Pure & Appl. Chem., Vol. 61, No. 3, pp. 289–292, 1989.
Printed in Great Britain.

A proposal for biosynthesis of the *Daphniphyllum* alkaloids

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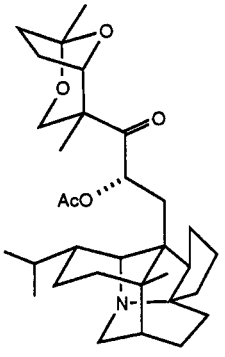
Abstract - A hypothesis has been formulated (Scheme 1) for biosynthesis of the pentacyclic, nitrogen-containing moiety of the *Daphniphyllum* alkaloid secodaphniphylline. The proposal starts with the squalene-derived dialdehyde **7** and employs pyridoxamine to introduce nitrogen and allow formation of the key cyclopentane ring by a variant of the enamine Michael reaction. Key steps in the proposal are the intramolecular Diels-Alder reaction of the hypothetical azadiene **12**, leading to imine **13**, and Mannich-type closure of the latter substance, giving the secodaphniphylline skeleton. Scheme 2 summarizes a proposed pyridoxal-mediated transformation of homosecodaphniphyllic acid (**15**) to unsaturated amino acid **19**, a skeletal type related to daphnilactone B and yuzurimine. Scheme 2 also suggests reactions whereby the key intermediate **19** might be transformed into daphnilactone A and homodaphniphyllic acid. As shown in Scheme 3, intermediate **13** might give rise to daphnigracine-type alkaloids. Finally, we present synthetic evidence (Scheme 5) in support of the proposed intramolecular Diels-Alder reaction.

The *Daphniphyllum* alkaloids are a group of structurally complex, polycyclic alkaloids derived from squalene (ref. 1). The group includes diverse structural types, including daphniphylline (**1**), secodaphniphylline (**2**), daphnilactone A (**3**), daphnilactone B (**4**), yuzurimine (**5**), and daphnigracine (**6**).



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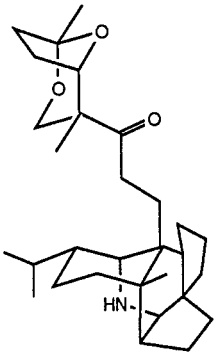

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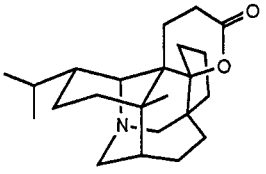

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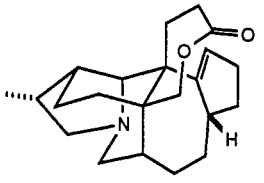

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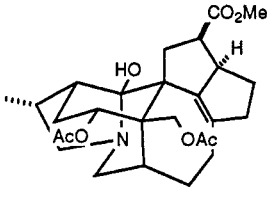

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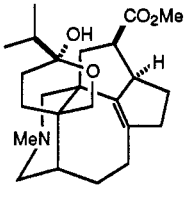

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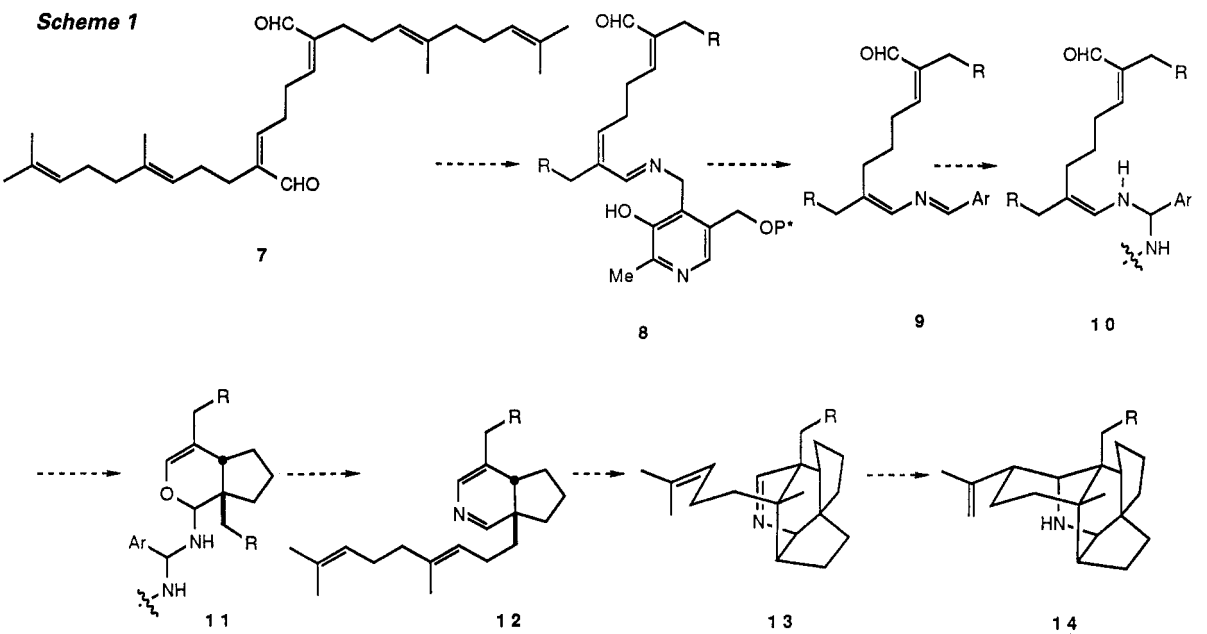
Although biosynthetic investigations on the *Daphniphyllum* alkaloids have been limited, it has been established that daphniphylline, codaphniphylline, and daphnilactone B originate from six mevalonate units *via* a squalene-like intermediate (ref. 2). Yamamura, Irikawa, and coworkers have studied formation of the bicyclic spiroketal moieties of daphniphylline, codaphniphylline, and daphnimacrine (ref. 2a) and have recently reported a biomimetic route to several 2,8-dioxabicyclo[3.2.1]octanes from geraniol (ref. 3). However, with regard to the more complex nitrogen-containing portions of the *Daphniphyllum* alkaloids, there has been essentially no actual biosynthetic experimental work, and the general schemes that have been advanced (ref 1,2) are not mechanistically satisfying.

In connection with our interest in total synthesis of *Daphniphyllum* alkaloids [ref. 4], we have formulated a proposal for the biogenesis of the nitrogenous moiety of these alkaloids. In this paper, we advance that proposal, along with an experimental demonstration of one of the key steps.

Our basic proposal is summarized in Scheme 1. We envision the squalene-derived dialdehyde **7** condensing with pyridoxamine, a well-known nitrogen-carrier in alkaloid biosynthesis (ref. 5), to provide azadiene **8**. Prototropic shift of this intermediate would give **9**, the unsaturated imine isomer (ref. 6). Addition of a nucleophile, such as a lysine amino group, to the imine double bond would lead to enamine **10**, which might then undergo an intramolecular enamine/enal cycloaddition reaction (ref. 7), leading to the loganin-type intermediate **11**. Loss of the pyridoxyl group and reorganization of the aminodihydropyran ring would provide the dihydropyridine **12**. Intramolecular Diels-Alder reaction of **12** would give tetrahydropyridine **13**, which could be further cyclized in a Mannich-type closure to deliver **14**, having the pentacyclic secodaphniphylline skeleton.

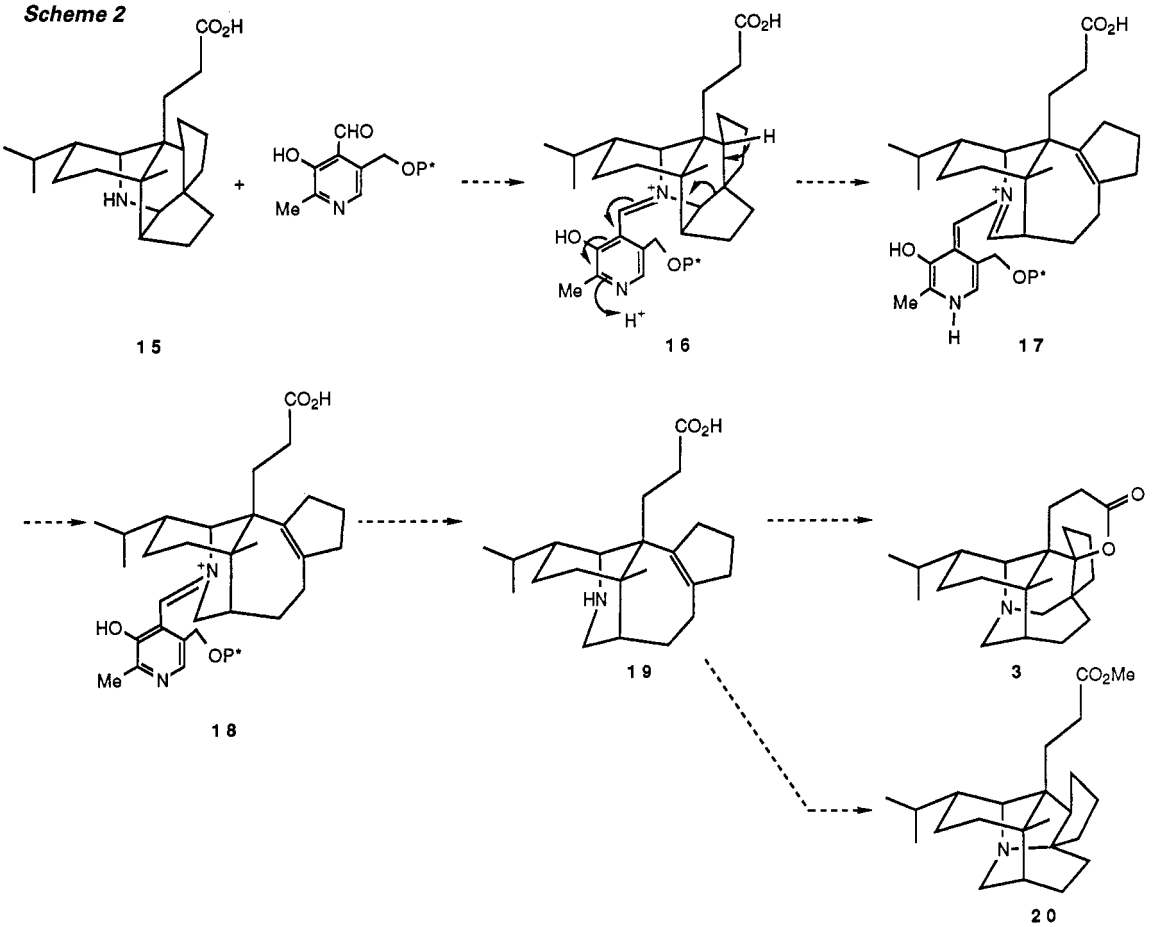
Scheme 1



Scheme 2 suggests a possible conversion of homosecodaphniphyllic acid (**15**) into **19**, a substance having the cyclononane ring common to daphnilactone B and yuzurimine. For this transformation, we invoke pyridoxal as a cofactor. It is proposed that immonium ion **16** is protonated on the pyridine nitrogen, thus initiating fragmentation of the indicated skeletal bond. The suggested fragmentation is mechanistically related to the pyridoxal-mediated decarboxylation of α-amino acids (ref. 5, page 41). Prototropy of **17** would lead to the exocyclic immonium structure **18**, which would hydrolyze to generate pyridoxal and unsaturated amino acid **19**. Hypothetical intermediate **19** has previously been proposed as a biosynthetic intermediate by Yamamura and Terada (ref. 6). Reaction of **19** with a formaldehyde equivalent could lead to daphnilactone A as proposed by Yamamura and Hirata (ref. 1a, page 56). Methyl homodaphniphyllate (**20**) probably arises from **19** by addition of the secondary amine to the cyclopentene double bond (ref. 7).

The existence of daphnigracine (**6**) and its congeners, in which the terminal isoprene unit has not been incorporated into a carbocycle, is in particular agreement with our overall biosynthetic proposal. As shown in Scheme 3, the key intermediate (**13**) resulting from the intramolecular Diels-Alder reaction is a reasonable precursor to the members of this *Daphniphyllum* subgroup.

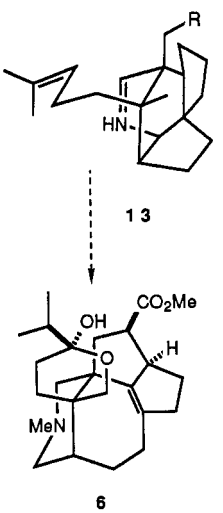
Scheme 2



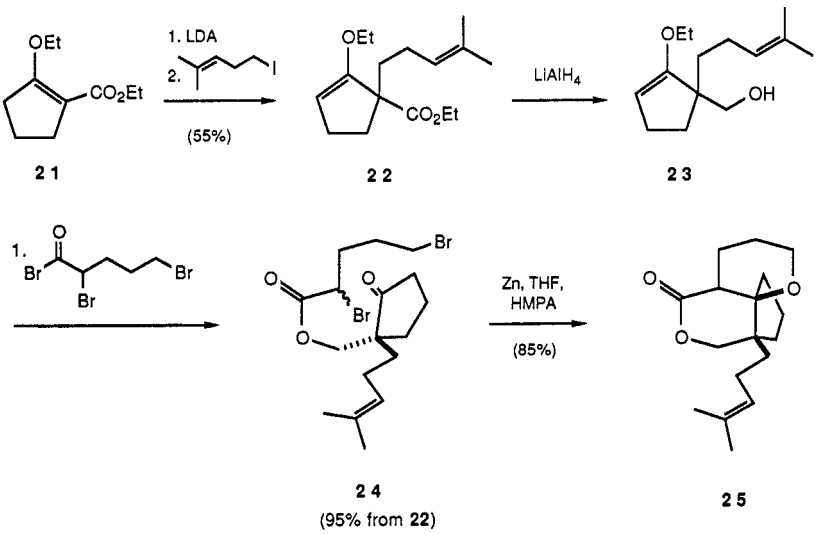
We are currently using the foregoing biosynthetic hypotheses to guide us in our attempts to find efficient synthetic routes to various *Daphniphyllum* alkaloids. Our first efforts in this regard have been concerned with a projected total synthesis of daphnilactone A.

We previously reported (ref. 4b) use of an intramolecular Reformatsky reaction to gain access to tricyclic lactams and lactones. An example of this strategy is shown in Scheme 4. Enol ether **21** is deprotonated and the resulting dienolate alkylated with homoprenyl iodide to obtain **22**, which is reduced to alcohol **23** by lithium aluminum hydride. Keto ester **24** is acquired by acylation of **23** with 2,5-dibromopentanoyl bromide and hydrolysis of the enol ether. Treatment of **24** with activated zinc in tetrahydrofuran, followed by addition of hexamethylphosphoric triamide, gives lactone ether **25**.

Scheme 3

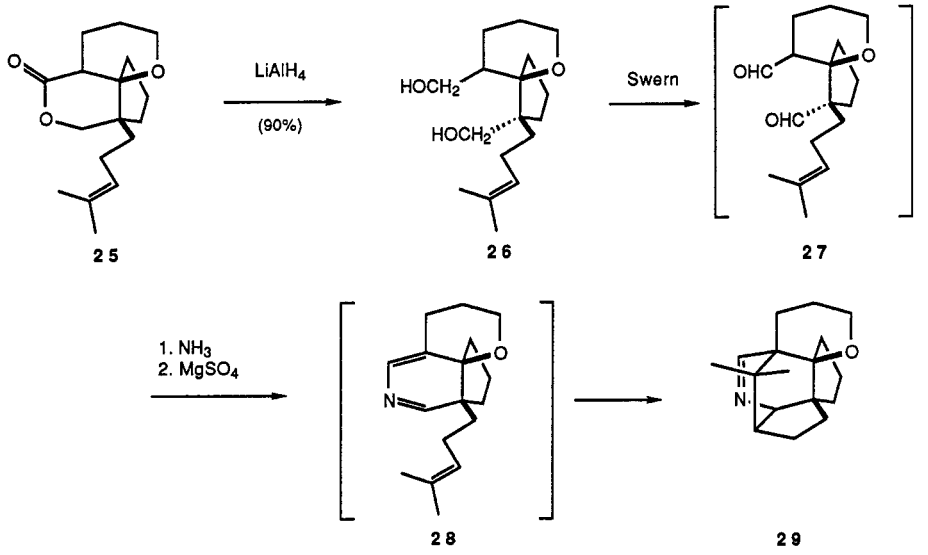


Scheme 4



Reduction of lactone **25** with lithium aluminum hydride provides a diol (**26**), which is oxidized by the Swern method to obtain the fragile dialdehyde **27**. Treatment of this material with anhydrous ammonia, followed by evaporation of volatile materials, provides azadiene **28**. Under mild protic conditions, compound **28** is smoothly converted into the Diels-Alder adduct **29**; the maximum yield that has been realized to date is 35%, based on diol **26**.

Scheme 5



The facility with which the foregoing Diels-Alder cyclization occurs provides experimental support for the viability of the biogenetic proposal in Scheme 1. We have recently applied the route shown in Scheme 4 with homogeranyl iodide, to obtain an analog of lactone **25** having a homogeranyl group in place of the homoprenyl group. With this material, we will be able to test further steps in the proposed biosynthesis of the secodaphniphylline skeleton (Scheme 1).

Acknowledgements

This work was supported by a research grant from the National Science Foundation, CHE-8418427, and by an American Chemical Society Organic Division Graduate Fellowship to R.B.R. from Smith Kline & French Laboratories. We thank Professor Michael Pirrung for a helpful discussion.

REFERENCES

1. (a) S. Yamamura and Y. Hirata, *in* "The Alkaloids," (R. H. F. Manske, ed.), Vol 15, p. 41, Academic Press, New York, 1975. (b) S. Yamamura and Y. Hirata, Int. Rev. Sci., Org. Chem., Ser. 2, 9, 161 (1976). (c) S. Yamamura, *in* "The Alkaloids," (A. Brossi, ed.), Vol. 29, p. 265, Academic Press, New York, 1986.

2. (a) K. T. Suzuki, S. Okuda, H. Niwa, M. Toda, Y. Hirata, and S. Yamamura, Tetrahedron Lett., 799 (1973). (b) H. Niwa, Y. Hirata, K. T. Suzuki, and S. Yamamura, ibid., 2129 (1973).

3. (a) H. Irikawa, T. Ishikura, and Y. Okumura, Bull. Chem. Soc. Jpn., 50, 2811 (1977). (b) S. Nishiyama, Y. Ikeda, and S. Yamamura, ibid., 59, 875 (1986).

4. (a) C. H. Heathcock, S. K. Davidsen, S. Mills, and M. A. Sanner, J. Am. Chem. Soc., 108, 5650 (1986). (b) R. B. Ruggeri and C. H. Heathcock, J. Org. Chem., 52, 5745 (1987).

5. (a) D. R. Dalton, "The Alkaloids, A Biogenetic Approach," Marcel Dekker, Inc., New York, 1979. (b) M. Akhtar, V. C. Emery, and J. A. Robinson, *in* "The Chemistry of Enzyme Action," (M. I. Page, ed.), p. 303, Elsevier, Amsterdam, 1984.

6. P. A. Wender and M. A. Eissenstat, J. Am. Chem. Soc., 100, 292 (1978).

7. (a) S. L. Schreiber, H. V. Meyers, and K. B. Wiberg, J. Am. Chem. Soc., 108, 8274 (1986). (b) S. E. Denmark and J. A. Sternberg, ibid., 108, 8277 (1986).

8. S. Yamamura and Y. Terada, Chem. Lett., 1381 (1976).

9. H. Niwa, M. Toda, S. Ishimaru, Y. Hirata, and S. Yamamura, Tetrahedron, 30, 3031 (1974).