Pergamon

Tetrahedron Letters 43 (2002) 7565–7568

TETRAHEDRON LETTERS

Asymmetric synthesis of myrioxazines A and B, novel alkaloids of *Myrioneuron nutans*

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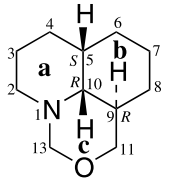
Received 20 August 2002; revised 21 August 2002; accepted 22 August 2002

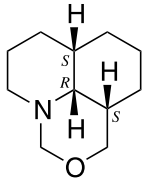
Abstract—Two new epimeric tricyclic alkaloids, myrioxazines A and B were isolated from the leaves of *Myrioneuron nutans* and their structures elucidated by spectral analysis (mass spectrometry and 2D NMR). Absolute configurations were determined by total asymmetric synthesis.

The Rubiaceae is a large family containing various and important alkaloid classes, such as purine (caffeine),[1] pyrrolidinoindoline (psychotridine),[2,3] indole (yohimbine), quinolizidine (emetine) and quinoline (quinine,[1] camptothecin[4]) alkaloids.

We report here, the first chemical study on *Myrioneuron nutans* Drake (Rubiaceae). Two tricyclic alkaloids, with a new natural skeleton were isolated from the leaves and named myrioxazines A (**1**) and B (**2**). Furthermore, the absolute configurations of the natural compounds were established by the total asymmetric syntheses of **1**, **2** and their enantiomers.



1
Myrioxazine A



2
Myrioxazine B

The dried leaves (5 kg) of *M. nutans*, collected in North Vietnam were extracted with CH_2Cl_2 at pH 9 (NH_4OH). The crude alkaloid obtained by acid–base purification was separated by cc on SiO_2 eluted with CH_2Cl_2/MeOH gradient to yield compounds **1** (25 mg) and **2** (40 mg).

Compound **1** was isolated as an optically active colourless oil, $[\alpha]_D^{20}$ +21 (*c* 1, MeOH). Its ESI-MS showed the protonated molecular $[M+H]^+$ ion at *m*/*z* 182.1559 (calcd 182.1545 for $C_{11}H_{20}NO$), indicating the molecular formula $C_{11}H_{19}NO$. The ^{13}C NMR spectrum presented eight methylene and three methine groups. Analysis of ^1H–^1H COSY spectrum showed complex connections, starting from the methylene at δ 2.55 and 3.09 (CH_2-2) to methine at δ 2.73 (CH-10) and also those of the methine at δ 2.13 (H-9) to the methylene at δ 3.13 and 3.80 (CH_2-11). The ^1H and ^{13}C chemical shifts (Table 1) suggested that the CH_2-2 and the CH-10 were linked to nitrogen atom and the CH_2-11 linked to oxygen atom. In the HMBC spectrum, the proton at δ 2.73 (H-10) was correlated to the methylene carbons at δ 73.1 (C-11), 44.7 (C-2), 23.7 (C-4) and 31.0 (C-6), thus depicting a decahydroquinoline substituted skeleton. The methylene CH_2-13, linked to both oxygen and nitrogen atoms (-O-CH_2-N<) as indicated by its chemical shifts (δ_C 86.2 and δ_H 4.42 and 4.36), was correlated to the protons of two methylenes CH_2-2 and CH_2-11, forming an 1,3-oxazine ring system. From further HMBC analysis, the structure perhydroquino [1,8-cd] [1,3] oxazine was assigned to myrioxazine A (**1**). The relative configuration of **1** was determined from vicinal ^1H–^1H coupling constants and NOESY data. The proton H-9 displayed three *trans*-diaxial coupling constants with H-11_{ax}, H-10 and H8_{ax} (11.1 Hz), and two *gauche*-coupling ones with H-11_{eq} and H-8_{eq} (4.3 and 3.3 Hz), indicating that it was axial on both **b** and **c**-rings.

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0040-4039/02/$ - see front matter
PII: S0040-4039(02)01771-9

Table 1. NMR data for **1** and **2**, ($CDCl_3$); ^1H (400.13 MHz), ^{13}C (75.47 MHz)

	1			2		
Cn°	δ_C	δ_H	m (*J*, Hz)	δ_C	δ_H	m (*J*, Hz)
2	44.7	3.09 (ax)	ddd (11.9; 11.9; 2.8)	50.0	2.57 (eq)	d (8.2)
–	–	2.56 (eq)	ddd (11.9; 3.8; 2.2)	–	1.73 (ax)	m
3	25.9	1.71 (eq)	m	20.3	1.76 (ax)	m
–	–	1.50 (ax)	m	–	1.38 (eq)	m
4	23.7	1.50 (ax)	m	30.1	1.47	m
–	–	1.26 (eq)	m	–	1.47	m
5	34.8	1.79	ddddd (12.0; 4.0; 4.0; 4.0; 4.0)	36.2	1.49	m
6	31.0	1.51	m	25.4	1.80 (ax)	m
–	–	1.51	m	–	1.16 (eq)	m
7	20.2	1.34	m	26.0	1.78 (eq)	m
–	–	1.34	m	–	1.27 (ax)	m
8	27.5	1.33 (eq)	m	25.2	1.95 (ax)	dddd (13.6; 13.6; 13.6; 3.6)
–	–	0.71 (ax)	dddd (12.2; 12.2; 11.1; 4.3)	–	1.35 (eq)	m
9	27.8	2.13	ddddd (11.1; 11.1; 11.1; 4.3; 3.3)	37.0	1.33	m
10	62.3	2.73	dd (11.1; 4.8)	63.3	2.16	br.s
11	73.1	3.80 (eq)	dd (10.8; 4.3; 1.0)	73.4	3.70 (ax)	dd (11.1; 0.9)
–	–	3.13 (ax)	dd (11.1; 10.8)	–	3.56 (eq)	dd (11.1; 2.7)
13	86.2	4.42 (ax)	d (10.4)	87.7	4.26 (eq)	d (7.6)
–	–	4.36 (eq)	dd (10.4; 1.0)	–	3.38 (ax)	d (7.6)

On the other hand, H-10 showed an additive *gauche*-coupling constant with H-5 (4.8 Hz). These results indicated the *cis*-**a**/**b** and *trans*-**b**/**c** rings junctions for compound **1**. Finally, the relative configuration 5*S**, 9*R** and 10*R** was confirmed by the NOESY spectrum, in which strong interactions of H-10 with H-5, H-8_{ax}, H-11_{ax} and H-13_{ax}, and of H-9 with both H-2_{ax} and H-11_{eq} were observed (Fig. 1). Complete analysis of NOE interactions determined that the three **a**, **b** and **c**-rings were in the chair conformation and that H-10 was equatorial in **a**-ring with *cis*-**a**/**c** rings junction. Myrioxazine A (**1**) was a *cis*-decahydroquinoline derivative, for which the *N-out* (N-outside)[5] conformation was constrained by the -O-CH_2- bridge.

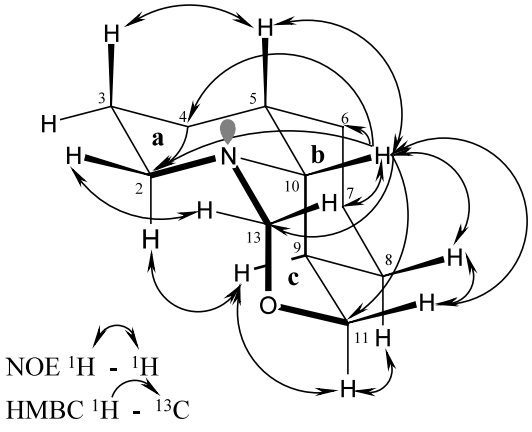

Figure 1. Selected NOE and HMBC correlations for myrioxazine A (**1**).

Compound **2** was obtained as a colourless oil, $[\alpha]_D^{20}$ +9 (*c* 1, MeOH). The ESI-MS showed the protonated molecular $[M+H]^+$ ion at *m*/*z* 182.1549, and the ^1H and ^{13}C NMR (*J*-modulated) spectra were similar to those of **1**, suggesting **1** and **2** to be isomers. The ^1H–^1H COSY spectrum of **1** indicated the same spin systems for a decahydroquinoline derivative. In the HMBC spectrum, the proton at δ 2.16 (H-10) showed correlations to the methylene carbons at δ 87.7 (C-13), 73.4 (C-11), 30.1 (C-4), 25.4 (C-6) and 25.2 (C-8). Furthermore, the methylene at δ 73.4 (C-11) correlated to the two methylenes CH_2-8 and CH_2-13 at δ 1.35, 1.95 and 3.38, 4.26, respectively. These results indicated that compound **2** has the same plane structure as compound **1**. In comparison with **1**, the stereochemical inversion at chiral carbon C-9 of **2** was depicted by the broad singlet signal for proton H-10 at δ 2.16, indicating small coupling constants between H-10 and both H-9 and H-5. These results showed *cis*-relationship of H-10 with both H-5 and H-9, defining thus *cis*-**a**/**b** and **b**/**c** ring fusions. Furthermore, the strong interactions observed in the NOESY spectrum of H-10 with H-2_{ax}, H-4_{ax}, H-5, H-9 and H-13_{ax}, and of H-9 with H-5, H-7_{ax} and CH_2-11 determined that the three **a**, **b**, **c**-rings were in

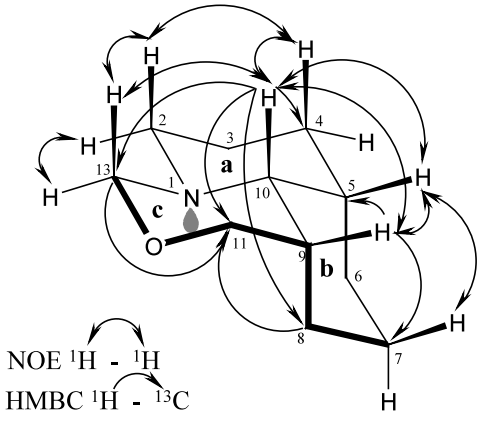

Figure 2. Selected NOE and HMBC correlations for myrioxazine B (**2**).

chair conformation and that H-10 was axial in the **a** and **c**-rings and equatorial in **b**-ring; the two **a** and **c**-ring were thus in *trans*-fusion. From foregoing studies, the relative stereochemistry 5*S**, 9*S** and 10*R** was assigned to myrioxazine B (**2**), a *cis*-decahydroquinoline derivative, possessing the *N-in* (N-inside)[5] structure, which was also locked by the -O-CH_2- bridge (Fig. 2).

In order to determine the absolute configurations of **1** and **2**, their total asymmetric syntheses were performed as described in Fig. 3. Tetrahydroquinoline **4**[6–8] was prepared by *Michael addition* of acroleine with the enamine of cyclohexanone, followed by cyclisation with hydroxylamine hydrochloride. Compound **4** reacted with paraformaldehyde at 90°C for 48 h, to give a racemic mixture of 8-hydroxymethyl tetrahydroquinoline **5** with 37% yield (50% of **4** recovered). This reaction was previously reported by Crabb et al.,[9] but with lower yield because of the formation of bis-substituted compounds. The two diastereoisomers **6**[10] and **7**[11] were obtained via esterification of the racemate **5** with (1*S*)-(−)-camphanyl chloride followed by SiO_2 cc (*n*-hexane/Et_2O/EtOH 10/1/0.5). Compound **6** ($[\alpha]_D^{20}$ +23; *c* 2, MeOH) was an oil and **7** ($[\alpha]_D^{20}$ −45; *c* 2, MeOH) was crystallised from *n*-hexane/Et_2O mixture.

The X-ray diffraction[12] analysis of **7** indicated that the absolute configuration of the chiral carbon C-9 was (*R*) (Fig. 4), and that of **6** was thus (*S*). The two

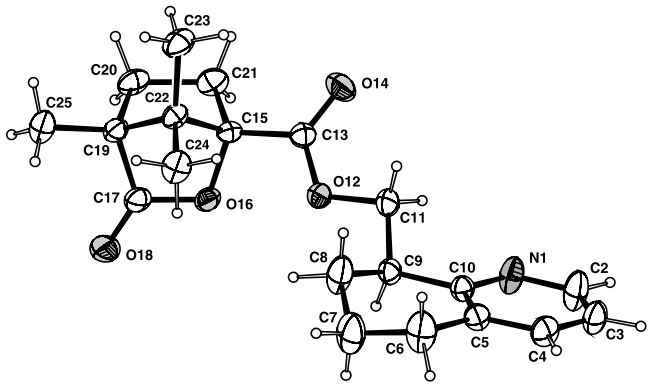

Figure 4. X-Ray crystallographic structure of compound **7** (ORTEP drawing with 30% probability ellipsoids).

diastereoisomers **6** (*S*) and **7** (*R*) were further hydrolysed to give two enantiomers **8** (9-S) ($[\alpha]_D^{20}$ +60; *c* 2, MeOH) and **13** (9*R*) ($[\alpha]_D^{20}$ −61; *c* 2, MeOH), respectively. Catalytic hydrogenation (H_2/PtO_2, AcOH) of **8** provided two stereoisomers **9**[13] ($[\alpha]_D^{20}$ −34; *c* 2, MeOH) and **10**[14] ($[\alpha]_D^{20}$ +2; *c* 1, MeOH): similarly, compound **13** yielded two stereoisomers **14**[13] ($[\alpha]_D^{20}$ +33; *c* 2, MeOH) and **15**[14] ($[\alpha]_D^{20}$ −2, *c* 1, MeOH), in ratio 4:1 for **9**:**10** and **14**:**15**. Finally, compounds **11**[15] ($[\alpha]_D^{20}$ −19; *c* 1, MeOH), **12**[16] ($[\alpha]_D^{20}$ +10; *c* 1, MeOH), **16**[15] ($[\alpha]_D^{20}$ +19; *c* 1, MeOH) and **17**[16] ($[\alpha]_D^{20}$ −9; *c* 1, MeOH) were obtained respectively from cyclisation of **10**, **9**, **15** and **14** with HCHO 30% at rt for 1 h.

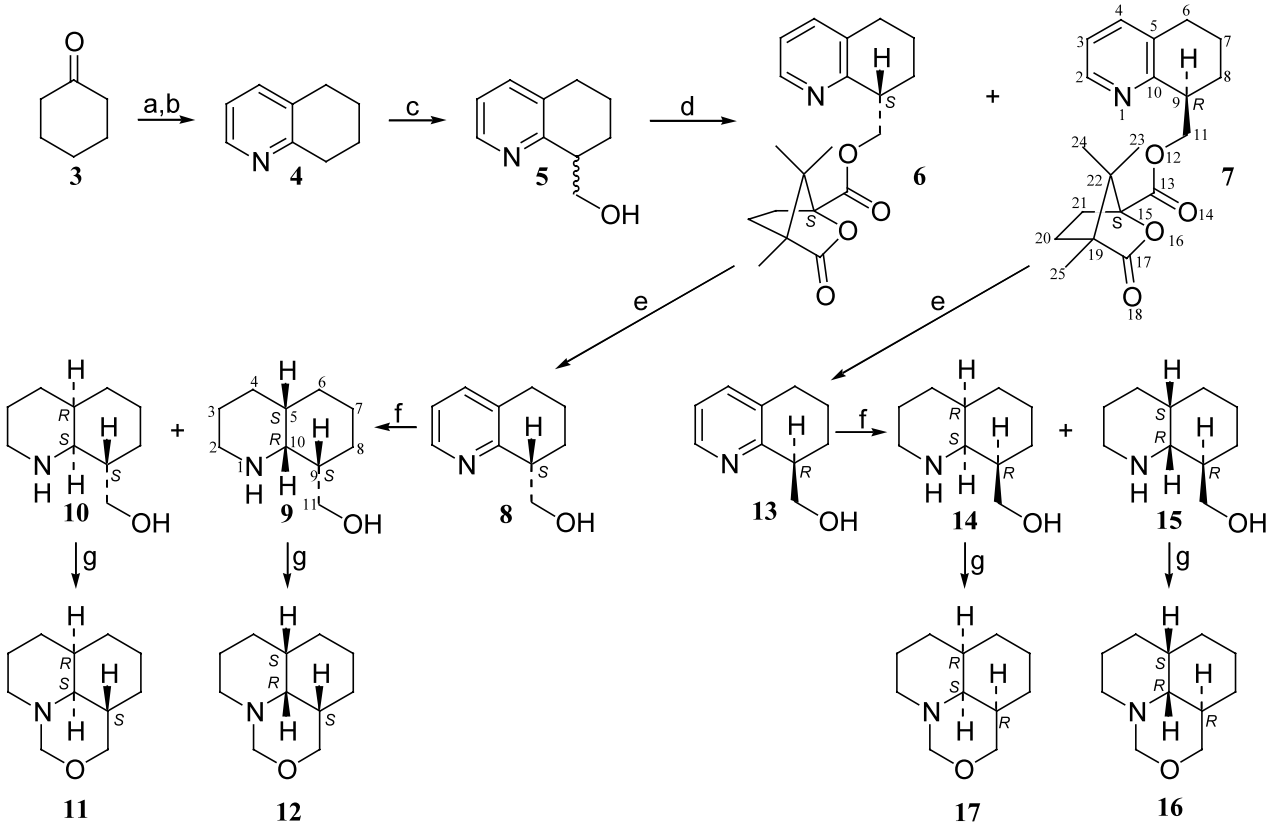

Figure 3. *Reagents and conditions*: (a) 1. Piperidine, toluene, *p*-TsOH, 110°C, 12 h; (2) acroleine, THF, 3 h; HCl 2N, 4 h, 35% overall. (b) NH_2OH–HCl, EtOH, 80°C, 3 h, 77%. (c) Paraformaldehyde, 90°C, 48 h, 37%. (d) (1*S*)-(−)-camphanic chloride, CH_2Cl_2/Py, 15 h, 91%. (e) NaOH 30%, 60°C, 5 h, 97%. (f) H_2/PtO_2, AcOH, 12 h, 82%. (g) HCHO 30%, 1 h, 95%.

Comparison of NMR data and optical activities of the natural myrioxazines A (**1**) and B (**2**) with the synthetic **11**, **12**, **16** and **17** revealed that they were identical to **16** and **12**, respectively. The absolute configurations 5*S*, 9*R* and 10*R* were thus assigned to myrioxazine A (**1**), and 5*S*, 9*S* and 10*R* for myrioxazine B (**2**).

Acknowledgements

We thank Dr V. H. Nguyen for the supporting of the program 'Research for Flora of Vietnam'. The CNRS is gratefully acknowledged for doctoral fellowship supporting (V.C.P.), and the 'Région Ile de France' for the distribution of NMR 400 MHz and the mass spectrometry equipment. We thank also Dr. J. P. Brouard and Mr. L. Dubost for the mass spectra, Mrs. C. Caux for the NMR spectra, and Mr. D. C. Dao and Mr. A. Gramain for the collect of plant materials.

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10. Compound **6**: $[\alpha]_D^{20}$ +23 (*c* 2, MeOH); ^{1}H ($CDCl_3$, 400.13 MHz): 8.33, 1H (m, 4.7; 1.8, H-2); 7.33, 1H (m, 7.7; 1.8, H-4); 7.00, 1H (dd, 7.7; 4.7, H-3); 4.61, 2H (d, 5.9, CH_2-11); 3.23, 1H (dddd, 6.2; 6.2; 6.1; 6.0; H-9); 2.72, 2H (dd, 6.1; 6.1, H-6); 2.30, 1H (ddd, 13.4; 10.7; 4.3, H-21a); 2.01, 1H (m, H-8a); 1.92, 1H (m, H-21b); 1.90, 1H (m, H-7a); 1.81, 2H (m, H-20a and H-8b); 1.71, 1H (m, H-7b); 1.59, 1H (ddd, 13.1; 9.3; 4.3, H-20b); 1.02, 3H (s, CH_3-25); 0.84, 3H (s, CH_3-24); 0.81, 3H (s, CH_3-23); ^{13}C ($CDCl_3$, 75.47 MHz): 178.0 (C-17); 167.1 (C-13); 155.3 (C-10); 146.8 (C-2); 136.8 (C-4); 133.1 (C-5); 121.4 (C-3); 91.1 (C-15); 68.3 (C-11); 54.5 (C-19 or C-22); 53.8 (C-22 or C-19); 39.9 (C-9); 30.4 (C-21); 28.8 (C-6; C-20); 26.0 (C-8); 20.0 (C-7); 16.4 (CH_3-24); 16.3 (CH_3-23); 9.5 (CH_3-25).
11. Compound **7**: mp 110–110.5°C; $[\alpha]_D^{20}$ −45 (*c* 2, MeOH); ^{1}H ($CDCl_3$, 400.13 MHz): 8.33, 1H (m, 4.7; 1.7, H-2); 7.33, 1H (m, 7.7; 1.7, H-4); 7.00, 1H (dd, 7.7, 4.7, H-3); 4.63, 1H (dd, 10.7; 8.1, H-11a); 4.61, 1H (dd, 10.7; 3.5, H-11b); 3.25, 1H (m, H-9); 2.72, 2H (m, H-6); 2.32, 1H (ddd, 13.3; 10.8; 4.3, H-21a); 2.03, 1H (m, H-8a); 1.95, 1H (m, H-21b); 1.90, 1H (m, H-7a); 1.84, 1H (m, H-20a); 1.83, 1H (m, H-8b); 1.71, 1H (m, H-7b); 1.61, 1H (ddd, 13.1; 9.3; 4.2, H-20b); 1.03, 3H (s, CH_3-25); 0.94, 3H (s, CH_3-24); 0.74, 3H (s, CH_3-23); ^{13}C ($CDCl_3$, 75.47 MHz): 178.2 (C-17); 167.3 (C-13); 155.4 (C-10); 146.9 (C-2); 136.8 (C-4); 133.2 (C-5); 121.5 (C-3); 91.2 (C-15); 68.4 (C-11); 54.6 (C-19 or C-22); 53.9 (C-22 or C-19); 40.0 (C-9); 30.4 (C-24); 28.8 (C-6; C-20); 26.1 (C-8); 20.1 (C-7); 16.6 (CH_3-21); 16.4 (CH_3-23); 9.6 (CH_3-25).
12. Structure solved with SHELXS-86 and refined with SHELXL-93. H atoms treated riding. Refinement converged to $R(F)=0.0548$ for the 3379 observed reflections and $wR(F^2)=0.1310$ for all the 4227 data, goodness-of-fit S = 1.083. Residual electron density between −0.17 and 0.28 e Å^{-3}. Full crystallographic results have been deposited as Supplementary Material (CIF file), at the Cambridge Crystallographic Data Centre, UK. Displacement ellipsoids are shown at the 30% probability level.
13. Compound **9**: mp 125–125.5°C; $[\alpha]_D^{20}$ −34 (*c* 2, MeOH). Compound **14**: $[\alpha]_D^{20}$ +33 (*c* 2, MeOH); ^{1}H ($CDCl_3$, 400.13 MHz): 3.79, 1H (m, H -11a); 3.52, 1H (dd, 2.7; 2.7, H-11b); 3.01, 1H (ddd, 13.0; 4.1; 1.9, H-2eq); 2.96, 1H (dd, 2.7; 2.7, H-10); 2.54, 1H (ddd, 13.0; 13.0; 3.3, H-2ax); 1.78, 1H (m, H-7eq); 1.66, 2H (m, H-4ax and H-6ax); 1.55, 1H (m, H-4eq); 1.48, 1H (m, H-3ax); 1.47, 1H (m, H-5); 1.42, 1H (m, H-9); 1.41, 2H (m, CH_2-8); 1.29, 1H (m, H-3eq); 1.28, 1H (m, H-6eq); 1.26, 1H (m, H-7ax); ^{13}C ($CDCl_3$, 75.47 MHz): 67.3 (C-11); 59.1 (C-10); 47.1 (C-2); 42.5 (C-9); 35.6 (C-5); 30.3 (C-4); 25.6 (C-7); 24.3 (C-6); 23.2 (C-8); 21.9 (C-3).
14. Compound **10**: mp 110–111°C $[\alpha]_D^{20}$ +2 (*c* 1, MeOH). Compound **15**: mp 110–111°C $[\alpha]_D^{20}$ −2 (*c* 1, MeOH); ^{1}H ($CDCl_3$, 400.13 MHz): 3.58, 1H (dd, 10.6; 3.6, H-11a); 3.45, 1H (dd, 10.6; 10.6, H-11b); 2.79, 1H (m, H-2eq); 2.77, 1H (dd, 10.6; 2.8, H-10); 2.74, 1H (m, H-2ax); 2.10, 1H (m, H-9); 1.73, 1H (m, H-4ax); 1.68, 1H (m, H-5); 1.68, 1H (m, H-3eq); 1.52, 1H (m, H-8eq); 1.44, 2H (m, CH_2-6); 1.39, 2H (m, CH_2-7); 1.38, 1H (m, H-4eq); 1.36, 1H (m, H-3ax); 0.79, 1H (m, H-8ax); ^{13}C ($CDCl_3$, 75.47 MHz): 70.6 (C-11); 60.9 (C-10); 40.0 (C-2); 37.4 (C-5); 33.4 (C-9); 31.3 (C-6); 28.3 (C-8); 27.7 (C-3); 25.1 (C-4); 19.9 (C-7).
15. Compound **11**: $[\alpha]_D^{20}$ −19 (*c* 1, MeOH). Compound **16**: $[\alpha]_D^{20}$ +19 (*c* 1, MeOH).
16. Compound **12**: $[\alpha]_D^{20}$ +10 (*c* 1, MeOH). Compound **17**: $[\alpha]_D^{20}$ −9 (*c* 1, MeOH).