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Five Novel Macrocyclic Spermine Alkaloids from *Incarvillea sinensis*

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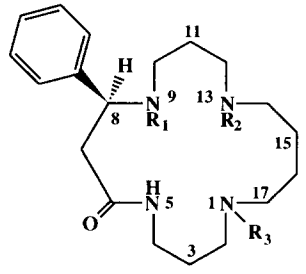
Abstract: Five novel macrocyclic spermine alkaloids named incasines A, A', B, B' and C have been isolated together with verballocine from *Incarvillea sinensis*, and their structures have been elucidated on the basis of chemical and spectroscopic evidence. © 1997 Elsevier Science Ltd.

Incarvillea sinensis LAM. (Bignoniaceae) is a wild plant which is prevalent in the northern area of China, and the dried whole plant has been historically used in treating rheumatism and relieving pain as an ancient Chinese crude drug designated as "*Jiaohao* (Kakko)". In our chemical search for the active *Incarvilleae* alkaloids, we previously demonstrated the absolute structure of incarvilline, together with nine other monoterpene- or C_6-C_3-conjugated alkaloidal derivatives,[1] and recently reported the potent analgesic activity displayed by incarvillateine.[2] This paper deals with the structural characterization of five newly-isolated macrocyclic spermine alkaloids named incasines A, A', B, B' and C (**1**-**5**).

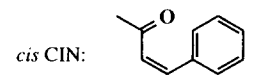
Isolation and separation of spermine alkaloids were performed by extracting the dried whole part of *I. sinensis* (18kg) with EtOH, followed by subjection of the extract to a variety of column chromatographies (MCI gel CHP 20P, Sephadex LH-20, Bondapak C_{18}, silica gel, Al_2O_3) to yield incasine C (**5**) (75.9mg) and verballocine (**6**)[3] (115.4mg), the latter of which was recently isolated from *Verbascum pseudonobile* (Scrophulariaceae).[4] Subsequent preparative HPLC separation successfully afforded incasines A (**1**) (11.3mg), A' (**2**) (48.3mg), B (**3**) (14.4mg) and B' (**4**) (28.3mg).[5]

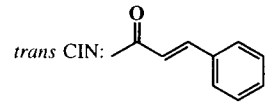
Incasines A (**1**)[6] and A' (**2**)[7] were obtained as an off-white amorphous powder. Comparison of their NMR spectral data[8,9] with those of **6** revealed that additional signals appeared at δ 8.00 (1H, m) for **1** and at δ 8.02 (1H, m) for **2** in the ^{1}H-NMR spectra, and at δ 163.2, 163.0, 162.9, 162.7 (d) for **1** and at δ 163.2, 163.0, 162.9 (d) for **2** in the ^{13}C-NMR spectra,[8] respectively, clearly indicating the presence of an imine group (-CH=NH). It was noted that a complexity, mostly with doublet signals for each carbon assignment in the ^{13}C-NMR spectra of the macrocyclic spermine alkaloidal derivatives, was due to the presence of *E*- and *Z*-isomers of the amide groups.[9] However, the presence of more complex structural isomers due to the additional existence of a nitrogen-bearing group was suggested because several signals appeared as triplet or quartet assignments in the ^{13}C-NMR spectra. The EI-MS of both **1** and **2**[6,7] showed a *quasi*-molecular ion peak at *m/z* 490, the MS number of which was counted by 28 more units than that of **6**. And the peak exhibited at *m/z* 155 was clearly recognized as a characteristic fragment ion which is due to the initial cleavage of an unstable bond between C-8 and N-9, followed by a process of splitting bond and of hydrogen transfer between N-1 and C-

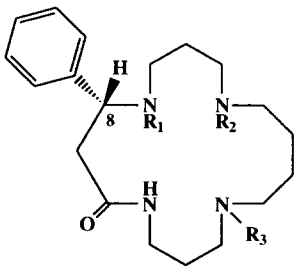
17.[4] Furthermore, the appearance of a peak at *m/z* 127 was also counted by 28 mass units less than that of the peak at *m/z* 155. On the basis of these spectral observations, it was shown that incasines A and A' possessed an imine group which was located at the alternative N-9 or N-13,[4] respectively. The HMBC spectral examination showed a correlation between the imine proton and C-12 and C-14; thus, the location of the imine group was concluded to be attached to N-13. Moreover, the ^{1}H-NMR spectra of **1** and **2** showed a pair of olefinic protons at δ 6.05, 6.62 (each 1H, d, *J*=12.8 Hz) for **1** and at δ 6.83 and 7.72 (each 1H, d, *J*=15.3 Hz) for **2**, clearly suggesting that an amidically bonded cinnamoyl group was *cis* and *trans*, respectively.



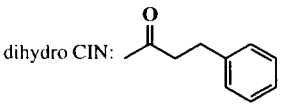
		R_1	R_2	R_3
1	incasine A	H	-CH=NH	*cis* CIN
2	incasine A'	H	-CH=NH	*trans* CIN
3	incasine B			*cis* CIN
4	incasine B'			*trans* CIN
6	verballocine	H	H	*cis* CIN
7		H	-CH=NH	dihydro CIN
8				dihydro CIN
10		H	H	dihydro CIN







		R_1	R_2	R_3
5	incasine C		$-CH_2-$	*cis* CIN
9			$-CH_2-$	dihydro CIN



Incasine B (**3**)[10] and B' (**4**)[11] were also obtained as an off-white amorphous powder. Treatment of **3** and **4** with methanolic $AgNO_3$ promptly afforded white AgCl precipitates, which indicated that they were obtained as quaternary ammonium chlorides. The ^{1}H and ^{13}C-NMR spectra of **3** and **4** were also closely related to those of **1** and **2** except for the signals at δ 9.91 (1H, s) for **3** and at δ 9.93 (1H, s,) for **4** in the ^{1}H-NMR, and at δ 153.4 (d, C-18) for **3** and at δ 153.0 (d, C-18) for **4** in the ^{13}C-NMR spectra, respectively. In the EI-MS of **3** and **4** both exhibited a molecular ion peak at *m/z* 473 and a cinnamoyl fragment ion peak at *m/z* 131 (base). The occurrence of a peak at *m/z* 138 was also due to the fragment ion of fissions between C-8 and N-9 bonds and between N-1 and C-17 bonds, respectively, suggesting the presence of a sp^2 carbon located in between N-9 and N-13. The ^{1}H-NMR spectra of **3** and **4** showed two olefinic protons at δ 6.08 and 6.61 (each 1H, d, *J*=12.8 Hz) for **3** and at δ 6.81 and 7.70 (each 1H, d, *J*=15.3 Hz) for **4**, respectively, indicating the presence of *Z*- and *E*-cinnamoyl groups, respectively. Thus, in the structures of **3** and **4** it was established that one sp^2 methine carbon was bridged to both N-9 and N-13 positions, respectively.

Incasine C (**5**)[12] was obtained as an off-white amorphous powder. In the EI-MS, a molecular ion peak was shown at *m/z* 474, and a characteristic ion peak at *m/z* 139 which is also due to the cleaved fragment ion between C-8 and N-9 bonds and between N-1 and C-17 bonds, suggesting the presence of a methylene group attached to N-9 and N-13 on a 17-membered lactam ring. In the ^{1}H-NMR spectrum, two pairs of olefinic protons were assigned at δ 6.06 (0.5H, d, *J*=12.2 Hz), 6.07 (0.5H, d, *J*=12.8 Hz) and 6.60 (0.5H, d, *J*=12.2

Hz), 6.62 (0.5H, d, *J*=12.8 Hz); thus, the cinnamoyl group was assigned as *cis*. This split pattern of these seemingly two pairs of olefinic protons was probably due to the presence of *E*- and *Z*-isomers of the amide groups. Thus, the structure of **5** was established as described in the figure.

In order to confirm the absolute configuration involving a chirality at C-8 position, the CD spectra of their saturated products **7**,[13] **8**,[14] **9**[15] and **10**[16] derived from **1/2**, **3/4**, **5** and **6** by hydrogenation with 10% Pd/C under H_2 were compared with those of (*R*)-(+)- and (*S*)-(-)-α-phenylethylamines.[17] The CD spectra of **7**, **8** and **10** were found to be quite similar to that of (*S*)-(-)-α-phenylethylamine, thus indicating them to be all *S* configuration. On the other hand, the CD spectra of **9** was shown to be quite similar to that of (*R*)-(+)-α-phenylethylamine; thus, the absolute configuration of **5** was determined to be *R*.[18] It should be noted that five novel macrocyclic spermine alkaloids have been obtained from the same origin with the detailed NMR data.

REFERENCES AND NOTES:

1. (a) Chi, Y. M.; Yan, W. M.; Li, J. S. *Phytochemistry*, **1990**, *29*, 2376-2378; (b) Chi, Y. M.; Yan, W. M.; Chen, D. C.; Noguchi, H.; Iitaka, Y.; Sankawa, U. *ibid.*, **1992**, *31*, 2930-2932; (c) Chi, Y. M.; Hashimoto, F.; Yan, W. M.; Nohara, T. *ibid.*, **1995**, *39*, 1485-1487; (d) *idem ibid.*, **1995**, *40*, 353-354; (e) *idem ibid.*, in press; (f) Chi, Y. M.; Hashimoto, F.; Yan, W. M.; Nohara, T.; Yamashita, M.; Marubayashi, N. *Pharm. Chem. Bull.*, in press.
2. Chi, Y. M.; Hashimoto, F.; Nohara, T.; Nakamura, M.; Yoshizawa, T.; Yamashita, M.; Marubayashi, N. *38th Symposium on the Chemistry of Natural Products*, **1996**, Sendai, Symposium Papers pp 43-48. On this symposium, both incarvilline alkaloid derivatives having analgesic activity and spermine alkaloids were presented.
3. Verballocine (**6**): $[\alpha]_D^{24}$ -15.9° (*c*=0.77, $CHCl_3$); IR λ_{max} (cm^{-1}): 3290 (NH assoc.), 1646 (C=O, amide I), 1606 (C=C), 1558 (amide II); *Anal*: $C_{28}H_{38}N_4O_2$; EI-MS (*m/z*): 462 $[M]^+$ (35), 331 (39), 146 (17), 131 (100), 127 (18); ^{1}H-NMR ($CHCl_3$): δ 1.58-1.94 (8H, m, 3, 11, 15, 16-H), 2.46-3.78 (14H, m, 2, 4, 7, 10, 12, 14, 17-H), 4.08 (1H, m, 8-H), 6.15 (0.5H, d, *J*=12.2 Hz), 6.18 (0.5H, d, *J*=12.8 Hz), 6.71 (0.5H, d, *J*=12.2 Hz), 6.72 (0.5H, d, *J*=12.8 Hz), 7.23-7.41 (10H, m, 2', 3', 4', 5', 6', 2", 3", 4", 5", 6"-H); ^{13}C-NMR ($CDCl_3$): δ 24.7, 25.1, 25.2, 25.4, 25.9, 26.9, 30.4, 30.7 (C-3, 11, 15, 16), 37.7, 38.2, 43.5, 45.1, 46.5, 47.8, 48.4, 48.6, 49.8, 50.1, 51.1 (C-2, 4, 7, 10, 12, 14, 17), 59.5, 59.6 (C-8), 124.3, 124.5 (C-8'), 127.8, 127.9 (C-2", 6"), 128.5, 129.4, 129.7, 129.8 (C-2', 3', 4', 5', 6', 3", 4", 5"), 134.7, 134.8 (C-7'), 136.7, 136.8 (C-1'), 143.2, 143.3 (C-1"), 172.0 (C-9'), 173.5, 173.6 (C-6).
4. Drandarov, K. *Tetrahedron Lett.*, **1995**, *36*, 617-620. There were no detailed NMR assignments.
5. HPLC was performed with a TOYOSODA HPLC system (detector, JASCO UV- 970) equipped with a μBondasphere C_{18} 5μ 19x150 mm column (solv. 38% CH_3CN + 2% AcOH).
6. Incasine A (**1**): $[\alpha]_D^{24}$ -11.8° (*c*=0.70, $CHCl_3$); IR λ_{max} (cm^{-1}): 3437 (NH free), 3317 (NH assoc.), 1660 (C=O, amide I), 1612 (C=C), 1552 (amide II); *Anal*: $C_{29}H_{39}N_5O_2$; EI-MS (*m/z*): 490 $[M+1]^+$ (6), 473 (53), 359 (11), 341 (92), 155 (9), 131 (100), 125 (22); ^{1}H-NMR ($CDCl_3$): δ 1.41-1.90 (8H, m, 3, 11, 15, 16-H), 2.33-2.53, 3.13-3.52 (14H, m, 2, 4, 7, 10, 12, 14, 17-H), 3.86-4.03 (1H, m, 8-H), 6.05 (1H, d, *J*=12.8 Hz, 8'-H), 6.62 (1H, d, *J*=12.8 Hz, 7'-H), 7.23-7.41 (10H, m, 2', 3', 4', 5', 6', 2", 3", 4", 5", 6"-H), 8.00 (1H, m, 18-H); ^{13}C-NMR ($CDCl_3$): δ 24.3, 24.8, 25.4, 25.9, 26.2, 26.4, 28.0, 28.1, 28.5, 29.2, 29.6, 30.2 (C-3, 11, 15, 16), 36.6, 37.2, 37.3, 42.0, 42.4, 43.1, 43.6, 43.7, 43.8, 44.0, 44.2, 44.3, 44.5, 44.8, 45.3, 46.5, 46.9, 47.0, 47.2, 48.6, 49.0, 49.4 (C-2, 4, 7, 10, 12, 14, 17), 59.3, 59.5 (C-8), 123.4 (C-8'), 126.2, 126.3, 126.4, 126.5, 127.4, 127.5, 128.5, 128.7, 128.8 (C-2', 3', 4', 5', 6', 2", 3", 4", 5", 6"), 133.1, 133.2, 133.3 (C-7'), 135.3, 135.4 (C-1'), 142.3, 142.7 (C-1"), 162.7, 162.9 163.0, 163.2 (C-18), 168.9, 169.1 (C-9'), 171.5, 171.6 (C-6).
7. Incasine A' (**2**): $[\alpha]_D^{24}$ -17.9° (*c*=0.65, $CHCl_3$); *Anal*: $C_{29}H_{39}N_5O_2$; EI-MS (*m/z*): 490 $[M+1]^+$ (20), 359 (51), 155 (14), 146 (47), 131 (100); ^{1}H-NMR ($CDCl_3$): δ 1.67-1.94 (8H, m, 3, 11, 15, 16-H), 2.41-2.61, 3.19-3.62 (14H, m, 2, 4, 7, 10, 12, 14, 17-H), 3.99-4.07 (1H, m, 8-H), 6.83 (1H, d, *J*=15.3 Hz, 8'-H), 7.21-7.39 (10H, m, 2', 3', 4', 5', 6', 2", 3", 4", 5", 6"-H), 7.72 (1H, d, *J*=15.3 Hz, 7'-H), 8.02 (1H, m, 18-H); ^{13}C-NMR ($CDCl_3$): δ 25.0, 25.1, 26.4, 26.7, 27.2, 28.6, 28.8, 29.2, 30.1, 30.9 (C-3, 11, 15, 16), 36.6, 37.4, 37.5, 42.1, 42.5, 43.2, 43.8, 44.2, 44.7, 44.9, 46.0, 46.3, 46.5, 46.7, 47.2, 48.6, 48.9, 49.1, 49.2 (C-2, 4, 7, 10, 12, 14, 17), 59.6 (C-8), 117.0, 117.3 (C-8'), 126.3, 126.5, 127.9, 128.8, 128.9, 129.0, 129.8 (C-2', 3', 4', 5', 6', 2", 3", 4", 5", 6"), 135.2 (C-1'), 143.0, 143.3 (C-7'), 143.1 (C-1"), 162.9, 163.0, 163.2 (C-18), 166.5, 166.6, 166.8 (C-9'), 171.4, 171.8 (C-6).
8. The ^{13}C-NMR signals were complicated by rotamers of the amide groups; however, at elevated temperature (90-100°C) most of the signals turned to singlets. Therefore, the obtained compounds **1-6** were regarded as pure.

9. Koblicova, Z.; Turecek, F.; Ninova, P.; Trojanek, J.; Blaha, K. *Tetrahedron Lett.*, **1983**, *24*, 4381-4384.
10. Incasine B (**3**): $[\alpha]_D^{32}$ +62.5° (*c*=0.48, $CHCl_3$); *Anal*: $C_{29}H_{37}N_4O_2$; EI-MS (*m/z*): 473 $[M]^+$ (21), 472 (50), 342 (24), 341 (89), 138 (8), 131 (100), 125 (27); ^{1}H-NMR ($CDCl_3$): δ 1.32-1.99 (8H, m, 3, 11, 15, 16-H), 2.71, 2.96, 3.12-3.62 (14H, m, 2, 4, 7, 10, 12, 14, 17-H), 3.92-4.08 (1H, m, 8-H), 6.08 (1H, d, *J*=12.8 Hz, 8'-H), 6.61 (1H, d, *J*=12.8 Hz, 7'-H), 7.26-7.38 (10H, m, 2', 3', 4', 5', 6', 2", 3", 4", 5", 6"-H), 9.91 (1H, S, 18-H); ^{13}C-NMR ($CDCl_3$): δ 19.0, 22.4, 22.7, 22.9, 24.0, 27.5, 29.3 (C-3, 11, 15, 16), 36.2, 36.9, 38.8, 38.9, 42.1, 44.5, 44.6, 47.1, 48.2, 53.3, 53.6 (C-2, 4, 7, 10, 12, 14, 17), 65.4 (C-8), 123.4+123.7 (C-8'), 127.0, 128.5, 128.6, 129.1, 129.4 (C-2', 3', 4', 5', 6', 2", 3", 4", 5", 6"), 132.9.+133.5 (C-7'), 135.3+135.4 (C-1'), 136.6 (C-1"), 153.4 (C-18), 169.0, 168.9 (C-6, 9').
11. Incasine B' (**4**): $[\alpha]_D^{31}$ +49.2° (*c*=1.27, $CHCl_3$); *Anal*: $C_{29}H_{37}N_4O_2$; EI-MS (*m/z*): 473 $[M]^+$ (15), 472 (39), 342 (20), 341 (70), 138 (8), 131 (100), 125 (21); ^{1}H-NMR ($CDCl_3$): δ 1.26-2.05 (8H, m, 3, 11, 15, 16-H), 2.73, 3.11-3.70 (14H, m, 2, 4, 7, 10, 12, 14, 17-H), 4.04 (1H, m, 8-H), 6.81 (1H, d, *J*=15.3 Hz, 8'-H), 7.70 (1H, d, *J*=15.3 Hz, 7'-H), 7.28-7.51 (10H, m, 2', 3', 4', 5', 6', 2", 3", 4", 5", 6"-H), 9.93 (1H, s, 18-H); ^{13}C-NMR ($CDCl_3$): δ 19.0, 22.4, 22.8, 23.1, 25.2, 27.7, 30.4 (C-3, 11, 15, 16), 36.4, 36.9, 38.5, 39.1, 42.2, 43.0, 46.8, 47.4, 53.7 (C-2, 4, 7, 10, 12, 14, 17), 65.6 (C-8), 117.4+117.5 (C-8'), 127.0, 127.8, 128.5, 128.8, 129.3, 129.5, 129.6 (C-2', 3', 4', 5', 6', 2", 3", 4", 5", 6"), 142.6.+142.7 (C-7'), 135.3 (C-1'), 136.6 (C-1"), 153.0 (C-18), 166.3 (C-9'), 169.0 (C-6).
12. Incasine C (**5**): $[\alpha]_D^{24}$ +4.2° (*c*=0.41, $CHCl_3$); IR λ_{max} (cm^{-1}): 3305 (NH assoc.), 1648 (C=O, amide I), 1606 (C=C), 1551 (amide II); *Anal*: $C_{29}H_{38}N_4O_2$; EI-MS (*m/z*): 474 $[M]^+$ (28), 473 (39), 139 (21), 131 (23); ^{1}H-NMR ($CDCl_3$): δ 1.57-2.07 (8H, m, 3, 11, 15, 16-H), 2.44-3.76 (14H, m, 2, 4, 7, 10, 12, 14, 17-H), 4.08 (1H, m, 8-H), 6.06 (0.5H, d, J=12.2 Hz), 6.07 (0.5H, d, *J*=12.8 Hz), 6.60 (0.5H, d, *J*=12.2 Hz), 6.62 (0.5H, d, *J*=12.8 Hz), 7.25-7.39 (10H, m, 2', 3', 4', 5', 6', 2", 3", 4", 5", 6"-H); ^{13}C-NMR ($CDCl_3$): δ 24.5, 24.7, 24.9, 25.2, 26.8, 28.6, 28.7 (C-3, 11, 15, 16), 36.7, 37.8, 42.6, 43.1, 45.0, 46.9, 47.0, 47.2, 47.3, 48.3, 50.3, 50.4 (C-2, 4, 7, 10, 12, 14, 17), 64.0 (C-8), 123.5, 123.6 (C-8'), 126.9, 127.1, 127.6, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 128.6, 128.8, 128.9 (C-2', 3', 4', 5', 6', 2", 3", 4", 5", 6"), 133.3, 133.4 (C-7'), 135.3, 135.4 (C-1'), 140.8, 141.3 (C-1"), 169.8, 170.0 (C-9'), 171.4, 171.5 (C-6).
13. Dihydroincasine A (A') (**7**): $[\alpha]_D^{24}$ -19.4° (*c*=2.23, $CHCl_3$); EI-MS (*m/z*): 492 $[M+1]^+$ (13), 360 (15), 155 (14), 146 (19), 131 (23), 58 (100); ^{1}H-NMR ($CDCl_3$): δ 1.51-1.99 (8H, m, 3, 11, 15, 16-H), 2.34-2.63, 2.96-3.09, 3.12-3.52 (14H, m, 2, 4, 7, 10, 12, 14, 17-H), 3.92-4.04 (1H, m, 8-H), 7.22-7.34 (10H, m, 2', 3', 4', 5', 6', 2", 3", 4", 5", 6"-H), 8.00 (1H, m, 18-H); CD (MeOH, *c*=24.0 mg/10ml, 220-300 nm): $[\theta]_{247}$ 0, $[\theta]_{255}$ +840 (peak), $[\theta]_{257}$ +10 (trough), $[\theta]_{260}$ +2050 (peak), $[\theta]_{264}$ +346 (trough), $[\theta]_{266}$ +1760 (peak), $[\theta]_{271}$ 0.
14. Dihydroincasine B (B') (**8**): $[\alpha]_D^{25}$ +69.0° (*c*=0.26, $CHCl_3$); EI-MS (*m/z*): 475 $[M]^+$ (30), 474 (79), 343 (24), 341 (39), 314 (100), 139 (29), 131 (79), 125 (57); ^{1}H-NMR ($CDCl_3$): δ 1.26-2.07 (8H, m, 3, 11, 15, 16-H), 2.27-2.49, 2.95-3.70 (14H, m, 2, 4, 7, 10, 12, 14, 17-H), 4.09 (1H, m, 8-H), 7.21-7.41 (10H, m, 2', 3', 4', 5', 6', 2", 3", 4", 5", 6"-H); CD (MeOH, *c*=2.6 mg/2ml, 220-300 nm): $[\theta]_{254}$ +6060 (peak), $[\theta]_{258}$ +1150 (trough), $[\theta]_{260}$ +3680 (peak), $[\theta]_{264}$ +160 (trough), $[\theta]_{266}$ +2020 (peak), $[\theta]_{272}$ 0.
15. Dihydroincasine C (**9**): $[\alpha]_D^{25}$ +8.6° (*c*=0.62, $CHCl_3$); Anal: $C_{29}H_{38}N_9O_2$; EI-MS (*m/z*): 476 $[M]^+$ (90), 475 (100), 131 (18), 125 (12); ^{1}H-NMR ($CDCl_3$): δ 1.47-1.83 (8H, m, 3, 11, 15, 16-H), 2.37-3.90 (14H, m, 2, 4, 7, 10, 12, 14, 17-H), 3.98 (1H, m, 8-H), 7.08, 7.20, 7.26-7.35 (10H, m, 2', 3', 4', 5', 6', 2", 3", 4", 5", 6"-H); CD (MeOH, *c*=6.7 mg/2ml, 220-300 nm): $[\theta]_{249}$ 0, $[\theta]_{250}$ -1010 (peak), $[\theta]_{252}$ +270 (trough), $[\theta]_{254}$ -1560 (peak), $[\theta]_{256}$ -510 (trough), $[\theta]_{260}$ -2270 (peak), $[\theta]_{264}$ -850 (trough), $[\theta]_{266}$ -2260 (peak), $[\theta]_{273}$ 0.
16. Dihydroverballocine (**10**): $[\alpha]_D^{24}$ -1.2° (*c*=0.33, $CHCl_3$); EI-MS (*m/z*): 464 $[M]^+$ (51), 421 (100), 146 (25), 131 (18); ^{1}H-NMR ($CDCl_3$): δ 1.47-1.90 (8H, m, 3, 11, 15, 16-H), 2.38-3.80 (14H, m, 2, 4, 7, 10, 12, 14, 17-H), 3.99 (1H, m, 8-H), 7.08, 7.21, 7.26-7.35 (10H, m, 2', 3', 4', 5', 6', 2", 3", 4", 5", 6"-H); CD (MeOH, *c*=3.3 mg/2ml, 220-300 nm): $[\theta]_{247}$ 0, $[\theta]_{254}$ +910 (peak), $[\theta]_{256}$ +490 (trough), $[\theta]_{260}$ +1710 (peak), $[\theta]_{264}$ +390 (trough), $[\theta]_{266}$ +1680 (peak), $[\theta]_{271}$ 0. No CD spectrum assignment of dihydroverballocine in the literature 4.
17. (a) Smith, H. E.; Warren, M. E.; Katzin, L. I. *Tetrahedron*, **1968**, *24*, 1327-1335; (b) Seifert, K.; Johne, S.; Hesse, M. *Helv. Chim. Acta*, **1982**, *65*, 2540-2547.
18. This would be due to a configuration change around C-8 by introduction of a methylene between N-9 and N-13 to form a hexahydropyrimidine cycle in **5**.

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