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ASYMMETRIC SYNTHESIS III[1].
ENANTIOSPECIFIC SYNTHESIS OF THE NATURAL 3R, 5R, 9R (-) GEPHYROTOXIN-223 AB

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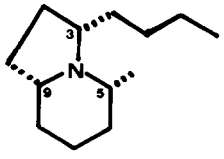
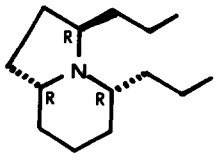
Abstract

The first enantiospecific synthesis of the indolizidine alkaloid (-) gephyrotoxin-223 AB 2 has been achieved from the chiral 2-cyano-6-oxazolopiperidine synthon 3.

Recently, we reported the first enantiospecific total synthesis of the ant trail pheromone (-) monomorine I, 1 (scheme 1) which permitted the assignement of the absolute configuration for the natural (+) enantiomer [1]. A key feature in our approach was the development of methods for the stereoselective introduction of substituents at the C-2 and C-6 centers of the chiral 1,4-dihydropyridine equivalent 3 [2] (scheme 2) thus fixing the absolute configuration at C-5 and C-9 centers (indolizidine numbering) of 1. Another merit of this pathway was the observation that nucleophilic attack (H^-) at position C-3 of the intermediate $\geq N^+ =$ C-3 pyrrolidinium ion occurred preferentially from the β face of the molecule [1].



1 (-) monomorine

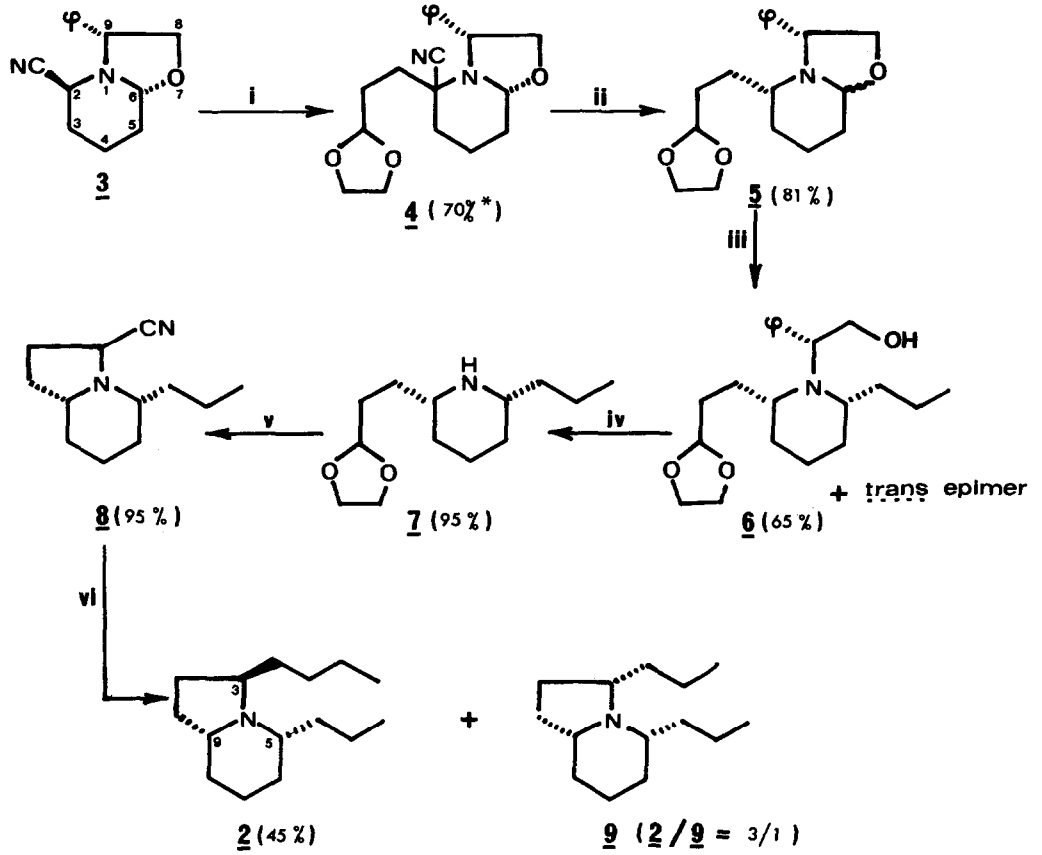


2 (-) gephyrotoxin-223 AB

Scheme 1

Since monomorine I 1 and gephyrotoxin-223 AB 2 essentially differ in the stereochemistry at C-3 we were prompted to undergo the asymmetric synthesis of the latter alkaloid in order to test the flexibility of our strategy.

The structure and relative configuration of gephyrotoxin-223 AB 2, a neurotoxic alkaloid extracted from the skin of tropical frogs, have been well established [3,4] but the absolute configuration of this molecule remained unknown. We thus arbitrarily choose to prepare 3R, 5R, 9R enantiomer of 2 following a variation of the scheme that was used for the introduction of 5,9-dialkyl cis substituents of 3S, 5R, 9R (-) monomorine I, 1 [1].



Scheme 2

Reagents i) LDA, THF, -78°C, $BrCH_2CH_2$-CH(O,O), 3h. ; ii) $AgBF_4$, THF, 5 min., r.t. $Zn(BH_4)_2$, -50°C, 1 h. ; iii) PrMgBr, ether, -50°C, 1 h. ; iv) H_2, Pd/C 10%, MeOH, 30 min. ; v) CH_2Cl_2-HCl 1N, KCN ; vi) nBuMgBr, ether, 0°C.
* Yields of pure isolated products.

Alkylation of the anion of 3 [2] with 3-bromo-1-pentanal ethylene ketal led to the formation of a single product 4 [6]. The cyano group of 4 was then selectively cleaved by complexation with $AgBF_4$ and treatment with $Zn(BH_4)_2$ at low temperature. As previously observed compound 5 was obtained as a 3:2 mixture of C-6 epimeric oxazolidines [1]. The reaction of epimeric 5 with PrMgBr gave the desired cis compound 6 [7] accompagnied by small amounts of its trans epimer (cis/trans : 85/15).

Hydrogenolysis of 6 led to 7 [8] which was treated in a biphasic medium (CH_2Cl_2-H_2O) with HCl 1N and KCN (pH 3-4) to furnish the aminonitrile 8 [9] as a single epimer. Finally the butyl side chain was introduced stereoselectively at C-3 of 8 on reaction with BuMgBr ; as anticipated [1,5] this reaction generated preferentially the desired R epimer (R/S : 7/3).

Synthetic (-) gephyrotoxin-223 AB 2 [10] (45% from 8) $[\alpha]_D^{20}$ -101° (n-hexane, C 2.3) exhibited spectral data (^1H and ^{13}C NMR and mass spectra) identical to those published for the racemic material [4a].

As our synthetic material exhibited the same sign of optical rotation as the natural product, we can then deduced that the absolute configuration of the natural (-) gephyrotoxin 223 AB is 3R, 5R, 9R [11].

In conclusion we have devised a method for the synthesis of chiral indolizidine alkaloids that could be extended to the preparation of a large variety of derivative and be specially useful for the determination of relative and absolute configuration of natural products isolated in trace amounts [12].

References and Notes

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3 A non stereoselective synthesis of (±)gephyrotoxin-223 AB led to the formation of the four racemic possible diastereoisomers : T.F. Spande, J.W. Daly, D.J. Hart, Y.M. Tsai and T.L. Macdonald, Experientia, 1981, 37, 1242. All further stereoselective synthesis have afforded (±) gephyrotoxin-223 AB stereoisomers but not the natural product [4].

4 a) T.L. Macdonald, J. Org. Chem., 1980, 45, 193 ; b) R.V. Stevens and A.W.M. Lee, J. Chem. Soc. Chem. Commun., 1982, 103 ; c) D.J. Hart and Y.M. Tsai, J. Org. Chem., 1982, 47, 4403.

5 N. Maigrot, J.-P. Mazaleyrat and Z. Welvart, J. Chem. Soc. Chem. Commun., 1984, 40.

6 4 : mp 45-50°C (hexane-ether) ; MS m/e (relative intensity) : 328 ($M^{+\cdot}$, 17), 327 (17), 228 (22), 227 (44), 104 (100), 91 (22) ; ^1H NMR ($CDCl_3$, 400 MHz) : 1-2 ppm (m, 10H, CH_2), 3.55 (m, 4H, OCH_2-CH_2O), 3.73 (dd J = 8.5 Hz, J' = 4.5 Hz, 1H, H-8 or H-9), 4.0 (dd, J = 8.5 Hz, J' = 4.5 Hz, 1H, H-8 or H-9), 4.14 (dd,

J = 9.5 Hz, J' = 2.5 Hz, 1H, H-6), 4.26 (t, J = 8.5Hz, 1H, H-8 or H-9), 4.45 (t, J = 3.75Hz, 1H, H-C(=O)-O), 7.3 (m, 5H, ar.) ; ^{13}C NMR ($CDCl_3$, 50 MHz) : 20.1 (C-4) 28.4 (C-11), 29.6 (C-5), 33.2 (C-10), 34.5 (C-3), 62.1 (C-2), 62.4 (C-9), 64.9 (OCH_2CH_2O), 74.8 (C-8), 92.2 (C-6), 103,1 (C(=O)-O), 118.5 (CN), 127.4, 127.2, 128.6, 144.2 (ar.).

7 6 : oil ; MS (c.i) m/e : 348 (MH^+), 330, 228 ; ^1H NMR ($CDCl_3$, 400 MHz) 0.82 (t, J = 7 Hz, 3H, CH_3), 0.95-1.9 (m, 14H, CH_2), 2.78 and 2.96 (2m, 2H, H-2 and H-6), 3.75-4.0 (m, 7H, OCH_2CH_2O, H-8, H-9), 4.86 (t, J = 4 Hz, 1H, H-C(=O)-O), 7.33 (m, 5H, ar.) ; microanalysis, calcd. for $C_{21}H_{33}NO_3$: C 72.58, H 9.57, N 4.03, found : C 72.24, H 9.47, N 4.07.

8 7 : oil ; MS, m/e (relative intensity) : 227 ($M^{+\cdot}$ 6), 226 (5), 184 (78), 155 (10), 126 (100), 112 (30) ; ^1H NMR ($CDCl_3$, 400 MHz) 0.9 (t, J = 7 Hz, 3H, CH_3), 1-1.9 (m, 14H, CH_2), 2.67 (m, 2H, H-2 and H-6) 3.83 and 3.96 (2m, 4H, OCH_2-CH_2-O) 4.88 (t, J = 4, H-C(=O)-O).

9 8 : oil ; MS, m/e (relative intensity) : 192 ($M^{+\cdot}$, 1), 166 (1), 149 (100), 122 (7) ; ^1H NMR ($CDCl_3$, 400 MHz) 0.91 (t, J = 7.5 Hz, 3H, CH_3), 1-2.2 (m, 14H, CH_2), 2.4 (m, 2H, H-2 and H-6), 4.16 (d, J = 7.5 Hz, 1H, CH-CN) ; ^{13}C NMR ($CDCl_3$, 50 MHz) 14.2 (CH_3), 18.1, 23.9, 26.7, 29.0, 30.1, 31.1, 36.1 (CH_2), 51.1 (C-3) 58.8 (C-9), 61.2 (C-5), 117.6 (CN).

10 2 : oil ; MS, m/e (relative intensity) : 223 ($M^{+\cdot}$, 1), 222 (1), 181 (15), 180 (99), 167 (15), 166 (100), 149 (17) ; ^{13}C NMR ($CDCl_3$, 50 MHz) 14.2, 14.6 (2 CH_3), 19.0, 23.0, 24.7, 25.1, 26.5, 29.2, 30.1, 31.0, 32.4, 35.9 (CH_2), 56.7, 58.6, 59.1 (CH).

11 We thank Drs. J.W. Daly and T. Tokuyama for communicating to us that the $[\alpha]_D$ of the natural gephyrotoxin-223AB is also negative. Due to the instability and minute amount of material in their possession precise $[\alpha]_D$ value for the natural product has not as yet been obtained.

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