Pergamon

Tetrahedron Letters 40 (1999) 645–648

TETRAHEDRON LETTERS

Asymmetric Synthesis of the Core Structure of the Melodinus Alkaloids

Arthur G. Schultz* and Mingshi Dai

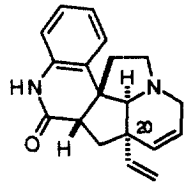
Department of Chemistry
Rensselaer Polytechnic Institute
Troy, NY 12180-3590

Received 11 September 1998; revised 12 November 1998; accepted 16 November 1998

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**.

Keywords: Asymmetric synthesis; Enolates; Mannich reactions; Alkaloids

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

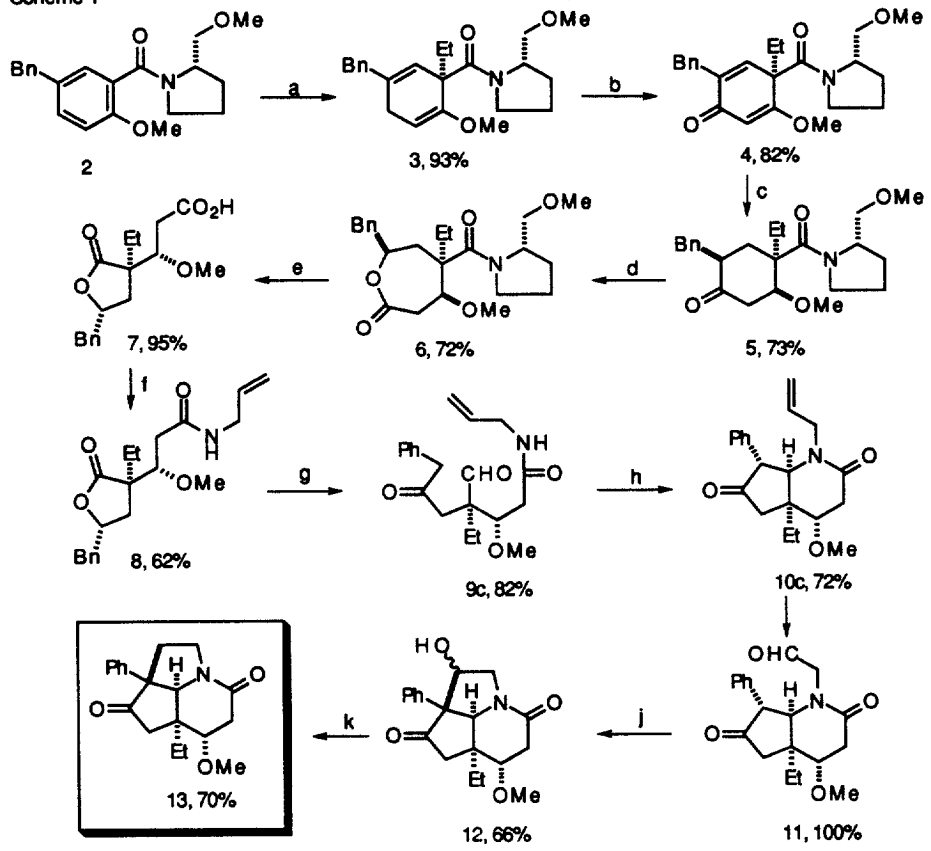
In this note we describe an asymmetric synthesis of the meloscine core structure **13** by utilization of the asymmetric Birch reduction-alkylation **2** → **3** to establish absolute configuration at C(20) of the alkaloid and the Mannich cyclization **9c** → **10c** to provide the *cis*-pyrindin-6-one 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 NH_3, 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 $LiBH_4$; Swern oxidation of the diol gave the key Mannich cyclization substrate **9c**.

0040-4039/99/$ - see front matter
PII: S0040-4039(98)02510-6

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)imidazolide (not

Scheme 1[a]



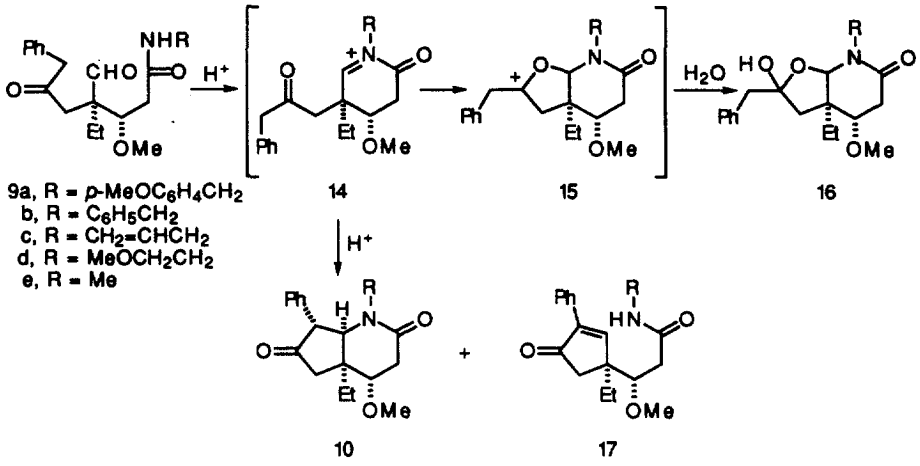
[a]Reaction conditions: (a) K, NH_3, THF, *t*-BuOH (1 equiv), -78 °C; piperylene; EtI. (b) PDC (cat.), Celite, *t*-BuOOH, PhH. (c) H_2, 5% Pd/C, THF (60 psi). Li, NH_3, THF, *t*-BuOH, -78 °C; piperylene; NH_4Cl. (d) *m*-CPBA, CH_2Cl_2. (e) TsOH, PhH/H_2O, reflux. (f) allyl amine, CH_2Cl_2, EDC, 0 °C. (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) $Im_2C{=}S$; 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** → **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 CF_3CO_2H 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**.

Scheme 2



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]
a, R = *p*-$MeOC_6H_4CH_2$	15:1	--
b, R = $C_6H_5CH_2$	10:1	1:1
c, R = CH_2=$CHCH_2$	3:1	--
d, R = $MeOCH_2CH_2$	1:1	1:2
e, R = Me	1:10	2:1

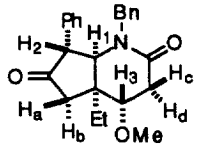
[a]CF_3SO_3H, CH_2Cl_2, 0 °C, 12 h. [b]KOH, MeOH, reflux, 12 h. [c]Product ratios determined by ^1H NMR integration; isolated yields of **10** + **17** generally were 60-75%.

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]

Acknowledgment. This work was supported by the National Institutes of Health (GM 26568).

References and Notes

1. Hugel, G.; Lévy, J. *J. Org. Chem.* 1984, *49*, 3275-3277.
2. Hugel, G.; Lévy, J. *J. Org. Chem.* 1986, *51*, 1594-1595.
3. Palmisano, G.; Danieli, B.; Lesma, G.; Riva, R.; Riva, S. *J. Org. Chem.* 1984, *49*, 4138-4143.
4. Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* 1991, *113*, 2598-2610.
5. For the most recent application of the asymmetric Birch reduction-alkylation in the synthesis of natural products, see: Schultz, A. G.; Wang, A. *J. Am. Chem. Soc.* 1998, *120*, 8259-8260.
6. Schultz, A. G.; Dai, M.; Khim, S.-K.; Pettus, L.; Thakkar, K. *Tetrahedron Lett.* 1998, *39*, 4203-4206.
7. 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**.
8. The structure of **10** was determined by 1D and 2D NOESY ^{1}H NMR studies. A trans relationship between H_1 and H_2 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 H_3 (10.8 Hz). Strong through space interactions between the phenyl substituent and H_1, between H_1 and the ethyl group, between H_3 and H_a, between H_1 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 H_3 and the phenyl group, H_3 and the ethyl group, and H_1 and H_3.



10b

9. For an alternative mode of reactivity of a (thiocarbonyl)imidazolide of a β-hydroxycarbonyl derivative with *n*-Bu_3SnH, see: Chang, H. S.; Bergmeier, S. C.; Frick, J. A.; Bathe, A.; Rapoport, H. *J. Org. Chem.* 1994, *59*, 5336-5342.
10. **13**: mp 162.5 °C, $[\alpha]_D^{25}$ 38 (*c* 1.6, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 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). ^{13}C ($CDCl_3$, 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).
11. For a recent review of the Mannich reaction, see: Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Intl. Ed. Engl.* 1998, *37*, 1044-1070.
12. Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* 1992, *114*, 1824-1829.