BIOMIMETIC FORMATION AND INTER-CONVERSION IN THE HETEROYOHIMBINE SERIES

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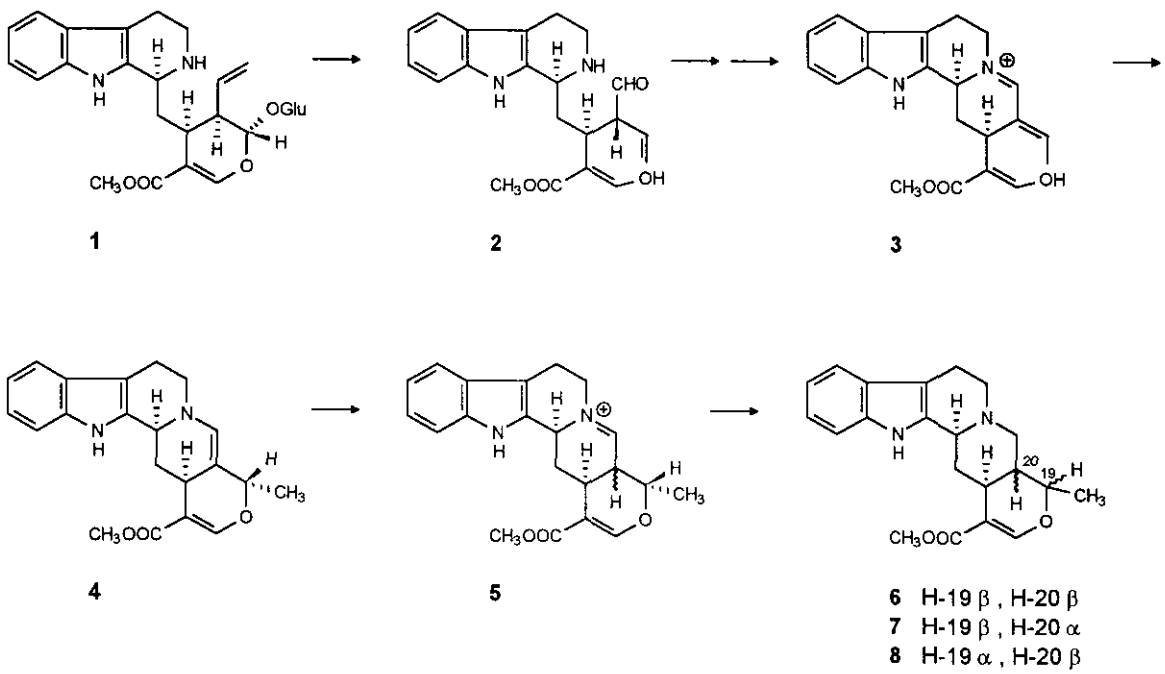
Abstract - A general scheme, based on three currently accepted transformation reactions, is proposed for the biomimetic formation and interconversion of the four possible $\Delta^{20(21)}$-didehydroheteroyohimbines (cathenamines) (**4**, **9-11**). The reactions permit, after reduction, access to all eight basic heteroyohimbine alkaloids (**6-8**, **12-16**).

INTRODUCTION

For more than twenty years now the biogenetic formation of the heteroyohimbine alkaloids has been the subject of intense study.[1-5] The biogenetic formation of heteroyohimbine alkaloids is considered to proceed from strictosidine (**1**) *via* intermediates (**2**) and (**3**) to $\Delta^{20(21)}$-didehydroheteroyohimbine (**4**), which is then protonated [the iminium form (**5**)] and reduced. In biomimetic experiments, ajmalicine (**6**), tetrahydroalstonine (**7**), and 19-epiajmalicine (**8**) were found among the reaction products (Scheme 1).[6-8]

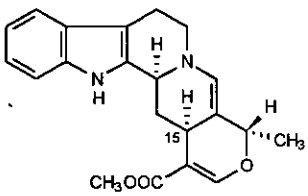


Scheme 1. Biogenetic formation of heteroyohimbine alkaloids.

Although the formation of ajmalicine (**6**) and tetrahydroalstonine (**7**) is straightforward, that of 19-epiajmalicine (**8**) necessitates further transformations due to the different stereostructure at C-19. Scott and coll.,[9] among others, have questioned the direct formation of 19-epiajmalicine (**8**) from $\Delta^{20(21)}$-didehydroheteroyohimbine (**4**).

DISCUSSION

The $\Delta^{20(21)}$-didehydroheteroyohimbine (cathenamine) structure, possessing two asymmetric centers (except C-15, which for biogenetic reasons must always be α),[10-12] can give rise to four (2^2=4)[13] stereoisomers [cathenamine (**4**), 3-isocathenamine (**9**), 19-epicathenamine (**10**), and 3-iso-19-epicathenamine (**11**)]. Two of these, **4** and **10**, have been isolated from nature,[14, 15] while all four (**4**, **9**-**11**) have been prepared by synthesis.[16-20]



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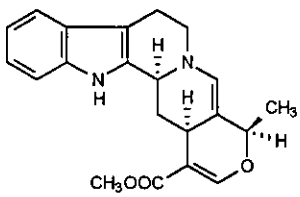

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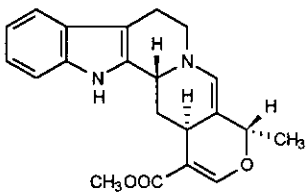

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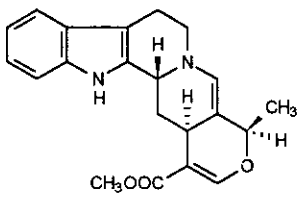

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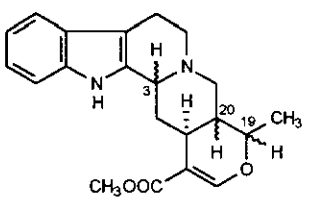
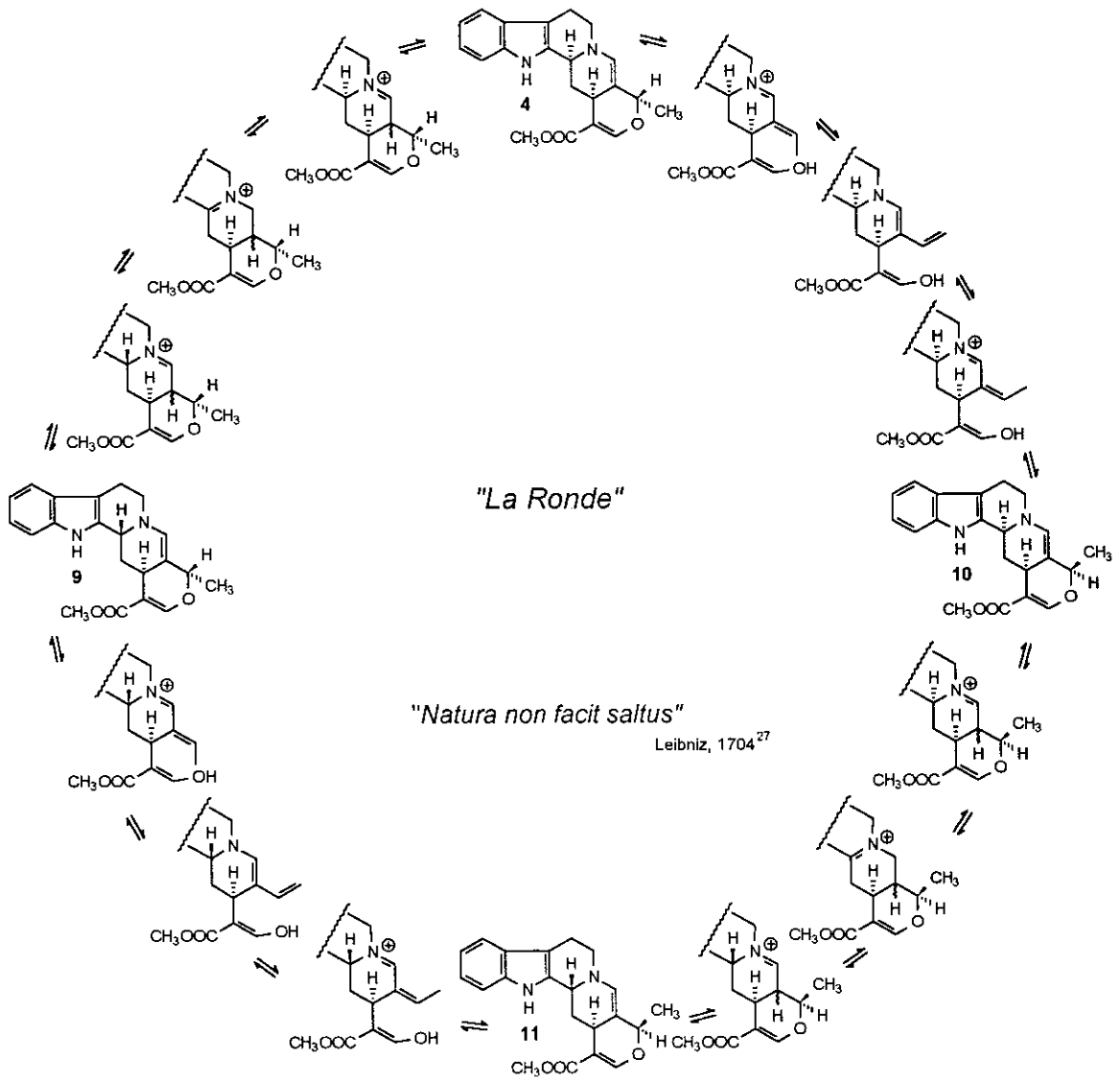
The heteroyohimbine structure, which possesses one asymmetric center more than cathenamines (*vide supra*), gives rise not to four but to eight ($2^3=8$)[13] stereoisomers. All eight (**6-8**, **12-16**) have been found in nature.[21,22]



ajmalicine **6**	H-3 α, H-19 β, H-20 β
tetrahydroalstonine **7**	H-3 α, H-19 β, H-20 α
19-epiajmalicine **8**	H-3 α, H-19 α, H-20 β
rauniticine **12**	H-3 α, H-19 α, H-20 α
3-isoajmalicine **13**	H-3 β, H-19 β, H-20 β
akuammigine **14**	H-3 β, H-19 β, H-20 α
3-iso-19-epiajmalicine **15**	H-3 β, H-19 α, H-20 β
3-isorauniticine **16**	H-3 β, H-19 α, H-20 α

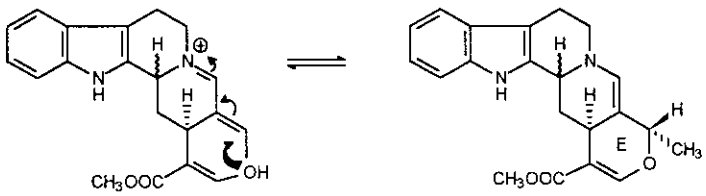
Despite the substantial amount of work done (*vide supra* and Refs. 23-26), the interconversions among the cathenamines (or their precursors) and their further transformation to the eight basic heteroyohimbine alkaloids have not been subjected to comprehensive examination. Considering the different results we think the time is now ripe for such an examination and propose, keeping in mind Leibniz's aphorism *"Natura non facit saltus"*,[27] a general Scheme, called *"La Ronde"* (Scheme 2).



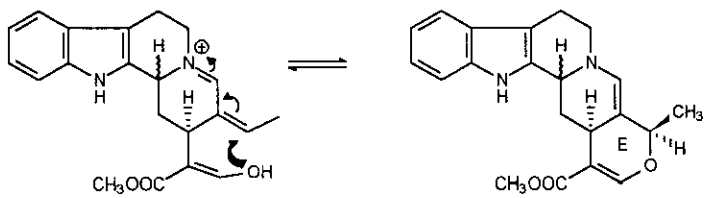
Scheme 2. *"La Ronde"*. Interconversion between the four $\Delta^{20(21)}$-didehydroheteroyohimbines (cathenamines)(**4**, **9-11**).

Scheme 2 is based on just three generally accepted, biomimetically mundane transformations: cyclization/opening equilibrium of ring E (Schemes 3a and 3b),[28-30] *E,Z*-epimerization of the ethylidene side-chain (Scheme 4),[31-35] and isomerization at C-3 *via* the $\Delta^{3(4)}$ iminium intermediate (Scheme 5).[36-38] Together these transformations permit the interconversion between the four possible cathenamines.

Mechanistically, the formation of cathenamine structures *via* $\Delta^{4(21)}$-iminium ions can be described as a Michael addition. The stereochemical conditions are such that the Michael addition can take place only from the β-face. In the cases of *E*- and *Z*-ethylidene side-chains, this means the H-19β and H-19α stereochemistries, respectively (Schemes 3a and 3b).[6, 28-30] The reversibility of the process is evident (retro-Michael ring opening).

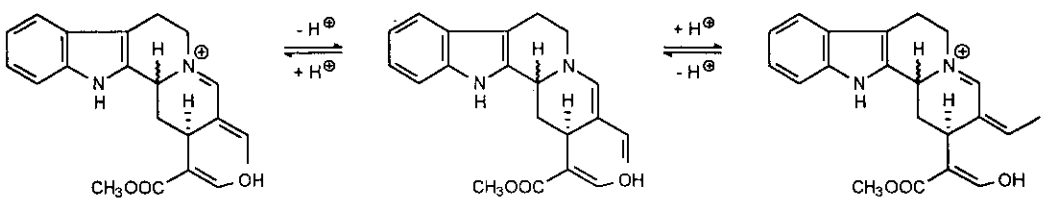


Scheme 3a. Cyclization/opening equilibrium of ring E (*E*-ethylidene side-chain).



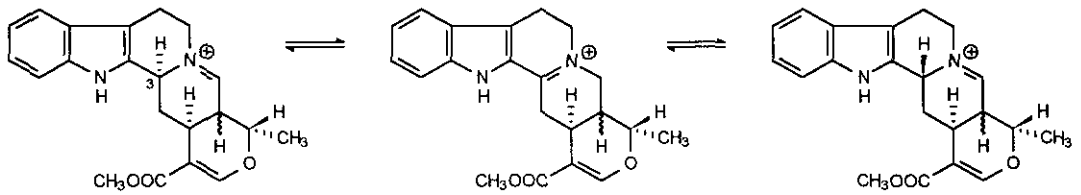
Scheme 3b. Cyclization/opening equilibrium of ring E (*Z*-ethylidene side-chain).

The *E,Z*-epimerization of the ethylidene side-chain of the $\Delta^{4(21)}$-didehydrogeissoschizine salts, *via* the corresponding enamine, is a well known transformation (Scheme 4).[31-35]



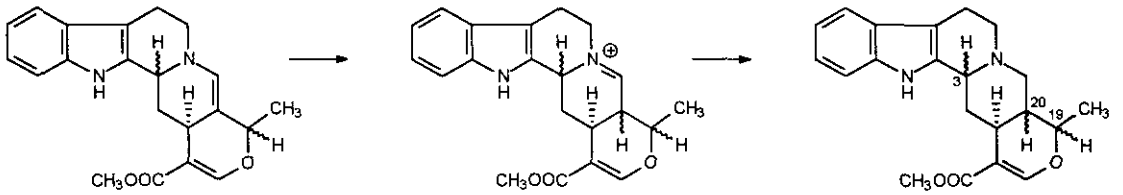
Scheme 4. *E,Z*-epimerization of the ethylidene side-chain.

Equilibration between $\Delta^{4(21)}$- and $\Delta^{3(4)}$-iminium intermediates, permitting the isomerization at C-3, has been shown to take place for compounds of the present type (Scheme 5).[36-39]



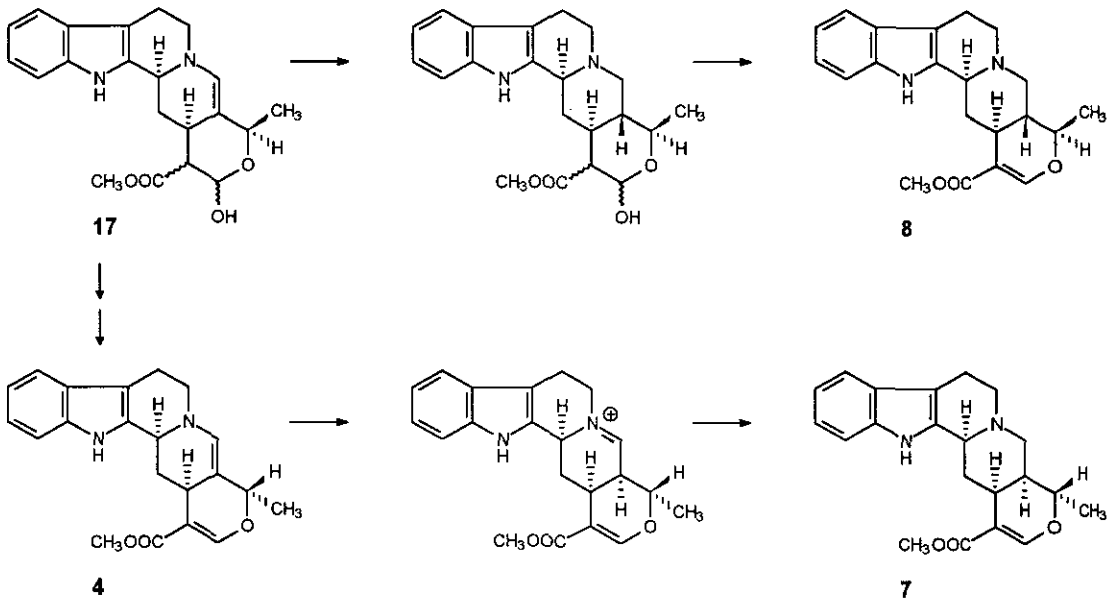
Scheme 5. Isomerization at C-3 *via* the $\Delta^{3(4)}$-iminium intermediate.

Since each cathenamine, apparently *via* the corresponding $\Delta^{4(21)}$-iminium form (protonation),[40] can give rise by reduction to two basic heteroyohimbine alkaloids (Scheme 6), all eight stereoisomers are connected to each other through the presented scheme *"La Ronde"* (Scheme 2).



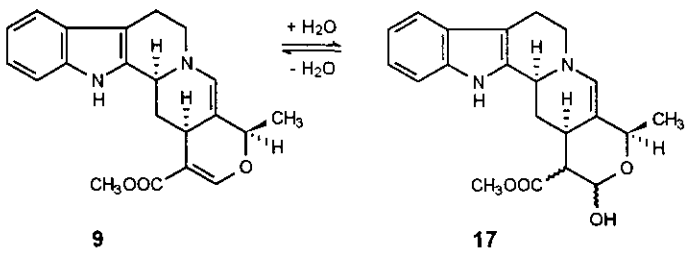
Scheme 6. Reduction of the cathenamines, *via* the corresponding $\Delta^{4(21)}$-iminium forms, to the corresponding heteroyohimbine alkaloids.

A few papers[16, 41, 42] have described the 19-epicathenamine water adduct (**17**) as a biomimetic intermediate which can be stereoselectively converted into both 19*R* and 19*S* series (Scheme 7).



Scheme 7. 19-Epicathenamine water adduct (**17**) as a common biomimetic intermediate in the formation of 19-epiajmalicine (**8**)(19*R* series) and tetrahydroalstonine (7)(19*S* series).

More convincing proofs of the intermediacy of the water adduct (**17**) are to be desired. On the other hand, even if the water adduct (**17**) were involved in the formation of heteroyohimbine alkaloids, this would sit well with the general scheme presented because of the equilibrium between 19-epicathenamine (**9**) and its water adduct (**17**) (Scheme 8).



Scheme 8. Equilibrium between 19-epicathenamine (**9**) and its water adduct (**17**).

CONCLUSIONS

A general biomimetic scheme *"La Ronde"* (Scheme 2), based on three commonly accepted biomimetic reactions, is proposed for the interconversion between the four $\Delta^{20(21)}$-didehydroheteroyohimbines (cathenamines) (**4**, **9-11**). Combined with reduction, these reactions permit access to all eight basic heteroyohimbine alkaloids (**6-8**, **12-16**).

REFERENCES AND NOTES

1. J. Stöckigt and M. H. Zenk, *J. Chem. Soc., Chem. Commun.*, 1977, 646.
2. J. Stöckigt, J. Treimer, and M. H. Zenk, *FEBS Lett.*, 1976, **70**, 267. See also, J. Stöckigt, *Phytochemistry*, 1979, **18**, 965.
3. J. Stöckigt, H.-P. Husson, C. Kan-Fan, and M. H. Zenk, *J. Chem. Soc., Chem. Commun.*, 1977, 164.
4. A. I. Scott, S. L. Lee, P. de Capite, M. G. Culver, and C. R. Hutchinson, *Heterocycles*, 1977, **7**, 979.
5. R. B. Herbert, *The Biosynthesis of Secondary Metabolites*, 2nd Ed., Chapman and Hall, London, 1989, pp. 168-169.
6. R. T. Brown, J. Leonard, and S. K. Sleigh, *J. Chem. Soc., Chem. Commun.*, 1977, 636. See also, R. T. Brown, C. L. Chapple, D. M. Duckworth, and R. Platt, *J. Chem. Soc. Perkin I*, 1976, 160.
7. M. Rueffer, C. Kan-Fan, H.-P. Husson, J. Stöckigt, and M. H. Zenk, *J. Chem. Soc., Chem. Commun.*, 1979, 1016.
8. J. Stöckigt, M. Rueffer, M. H. Zenk, and G.-A. Hoyer, *Planta Medica*, 1978, **33**, 188.
9. S. L. Lee, T. Hirata, and A. I. Scott, *Tetrahedron Lett.*, 1979, 691.
10. Atta-ur-Rahman and A. Basha, *Biosynthesis of Indole Alkaloids*, Clarendon Press, Oxford, 1983, p. 52.
11. M. Luckner, *Secondary Metabolism in Microorganisms, Plants, and Animals*, 3rd Ed., Springer, Berlin, 1990, pp. 356-357.

12. J. Bruneton, *Pharmacognosie, Phytochimie, Plantes Médicinales*, 2nd Ed., Technique et Documentation-Lavoisier, Paris, 1993, pp. 821-822.

13. E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, p. 64.

14. H.-P. Husson, C. Kan-Fan, T. Sévenet, and J.-P. Vidal, *Tetrahedron Lett.*, 1977, 1889.

15. J. Stöckigt, G. Höfle, and A. Pfitzner, *Tetrahedron Lett.*, 1980, **21**, 1925.

16. R. T. Brown and J. Leonard, *J. Chem. Soc., Chem. Commun.*, 1979, 877.

17. S. Sakai and N. Shinma, *Chem. Pharm. Bull.*, 1978, **26**, 2596.

18. S. F. Martin, B. Benage, and J. E. Hunter, *J. Am. Chem. Soc.*, 1988, **110**, 5925.

19. M. Lounasmaa, R. Jokela, P. Hanhinen, and U. Anttila, *Heterocycles*, 1997, **45**, 779.

20. M. Lounasmaa and P. Hanhinen, *Heterocycles*, 1997, **45**, 1529.

21. R. T. Brown, in *"The Monoterpenoid Indole Alkaloids"*, ed. by J. E. Saxton, Wiley, New York, 1983, pp. 63-146. See also, M. Lounasmaa, and A. Tolvanen, in *"Monoterpenoid Indole Alkaloids"*, ed. by J. E. Saxton, Supplement, Wiley, Chichester, 1994, pp. 57-159.

22. M. Lounasmaa and S.-K. Kan, *Tetrahedron*, 1980, **36**, 1607.

23. J. Stöckigt, in *"Indole and Biogenetically Related Alkaloids"*, ed. by J. D. Phillipson and M. H. Zenk, Academic Press, London, 1980, pp. 113-141.

24. H.-P. Husson, in *"Indole and Biogenetically Related Alkaloids"*, ed. by J. D. Phillipson and M. H. Zenk, Academic Press, London, 1980, pp. 185-200.

25. G. Richter, *Métabolisme des Végétaux*, Presses Polytechniques et Universitaires Romandes, Lausanne, 1993, p. 452.

26. P. M. Dewick, *Medicinal Natural Products*, Wiley, Chichester, 1997, p. 326.

27. G. W. Leibniz, *Nouveaux Essais sur l'Entendement Humain*, Vol. 4, Paris, 1704, p. 16.

28. C. Kan-Fan and H.-P. Husson, *Tetrahedron Lett.*, 1980, **21**, 4265.

29. M. Lounasmaa, M. Halonen, and R. Jokela, *Heterocycles*, 1995, **41**, 807.

30. M. Lounasmaa, R. Jokela, P. Hanhinen, J. Miettinen, and J. Salo, *Tetrahedron*, 1994, **50**, 9207.

31. M. R. Uskokovic, R. L. Lewis, J. J. Partridge, C. W. Despreaux, and D. L. Pruess, *J. Am. Chem. Soc.*, 1979, **101**, 6742.

32. M. Lounasmaa, R. Jokela, J. Miettinen, and M. Halonen, *Heterocycles*, 1992, **34**, 1497.

33. R. Jokela, M. Halonen, and M. Lounasmaa, *Heterocycles*, 1994, **38**, 189.

34. R. Jokela, M. Halonen, and M. Lounasmaa, *Heterocycles*, 1993, **36**, 1115.

35. M. Halonen, R. Jokela, and M. Lounasmaa, *Heterocycles*, 1995, **41**, 353.

36. M. Nakagawa, Y. Ogawa, Y. Miyake, K. Yamaguchi, T. Hina, C. C. Chiang, J. L. Flippen, and B. Witkop, *Heterocycles*, 1982, **19**, 663.

37. P. Heinstein, J. Stöckigt, and M. H. Zenk, *Tetrahedron Lett.*, 1980, **21**, 141.

38. C. Kan, S.-K. Kan, M. Lounasmaa, and H.-P. Husson, *Acta Chem. Scand.*, 1981, **B35**, 269.

39. T. Tamminen, R. Jokela, B. Tirkkonen, and M. Lounasmaa, *Tetrahedron*, 1989, **45**, 2683.

40. The existence of the enamine/iminium ion equilibrium for cathenamine (**4**) in solution has been firmly established.[37]

41. C. Kan-Fan and H.-P. Husson, *J. Chem. Soc., Chem. Commun.*, 1978, 618.

42. C. Kan-Fan and H.-P. Husson, *J. Chem. Soc., Chem. Commun.*, 1979, 1015.

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