SYNTHESES OF (−)-9-DEMETHYLPROTOEMETINOL AND (±)- AND (−)-10-DEMETHYLPROTOEMETINOLS

Tozo Fujii,*,† Masashi Ohba,† Hitoshi Suzuki,†
Satyesh C. Pakrashi,§ and Esahak Ali§

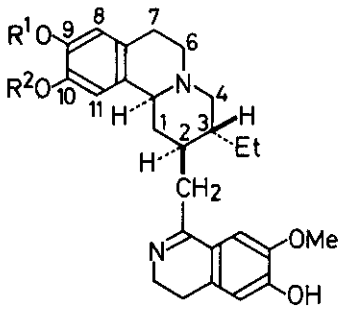
†*Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan*

§*Indian Institute of Chemical Biology, Calcutta-700032, India*

Abstract —— The synthesis of (−)-9-demethylprotoemetinol (X) was achieved by $LiAlH_4$ reduction of the (−)-tricyclic ester XIV followed by catalytic hydrogenolysis of the resulting (−)-tricyclic alcohol XI. Acetylation of (−)-X yielded the (−)-diacetate XVII. Parallel synthetic routes starting with the isomeric (±)- and (−)-tricyclic esters XV gave (±)- and (−)-10-demethylprotoemetinols (XII) and the corresponding diacetates [(±)- and (−)-XVIII] through the (±)- and (−)-tricyclic alcohols XIII, respectively.

The isolation of psychotrine (I),[1−3] cephaeline (IV),[1−4] and tubulosine (VII),[3−7] together with their demethylated bases such as 9-demethylpsychotrine (II),[3,8,9] demethylcephaeline (V or VI),[3,10] and 10-demethyltubulosine (VIII),[7,11] from Alangium lamarckii Thwaites (family Alangiaceae) suggested the possibility of co-occurrence of the 9-demethylated (X) and/or 10-demethylated (XII) bases of protoemetinol (IX), already encountered in A. lamarckii.[4,12] To facilitate the search from the natural source, we undertook the synthesis of (−)-9-demethylprotoemetinol (X)[13] and (±)- and (−)-10-demethylprotoemetinols (XII).

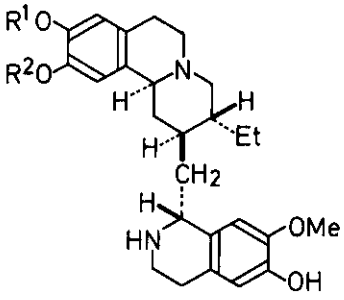
The first target selected for synthesis was (±)-10-demethylprotoemetinol (XII). It seemed accessible from the known (±)-tricyclic ester XV, the key intermediate used for the syntheses of (±)-10-demethylpsychotrine (III)[14] and (±)-10-demethyltubulosine (VIII),[11] through a route closely parallel to that[15] adopted by Fujii et al. for the synthesis of yet another Alangium alkaloid, ankorine (XVI).[12,15,16] Thus, reduction



I: $R^1 = R^2 = Me$

II: $R^1 = H$; $R^2 = Me$

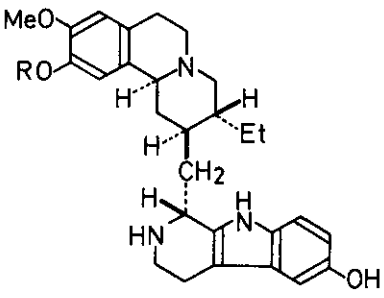
III: $R^1 = Me$; $R^2 = H$



IV: $R^1 = R^2 = Me$

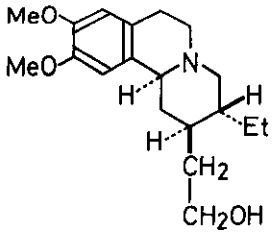
V: $R^1 = H$; $R^2 = Me$

VI: $R^1 = Me$; $R^2 = H$

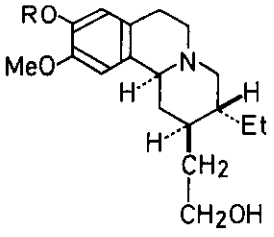


VII: R = Me

VIII: R = H

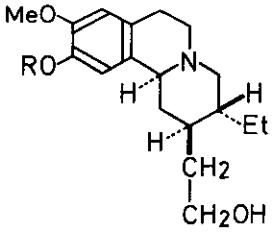


IX



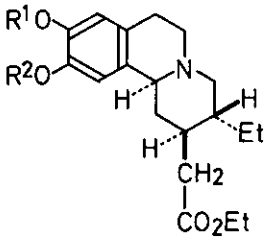
X: R = H

XI: $R = PhCH_2$



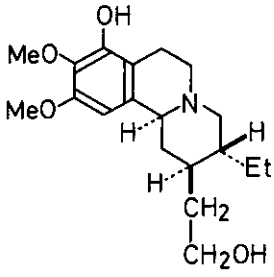
XII: R = H

XIII: $R = PhCH_2$

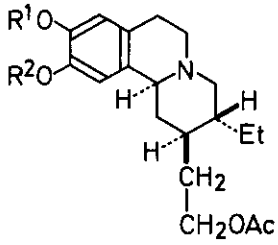


XIV: $R^1 = PhCH_2$; $R^2 = Me$

XV: $R^1 = Me$; $R^2 = PhCH_2$



XVI



XVII: $R^1 = Ac$; $R^2 = Me$

XVIII: $R^1 = Me$; $R^2 = Ac$

of (±)-XV with $LiAlH_4$ in ether afforded the (±)-tricyclic alcohol XIII[17] (mp 98.5–99.5°C) in 91% yield. On catalytic hydrogenolysis (10% Pd-C/H_2, EtOH, room temp., 1 atm, 2 h), (±)-XIII gave (±)-10-demethylprotoemetinol (XII) (mp 151–152°C) in 96% yield. The (±)-diacetate XVIII (mp 97–98°C) was obtained from (±)-XII in 85% yield by acetylation (Ac_2O/pyridine, 60°C, 0.5 h).

A parallel route starting with the known (–)-tricyclic ester XV,[18] the key intermediate utilized in our recent synthesis of (–)-10-demethylcephaeline (VI),[10] provided the second target (–)-10-demethylprotoemetinol (XII) [glass, $[\alpha]_D^{17}$–35.2° (c 0.50, EtOH)] and the corresponding (–)-diacetate XVIII [oil, $[\alpha]_D^{25}$–29.7° (c 0.38, $CHCl_3$)] in excellent overall yields *via* the (–)-tricyclic alcohol XIII [mp 85–86°C; $[\alpha]_D^{16}$–50.6° (c 0.50, EtOH)].

Finally, the same sequence of reactions with the known isomeric (–)-tricyclic ester XIV,[9] the key intermediate for our recent syntheses of (+)-9-demethylpsychotrine (II)[9] and (–)-9-demethylcephaeline (V),[10] produced the third target (–)-9-demethylprotoemetinol (X) [mp 157–158.5°C; $[\alpha]_D^{25}$–61.0° (c 0.50, EtOH)] and its (–)-diacetate XVII [oil, $[\alpha]_D^{25}$–34.3° (c 0.40, $CHCl_3$)] in high overall yields through the (–)-tricyclic alcohol XI [mp 103–104°C; $[\alpha]_D^{25}$–35.0° (c 0.50, EtOH)].

Recently, Pakrashi's group[19] has isolated two new alkaloids from the seeds of *A. lamarckii* and inferred them to be 9-demethylprotoemetinol (X) and 10-demethylprotoemetinol (XII). The structure and relative stereochemistry of the latter alkaloid were confirmed by comparison of the ir and nmr spectra of its diacetate [$[\alpha]_D$–15.8° ($CHCl_3$)] with those of synthetic (±)-10-demethylprotoemetinol diacetate (XVIII) described above. The absolute stereochemistry was, however, deduced from the identity of sign of the specific rotations of the diacetate of the natural base and synthetic (–)-XVIII. On the other hand, a direct comparison of the other alkaloid, inferred to be 9-demethylprotoemetinol, with synthetic (–)-X was not possible owing to paucity of the natural base.[19]

ACKNOWLEDGMENT This research has been made possible by financial support from the Foundation for the Promotion of Research on Medicinal Resources. One (E. A.) of the authors is grateful to the Japan Society for the Promotion of Science for the award of a grant under the Scientists Exchange Programme of INSA–JSPS, which enabled him to work in Kanazawa during October, 1978 to March, 1979.

REFERENCES

1. H. Budzikiewicz, S. C. Pakrashi, and H. Vorbrüggen, Tetrahedron, 1964, 20, 399.
2. S. C. Pakrashi and P. P. Ghosh-Dastidar, Indian J. Chem., 1964, 2, 379.
3. S. C. Pakrashi and B. Achari, Experientia, 1970, 26, 933.
4. J. D. Albright, J. C. Van Meter, and L. Goldman, Lloydia, 1965, 28, 212.
5. S. C. Pakrashi, Indian J. Chem., 1964, 2, 468.
6. S. C. Pakrashi, Curr. Sci. (India), 1966, 35, 468.
7. A. Popelak, E. Haack, and H. Spingler, Tetrahedron Lett., 1966, 1081.
8. S. C. Pakrashi and E. Ali, Tetrahedron Lett., 1967, 2143.
9. T. Fujii, M. Ohba, S. C. Pakrashi, and E. Ali, Tetrahedron Lett., 1979, 4955.
10. T. Fujii and M. Ohba, Heterocycles, 1982, 19, 857.
11. T. Fujii, M. Ohba, A. Popelak, S. C. Pakrashi, and E. Ali, Heterocycles, 1980, 14, 971.
12. A. R. Battersby, R. S. Kapil, D. S. Bhakuni, S. P. Popli, J. R. Merchant, and S. S. Salgar, Tetrahedron Lett., 1966, 4965.
13. Unless otherwise noted, the structural formulas of optically active compounds in this paper represent their absolute configuration.
14. T. Fujii, M. Ohba, S. C. Pakrashi, and E. Ali, Heterocycles, 1979, 12, 1463.
15. (a) T. Fujii, S. Yoshifuji, and K. Yamada, Tetrahedron Lett., 1975, 1527; (b) Idem, Tetrahedron, 1980, 36, 965; (c) S. Yoshifuji and T. Fujii, Tetrahedron Lett., 1975, 1965; (d) T. Fujii and S. Yoshifuji, J. Org. Chem., 1980, 45, 1889.
16. B. Dasgupta, J. Pharm. Sci., 1965, 54, 481.
17. Satisfactory microanalytical and/or spectroscopic data have been obtained for all new compounds described herein.
18. T. Fujii, M. Ohba, and H. Suzuki, Heterocycles, 1982, 19, 705.
19. E. Ali, R. R. Sinha, B. Achari, and S. C. Pakrashi, Heterocycles, preceding paper.

Received, 3rd September, 1982