

## Total Syntheses of Natural Occurring Spermidine Alkaloids: (+)-(2*S*)-Dihydromyricoidine and (+)-(2*S*)-Myricoidine

by Ursula A. Häusermann and Manfred Hesse\*

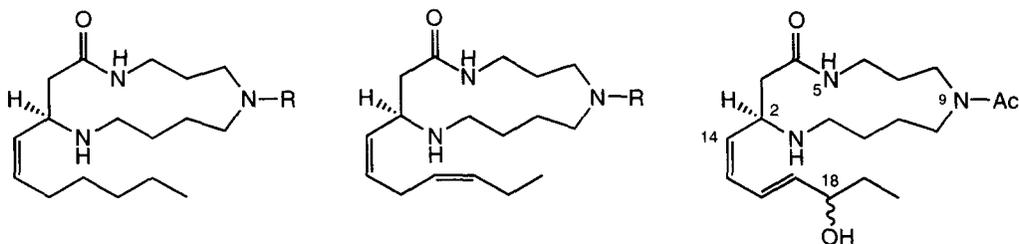
Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

Received 2 October 1997; accepted 31 October 1997

**Abstract:** The spermidine alkaloids (+)-(2*S*)-dihydromyricoidine (**5**) and (+)-(2*S*)-myricoidine (**4**) were synthesized under asymmetric conditions. The synthetic compounds **4** and **5** were found to have positive  $[\alpha]_D^{21}$  values in both cases, which agrees with those of the natural alkaloids. Therefore the absolute configuration of the natural products are (2*S*)-configured and not (2*R*)- as reported in the literature.  
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### INTRODUCTION

The spermidine alkaloids (+)-loesenerine (**1**), (+)-17,18-didehydroloesenerine (**2**), and (+)-16,17-didehydroloesenerin-18-ol (**3**) have previously been isolated from *Maytenus loeseneri* Urb. (Celastraceae)<sup>1,2</sup>. Their structures were elucidated mainly by spectroscopic means, particularly by interpretation of their mass spectral fragmentation patterns (electron impact) as well as by <sup>1</sup>H and <sup>13</sup>C NMR spectra.



**1** R = Ac (*R*)-loesenerine  
**5** R = H (*R*)-dihydromyricoidine

**2** R = Ac (*R*)-17,18-didehydroloesenerine  
**4** R = H (*R*)-myricoidine

**3** (*R*)-16,17-didehydroloesenerin-18-ol

At the same time, (+)-myricoidine (**4**) and (+)-dihydromyricoidine (**5**) were reported as constituents of *Clerodendrum myricoides* Vatke (Verbenaceae)<sup>3</sup>.

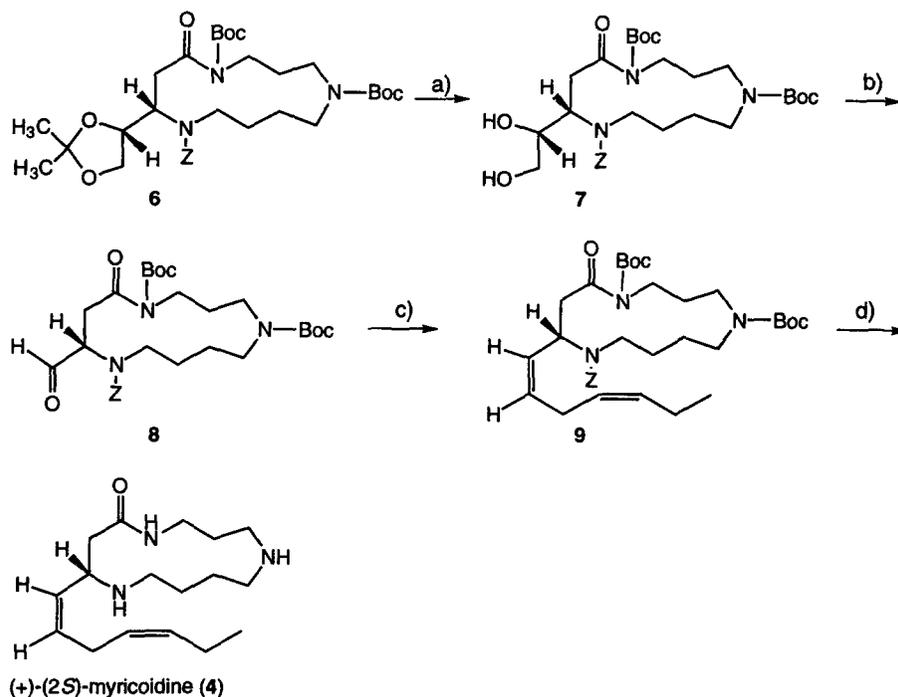
The five alkaloids contain the same 13-membered macrocyclic lactam ring formed by spermidine and part of a C<sub>10</sub>-fatty acid. The chiral center C(2) of (+)-loesenerine (**1**) was assumed to have the (*R*)-configuration by comparison of the specific rotation of **1** with that of (+)-(*R*)-3-methoxybut-1-ene. The absolute configurations of **2** and **3** were determined by comparison of their *Cotton* effects with that of **1**. The chiral centers of **4** and **5** were assumed to have the (*R*)-configuration because the specific rotation of samples

of *N,N'*-diacetyl-dihydromyricoidine prepared from **4**, **5**, and **1** were the same. The (*R*)-configuration at the chiral center, C(2), of these five alkaloids contrasts with the absolute configurations of all other structurally related, naturally occurring spermine and spermidine alkaloids, which have the (*S*)-configuration<sup>4</sup>.

In order to verify the proposed structures<sup>1,3</sup>, we synthesized (*2S*)-dihydromyricoidine (**5**) and (*2S*)-myricoidine (**4**) by enantioselective syntheses. Comparison of the specific rotations of the synthesized products with those reported for the natural products<sup>1,3</sup> should permit the absolute configurations of the natural alkaloids to be unambiguously assigned.

### SYNTHESES AND DISCUSSION

The synthesis of (+)-(*2S*)-dihydromyricoidine (**5**) was done in analogy to the synthesis of (-)-(*2R*)-dihydromyricoidine. For the synthesis of (+)-(*2S*)-myricoidine (**4**) we had to introduce a different side chain<sup>5,6</sup>.



a) ( $\pm$ )-campher-10-sulfonic acid, molecular sieve, MeOH, 85%; b) NaIO<sub>4</sub>, MeOH, Ar, 3 h, 93 %; c) Ph<sub>3</sub>P=CHCH<sub>2</sub>CH=CHCH<sub>2</sub>CH<sub>3</sub>, toluene, -80°, 9 h, 12%; d) i) Me<sub>3</sub>SiCl, CH<sub>2</sub>Cl<sub>2</sub>; ii) TFA, 37 %.

### Scheme

In order to synthesize **4** we introduced the side chain by a *Wittig* reaction. Studies on this *Wittig* reaction showed that the ylide reagent in solution is only stable for about 3 h. Therefore we added this solution in four (every time freshly prepared) portions every 2 h to get **9** in 12% yield only. Treatment of **9** with Me<sub>3</sub>SiI in acetonitrile followed by the addition of trifluoroacetic acid gave **4** in 36%<sup>8</sup>.

(+)-(2*S*)-Dihydromyricoidine (**5**) and (+)-(2*S*)-myricoidine (**4**) were characterized by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, TOCSY, <sup>1</sup>H, <sup>13</sup>C COSY, and mass spectra (electron impact as well as chemical ionization). The IR- and the electron impact mass spectra of the synthetic and the natural products were identical. With a TOCSY and <sup>1</sup>H, <sup>13</sup>C COSY spectrum, it was possible to assign all signals. The synthetic compounds **5** and **4**, have a specific rotation of  $[\alpha]_D^{21} = +57$  and  $[\alpha]_D^{21} = +61$ , respectively. In contrast, the natural **5** and **4** were reported to have  $[\alpha]_D^{21} = +77$  and  $[\alpha]_D^{21} = +87$ , respectively. The smaller values of  $[\alpha]_D^{21}$  obtained for the synthetic compounds can readily be attributed to the tendency of **8** to racemize. In consideration of these results, we suppose that the absolute configurations of (+)-dihydromyricoidine (**5**) and (+)-myricoidine (**4**) were proposed incorrectly<sup>3</sup>. This is also confirmed by the synthesis of (-)-(2*R*)-dihydromyricoidine<sup>5</sup>. On the basis of the syntheses of **5** and **4**, we propose that the opposite absolute configuration be assigned to C(2) of the naturally occurring compounds, namely the (*S*)-configuration, which is in accordance with all other structurally known macrocyclic spermidine alkaloids<sup>9</sup>.

We thank the *Swiss National Science Foundation* for financial support, the analytical departments of the University of Zurich for MS, and NMR spectra, and Mr. *Armin Guggisberg* for practical advisement.

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5. Häusermann U. A., Linden A., Song J., Hesse M. (1996) *Helv. Chim. Acta* **79**, 1995.
6. (+)-(2*S*)-Dihydromyricoidine (**5**):  $[\alpha]_D^{21} = +57.1$  ( $c = 0.312$ , MeOH). IR (CHCl<sub>3</sub>): 3660w, 3300m, 3060w, 3000m, 2960s, 2930s, 2840m, 1770w, 1660s, 1600m, 1540m, 1460m, 1440m, 1370w, 1310w, 1260m, 1200m, 1170m, 1140w, 1080m, 1030m, 1010m, 925m, 880m, 850m, 625m, 600m. <sup>1</sup>H NMR (DMSO, 42°): 7.89 (*t*,  $J = 6.2$ , HN-C=O); 5.63 (*dt*,  $J = 7.4, 10.6$ , H-C(15)); 5.18 (*t*,  $J = 10.6$ , H-C(14)); 4.03 (*dt* (*br.*),  $J = 4.0, 10.6$ , H-C(2)); 3.77-3.68 (*m*, H<sub>a</sub>-C(6)); 3.27-3.23 (*m*, H<sub>2</sub>C(8)); 3.20-3.09 (*m*, H<sub>b</sub>-C(6)); 3.08-3.01 (*m*, H<sub>a</sub>-C(10)); 2.92-2.83 (*m*, H<sub>b</sub>-C(10), H<sub>a</sub>-C(13)); 2.63-2.42 (*m*, H<sub>a</sub>-C(3), H<sub>b</sub>-C(13)); 2.37 (*dd*,  $J = 13.2, 4.0$ , H<sub>b</sub>-C(3)); 2.21-2.17 (*m*, H<sub>2</sub>C(7)); 2.12-1.97 (*m*, H<sub>a</sub>-C(11), H<sub>2</sub>C(16)); 1.92-1.87 (*m*, C(11)); 1.76-1.72 (*m*, H<sub>2</sub>C(12), NH); 1.42-1.26 (*m*, H<sub>2</sub>C(17), H<sub>2</sub>C(18), H<sub>2</sub>C(19)); 0.89 (*t*,  $J = 6.8$ , H<sub>3</sub>C(20)). <sup>13</sup>C NMR (DMSO, 42°): 171.3 (*s*, N-C=O); 133.3 (*d*, C(15)); 128.5 (*d*, C(14)); 51.7 (*d*, C(2)); 49.0 (*t*, C(10)); 48.3 (*t*, C(8)); 44.1 (*t*, C(13)); 42.1 (*t*, C(3)); 37.7 (*t*, C(6)); 30.5 (*t*, C(18)); 28.3 (*t*, C(17)); 26.8 (*t*, C(16)); 25.6 (*t*, C(11)); 25.5 (*t*, C(7)); 25.3 (*t*, C(12)); 21.5 (*t*, C(19)); 12.9 (*q*, C(20)). ESI-MS: 296 ([M + 1]<sup>+</sup>).
7. (2*S*)-5,9-Di(tert-butoxycarbonyl)-2-(1-(*Z*)-4-(*Z*)-heptadienyl)-1-benzyloxy-carbonyl-1,5,9-triazacyclotridecan-4-one (**9**):  $[\alpha]_D^{21} = +17.9$  ( $c = 1.0$ , CHCl<sub>3</sub>). IR (CHCl<sub>3</sub>): 3680w, 3620w, 3450w, 3010s, 2970s, 2930m, 2870m, 1725m, 1670s, 1520m, 1470s, 1450m, 1420s, 1390s, 1370s, 1310m, 1290m, 1220s, 1150s, 1090m, 1045s, 1030s, 950w, 930s, 875m, 850s, 625m, 590m. <sup>1</sup>H NMR (DMSO, 90°): 7.68-7.28 (*m*, 5 arom. H); 5.69 (*ddd*,  $J = 10.8, 9.0, 1.7$ , H-C(14)); 5.45 (*ddd*,  $J = 10.8, 7.4, 1.7$ , H-C(15)); 5.40

- (*ddd*,  $J = 10.7, 7.1, 1.6$ , H-C(18)); 5.29 (*ddd*,  $J = 10.7, 6.8, 1.3$ , H-C(17)); 5.12 (*dd*,  $J = 26.3, 12.7$ , OCH<sub>2</sub>Ph); 5.00 (*dt* (br.),  $J = 3.1, 9.0$ , H-C(2)); 3.90 (*dd*,  $J = 14.1, 5.2$ , H<sub>a</sub>-C(6)); 3.66 (*dd*,  $J = 16.5, 10.5$ , H<sub>a</sub>-C(3)); 3.55 (*dd*,  $J = 14.1, 6.6$ , H<sub>b</sub>-C(6)); 3.48-3.27 (*m*, H<sub>a</sub>-C(8), H<sub>a</sub>-C(10), H<sub>a</sub>C(13)); 3.23-2.86 (*m*, H<sub>b</sub>-C(8), H<sub>b</sub>C(10), H<sub>b</sub>C(13), H<sub>2</sub>C(16)); 2.79 (*dd*,  $J = 16.5, 3.1$ , H<sub>b</sub>-C(3)); 2.07 (*dq*,  $J = 1.3, 7.1$ , H<sub>2</sub>C(19)); 1.89-1.80 (*m*, H<sub>2</sub>C(7)); 1.58-1.40 (*m*, H<sub>2</sub>C(11), H<sub>2</sub>C(12)); 1.54, 1.43 (2 *s*, 2 CMe<sub>3</sub>); 0.96 (*t*,  $J = 6.3$ , H<sub>3</sub>C(20)). <sup>13</sup>C NMR (DMSO, 90°): 172.43 (*s*, N-C=O); 155.1, 154.4, 152.6 (3 *s*, 3 N-CO<sub>2</sub>); 136.5 (*s*, arom. C); 131.4, 129.0, 127.9, 127.6, 127.0, 126.9, 126.0 (7 *d*, C(14), C(15); C(17), C(18), 5 arom. C); 82.7, 77.8 (2 *s*, 2 CMe<sub>3</sub>); 65.6 (*t*, OCH<sub>2</sub>Ph); 52.7 (*d*, C(2)); 47.3 (*t*, C(3)); 45.9 (*t*, C(6)); 44.0 (*t*, C(8)); 41.7 (*t*, C(10)); 41.3 (*t*, C(13)); 28.3 (*t*, C(7)); 27.6, 27.1 (2 *q*, 2 CMe<sub>3</sub>); 26.8 (*t*, C(11)); 25.5 (*t*, C(12)); 24.9 (*t*, C(16)); 19.4 (*t*, C(19)); 13.1 (*q*, C(20)). CI-MS (NH<sub>3</sub>): 628 (13, [M + 1]<sup>+</sup>), 528 (100), 472 (11), 428 (15).
8. (+)-(2*S*)-Myricoidine (4):  $[\alpha]_D^{21} = +60.6$  ( $c = 0.33$ , MeOH). IR (CHCl<sub>3</sub>): 3430w, 2930s, 2850m, 3060w, 3000m, 2980s, 2930s, 2850m, 1660s, 1540m, 1460m, 1430m, 1370w, 1310w, 1280w, 1260s, 1230m, 1170m, 1090s, 1015m, 970w, 910s, 870w, 750m, 660m. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.76 (*s*, H-N(5)); 5.68-5.57 (*m*, H-C(15)); 5.47-5.39 (*m*, H-C(18)); 5.31-5.21 (*m*, H-C(17)); 5.25-5.18 (*m*, H-C(14)); 4.15-4.06 (*m*, H-C(2)); 3.72-3.60 (*m*, H<sub>a</sub>-C(6)); 3.35-3.22 (*m*, H<sub>b</sub>-C(6), H<sub>2</sub>C(8)); 3.05-2.95 (*m*, H<sub>a</sub>-C(10), H<sub>a</sub>-C(13)); 2.91-2.74 (*m*, H<sub>b</sub>-C(10), H<sub>2</sub>C(16)); 2.59-2.53 (*m*, H<sub>b</sub>-C(13)); 2.52-2.39 (*m*, H<sub>a</sub>-C(3)); 2.37-2.27 (*m*, H<sub>b</sub>-C(3)); 2.21-2.20 (*m*, H<sub>2</sub>C(7)); 2.13-1.98 (*m*, H<sub>2</sub>C(19)); 1.94-1.57 (*m*, H<sub>2</sub>C(11), H<sub>2</sub>C(12)); 1.03 (*t*,  $J = 7.2$ , H<sub>3</sub>C(20)). <sup>13</sup>C NMR (CDCl<sub>3</sub>): 131.5 (*d*, C(18)); 130.1 (*d*, C(14)); 129.4 (*d*, C(15)); 128.0 (*d*, C(17)); 52.4 (*d*, C(2)); 49.4 (*t*, C(10)); 48.4 (*t*, C(8)); 44.4 (*t*, C(13)); 42.0 (*t*, C(3)); 37.6 (*t*, C(6)); 25.8 (*t*, C(12)); 25.7 (*t*, C(11)); 25.4 (*t*, C(7)); 24.9 (*t*, C(16)); 18.8 (*t*, C(19)); 13.1 (*q*, Me). CI-MS (NH<sub>3</sub>): 294 ([M + 1]<sup>+</sup>).
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