^c	Basic Conditions ^b Ratio of 10 to 17 ^c
<i>a</i> , R = <i>p</i> -MeOC ₆ H ₄ CH ₂	15:1	--
<i>b</i> , R = C ₆ H ₅ CH ₂	10:1	1:1
<i>c</i> , R = CH ₂ =CHCH ₂	3:1	--
<i>d</i> , R = MeOCH ₂ CH ₂	1:1	1:2
<i>e</i> , R = Me	1:10	2:1

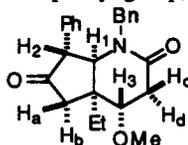
^a $\text{CF}_3\text{SO}_3\text{H}$, CH_2Cl_2 , 0°C , 12 h. ^bKOH, MeOH, reflux, 12 h. ^cProduct ratios determined by ¹H NMR integration; isolated yields of **10** + **17** generally were 60-75%.

The production of *cis*-pyrindin-6-one was most efficient from the acid-catalyzed cyclizations of **9a** and **9b**. Unfortunately, conversions of **10a** and **10b** to the desired tricycle **13** were problematic and the *N*-allyl derivative **9c** represented the best intermediate for conversion to the target of this study. It is expected that (+)-meloscine (**1**) will be available by utilization of a derivative of **2** containing a modified 5-benzyl substituent. The asymmetric Birch reduction-alkylation will be used to introduce a latent vinyl group.¹²

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References and Notes

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- The diastereomeric purity of **4** was determined to be >20:1 by HPLC comparison to a 1:1 mixture of diastereomers prepared from the racemic carboxylic acid corresponding to **3**.
- The structure of **10** was determined by 1D and 2D NOESY ¹H NMR studies. A *trans* relationship between H₁ and H₂ was established by the observation of a coupling constant of 10.8 Hz for these protons. H_a was located by the observation of a long range W-coupling (J_{a,2} = 1.6 Hz); H_d was located by its coupling with H₃ (10.8 Hz). Strong through space interactions between the phenyl substituent and H₁, between H₁ and the ethyl group, between H₃ and H_a, between H₁ and H_b, and between H_b along with H_d and the ethyl group indicated that these groupings were all *syn*-related. No interactions were observed for H₃ and the phenyl group, H₃ and the ethyl group, and H₁ and H₃.



10b

- For an alternative mode of reactivity of a (thiocarbonyl)imidazolidone of a β -hydroxycarbonyl derivative with *n*-Bu₃SnH, see: Chang, H. S.; Bergmeier, S. C.; Frick, J. A.; Bathe, A.; Rapoport, H. *J. Org. Chem.* 1994, *59*, 5336-5342.
- 13**: mp 162.5 °C, [α]_D²⁵ 38 (*c* 1.6, CHCl₃) ¹H NMR (CDCl₃, 500 MHz) δ 7.37-7.23 (m, 5 H), 4.42 (s, 1 H), 4.05 (m, 1 H), 3.59 (m, 1 H), 3.36 (s, 1 H), 3.33 (m, 1 H), 2.80 (d, *J* = 18.8 Hz, 1 H), 2.65 (m, 1 H), 2.43 (dd, *J* = 18.2, 4.2 Hz, 1 H), 2.40 (d, *J* = 19.2 Hz, 1 H), 2.15 (d, *J* = 19.2 Hz, 1 H), 2.06 (m, 1 H), 1.63 (m, 1 H), 0.90 (m, 1 H), 0.70 (t, *J* = 7.6 Hz, 3 H). ¹³C (CDCl₃, 125 Hz) δ 216.6, 166.1, 139.9, 128.9, 127.1, 125.9, 75.1, 70.3, 65.3, 56.7, 43.7, 42.3, 42.1, 38.6, 30.6, 27.1, 7.6. IR (film) 1737, 1638, 1457 cm⁻¹. CIMS, *m/z* 314 (*M*⁺ + 1, 100).
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