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

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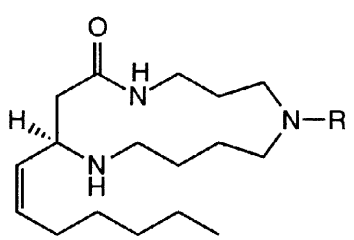
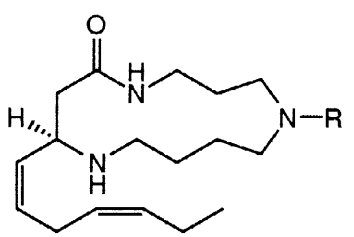
Abstract: The spermidine alkaloids (+)-(2*S*)-dihydromyricoidine (**5**) and (+)-(2*S*)-myricoidine (**4**) were synthesized under asymmetric conditions. The synthetic compounds **4** and **5** were found to have positive $[\alpha]_D^{21}$ values in both cases, which agrees with those of the natural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

INTRODUCTION

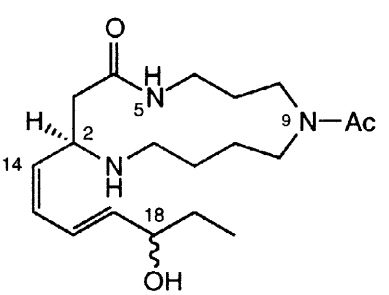
The spermidine alkaloids (+)-loesenerine (**1**), (+)-17,18-didehydroloesenerine (**2**), and (+)-16,17-didehydroloesenerin-18-ol (**3**) have previously been isolated from *Maytenus loeseneri* Urb. (Celastraceae)[1,2]. Their structures were elucidated mainly by spectroscopic means, particularly by interpretation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

The five alkaloids contain the same 13-membered macrocyclic lactam ring formed by spermidine and part of a C_{10}-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

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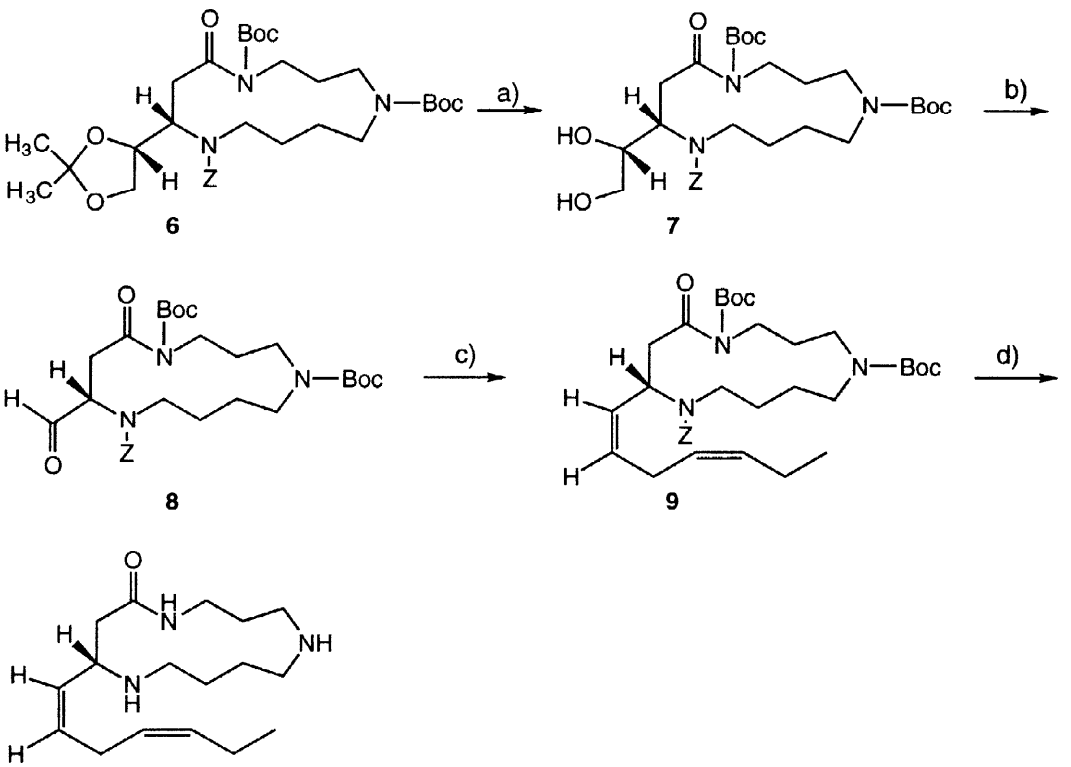
of *N,N'*-diacetyl-dihydromyricoidine prepared from **4**, **5**, and **1** were the same. The (*R*)-configuration at the chiral center, C(2), of these five alkaloids contrasts with the absolute configurations of all other structurally related, naturally occurring spermine and spermidine alkaloids, which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

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

SYNTHESES AND DISCUSSION

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



a) (±)-campher-10-sulfonic acid, molecular sieve, MeOH, 85%; b) $NaIO_4$, MeOH, Ar, 3 h, 93 %; c) $Ph_3P{=}CHCH_2CH{=}CHCH_2CH_3$, toluene, -80°, 9 h, 12%; d) i) Me_3SiCl, CH_2Cl_2; 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**[7] in 12% yield only. Treatment of **9** with Me_3SiI in acetonitrile followed by the addition of trifluoracetic acid gave **4** in 36%[8].

(+)-(2*S*)-Dihydromyricoidine (**5**) and (+)-(2*S*)-myricoidine (**4**) were characterized by IR, ^{1}H NMR, ^{13}C NMR, TOCSY, ^{1}H,^{13}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 ^{1}H,^{13}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[3]. This is also confirmed by the synthesis of (-)-(2*R*)-dihydromyridoidine[5]. 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[9].

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REFERENCES AND NOTES

1. Dìaz M., Preiss A., Ripperger H. (1987) *Phytochemistry* **26**, 1847.
2. Preiss A., Diaz M., Ripperger H. (1988) *Phytochemistry* **27**, 589.
3. Bashwira S., Hootele C. (1988) *Tetrahedron* **44**, 4521.
4. Guggisberg A. and Hesse M., in ‚The Alkaloids', A. Brossi (Ed.), Academic Press Inc., New York, (1983), XXII, p. 85.
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 ($CHCl_3$): 3660*w*, 3300*m*, 3060*w*, 3000*m*, 2960*s*, 2930*s*, 2840*m*, 1770*w*, 1660*s*, 1600*m*, 1540*m*, 1460*m*, 1440*m*, 1370*w*, 1310*w*, 1260*m*, 1200*m*, 1170*m*, 1140*w*, 1080*m*, 1030*m*, 1010*m*, 925*m*, 880*m*, 850*m*, 625*m*, 600*m*. ^{1}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_a-C(6)); 3.27-3.23 (*m*, H_2C(8)); 3.20-3.09 (*m*, H_b-C(6)); 3.08-3.01 (*m*, H_a-C(10)); 2.92-2.83 (*m*, H_b-C(10), H_a-C(13)); 2.63-2.42 (*m*, H_a-C(3), H_b-C(13)); 2.37 (*dd*, *J* = 13.2, 4.0, H_b-C(3)); 2.21-2.17 (*m*, H_2C(7)); 2.12-1.97 (*m*, H_a-C(11), H_2C(16)); 1.92-1.87 (*m*, C(11)); 1.76-1.72 (*m*, H_2C(12), NH); 1.42-1.26 (*m*, H_2C(17), H_2C(18), H_2C(19)); 0.89 (*t*, *J* = 6.8, H_3C(20)). ^{13}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 ($[M + 1]^+$).
7. (2*S*)-5,9-Di(tert-butoxycarbonyl)-2-(1-(*Z*)-4-(*Z*)-heptadienyl)-1-benzoxy-carbonyl-1,5,9-triazacyclotri-decan-4-one (**9**): $[\alpha]_D^{21}$ = +17.9 (c = 1.0, $CHCl_3$). IR ($CHCl_3$): 3680*w*, 3620*w*, 3450*w*, 3010*s*, 2970*s*, 2930*m*, 2870*m*, 1725*m*, 1670*s*, 1520*m*, 1470*s*, 1450*m*, 1420*s*, 1390*s*, 1370*s*, 1310*m*, 1290*m*, 1220*s*, 1150*s*, 1090*m*, 1045*s*, 1030*s*, 950*w*, 930*s*, 875*m*, 850*s*, 625*m*, 590*m*. ^{1}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_2Ph); 5.00 (*dt* (br.), J = 3.1, 9.0, H-C(2)); 3.90 (*dd*, J = 14.1, 5.2, H_a-C(6)); 3.66 (*dd*, J = 16.5, 10.5, H_a-C(3)); 3.55 (*dd*, J = 14.1, 6.6, H_b-C(6)); 3.48-3.27 (*m*, H_a-C(8), H_a-C(10), H_aC(13)); 3.23-2,86 (*m*, H_b-C(8), H_bC(10), H_bC(13), H_2C(16)); 2.79 (*dd*, J = 16.5, 3.1, H_b-C(3)); 2.07 (*dq*, J = 1.3, 7.1, H_2C(19)); 1.89-1.80 (*m*, H_2C(7)); 1.58-1.40 (*m*, H_2C(11), H_2C(12)); 1.54, 1.43 (2 *s*, 2 CMe_3); 0.96 (*t*, J = 6.3, H_3C(20)). ^{13}C NMR (DMSO, 90°): 172.43 (*s*, N-C=O); 155.1, 154.4, 152.6 (3 *s*, 3 N-CO_2); 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_3); 65.6 (*t*, OCH_2Ph); 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_3); 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_3): 628 (13, $[M + 1]^+$), 528 (100), 472 (11), 428 (15).

8. (+)-(2*S*)-Myricoidine (**4**): $[\alpha]_D^{21}$ = +60.6 (c = 0.33, MeOH). IR ($CHCl_3$): 3430*w*, 2930*s*, 2850*m*, 3060*w*, 3000*m*, 2980*s*, 2930*s*, 2850*m*, 1660*s*, 1540*m*, 1460*m*, 1430*m*, 1370*w*, 1310*w*, 1280*w*, 1260*s*, 1230*m*, 1170*m*, 1090*s*, 1015*m*, 970*w*, 910*s*, 870*w*, 750*m*, 660*m*. ^{1}H NMR ($CDCl_3$): 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_a-C(6)); 3.35-3.22 (*m*, H_b-C(6), H_2C(8)); 3.05-2.95 (*m*, H_a-C(10), H_a-C(13)); 2.91-2.74 (*m*, H_b-C(10), H_2C(16)); 2.59-2.53 (*m*, H_b-C(13)); 2.52-2.39 (*m*, H_a-C(3)); 2.37-2.27 (*m*, H_b-C(3)); 2.21-2.20 (*m*, H_2C(7)); 2.13-1.98 (*m*, H_2C(19)); 1.94-1.57 (*m*, H_2C(11), H_2C(12)); 1.03 (*t*, J = 7.2, H_3C(20)). ^{13}C NMR ($CDCl_3$): 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_3): 294 ($[M + 1]^+$).

9. Schultz K., Kuehne P., Häusermann U. A., Hesse M. (1997) *Chirality*, **9**, 523.