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# The biosynthesis of moenocinol, the lipid part of the moenomycin antibiotics

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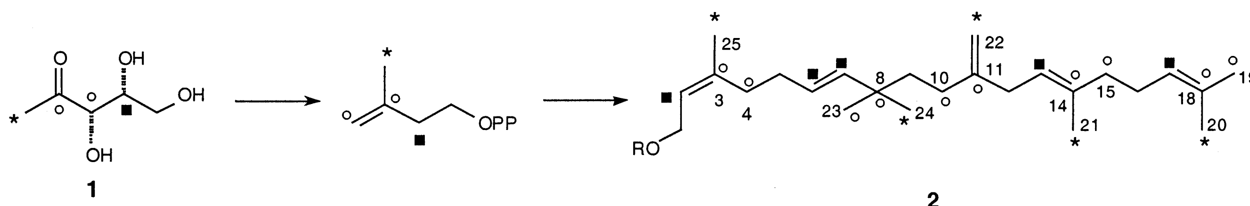
**Abstract**—The $C_{25}$ terpenoid moenocinol is suggested to originate from a farnesyl precursor and geranyl pyrophosphate. The new mechanism is in accord with all previous feeding experiments. Feeding of [2,5-$^{13}C_2$]-labeled 1-deoxy-D-xylulose proves how the two units are joined in the course of the moenocinol biosynthesis. © 2001 Published by Elsevier Science Ltd.

The moenomycin-type antibiotics[1] contain a $C_{25}$ lipid unit (the moenocinol part, see formula **2**, R = remainder of the moenomycin molecule) that has an interesting structure. Three isoprenoid $C_5$ units are easily discernible whereas the central $C_{10}$ part (C-5 through C-11) does not obey the isoprene rule in an obvious way. We have recently shown that the complete moenocinol unit is of isoprenoid origin and that it is formed via the non-mevalonate pathway.[2] This result paved the way to a series of successful feeding experiments starting from differently labeled 1-deoxy-D-xylulose (**1**) preparations. Known routes centered on an asymmetric Sharpless dihydroxylation have been adapted to introduce $^{13}$C labels into various positions.[3,4] The results of three of such feeding experiments (with [1-$^{13}$C]-, [2,3-$^{13}C_2$]-, and [4-$^{13}$C]-labeled 1-deoxy-D-xylulose) are summarized in Scheme 1.[5,6] On the basis of these results a hypothesis for the formation of the central C-5–C-11 unit has been formulated. Although the isoprenoid origin could nicely be explained by a number of rearrangements the hypothesis had a real drawback: It could not explain in which way the other isoprenoid units are attached to C-5 and to C-11 of the central $C_{10}$ part in the course of the biosynthesis.

A careful inspection of the moenocinol structure reveals the presence of eight terminal groups (C-1, C-22 and six methyl groups). This is inconsistent with its derivation from a regularly built isoprenoid $C_{25}$ precursor, which would contain only seven terminal groups. In addition, both C-8 and C-18 of moenocinol are linked to two intact methyl groups of known biosynthetic origin (cf. above), a fact best explained by the involvement of two dimethylallyl starter units in the biosynthetic process. Thus, the available evidence makes it most probable that moenocinol is assembled by the union of a $C_{10}$ with a $C_{15}$ isoprenoid precursor. On this assumption the detailed biosynthetic mechanism illustrated in Scheme 2 can be put forward. This mechanism is in excellent agreement with all the experimental data collected so far.




**Scheme 1.**

*Keywords*: terpenes; biosynthesis; antibiotics; rearrangement.

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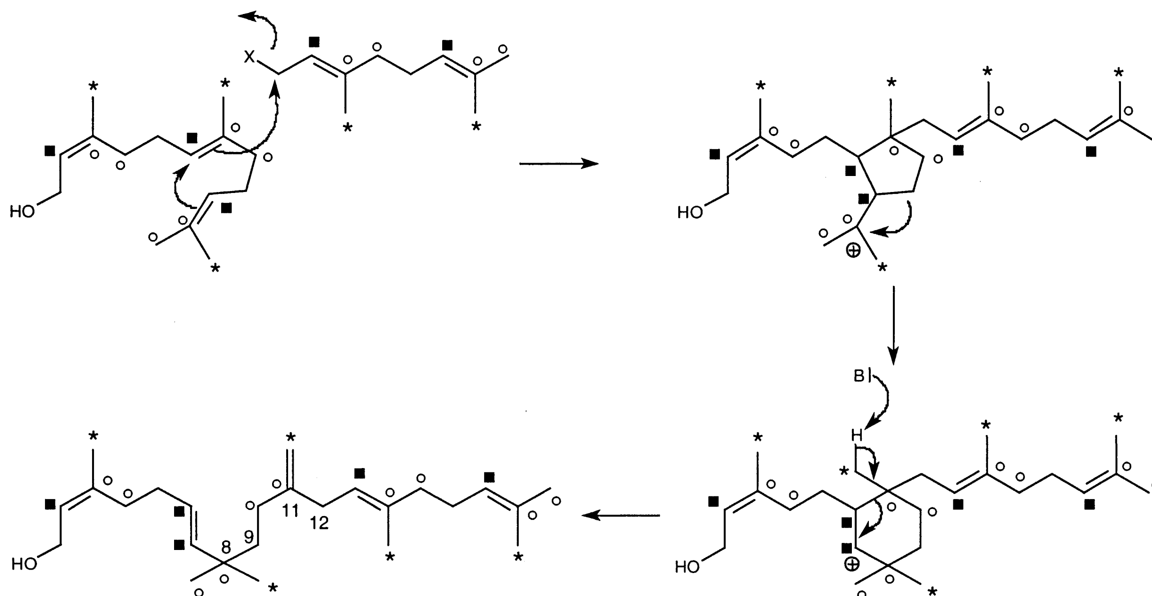
According to the mechanism illustrated in Scheme 2, two new C–C bonds must be generated on the way from the precursors to the moenocinol moiety, namely the C-11–C-12 bond in the alkylation step and the C-8–C-9 bond in the subsequent rearrangement step. To gain corroborative evidence for this proposal we have carried out an additional feeding experiment with [2,5-$^{13}C_2$]-labeled 1-deoxy-D-xylulose (**3**). Compound **3** was prepared as indicated in Scheme 3.[7]

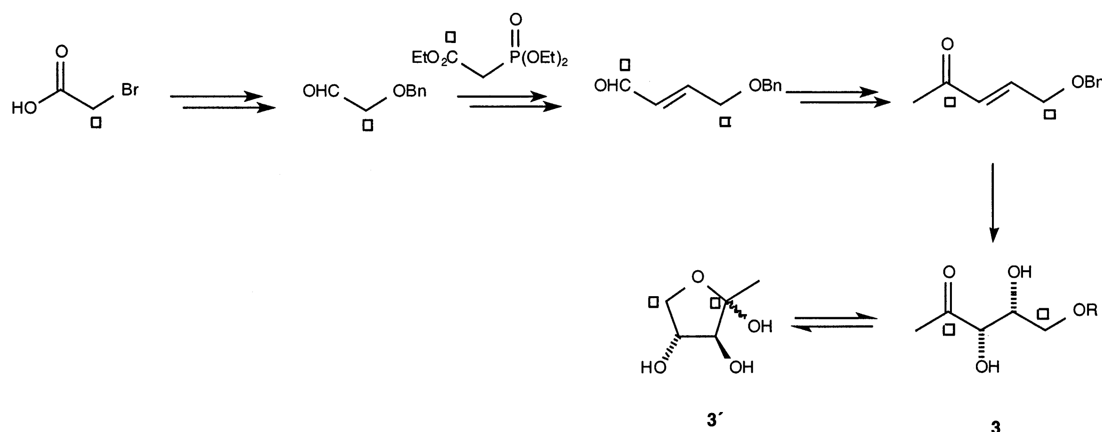
The feeding experiment (160 mg of **3**, *Streptomyces ghanaensis* H2, a semi-producing strain from the BC Biochemie GmbH collection[8]) was performed as described previously.[6]

$^{13}$C NMR spectra were recorded in 10:1 methanol–water. Well-resolved spectra were obtained. All signals of the lipid part could be assigned by comparison with previous results.[9] For a quantitative analysis the $^{13}$C NMR spectrum of the unlabeled moenomycin mixture was recorded under the same conditions. The enrichments were calculated by comparing the corresponding signals (referenced to C-2 of moenomycin unit A[1]) of labeled and unlabeled moenomycin samples using a known procedure.[10] Analysis of the $^{13}$C NMR spectrum of the isolated moenomycin (300 mg) provided $^{13}$C enrichments in the following positions (see □ in formula **6**, moenocinol numbering): C-11 (1.6%, $^1J_{11,12}$=40.7 Hz), C-3 (1.5%), C-14 (1.0%), C-18 (0.5%), C-9 (1.9%, $^1J_{9,8}$=33.6 Hz), C-8 (1.7%, $^1J_{8,9}$=33.6 Hz), C-12 (1.8%, $^1J_{12,11}$=40.7 Hz), C-5 (1.6%), C-16 (2.1%), the C-1 signal was hidden by the sugar signals. The observed labeling pattern matches the one predicted by the operation of Scheme 4. Specifically, the appearance of correlated doublets for the enriched signals of C-8 and C-9 as well as for the signals of C-11 and C-12 demonstrates that the corresponding bonds have indeed been formed by joining labeled atoms of the precursor **3**.

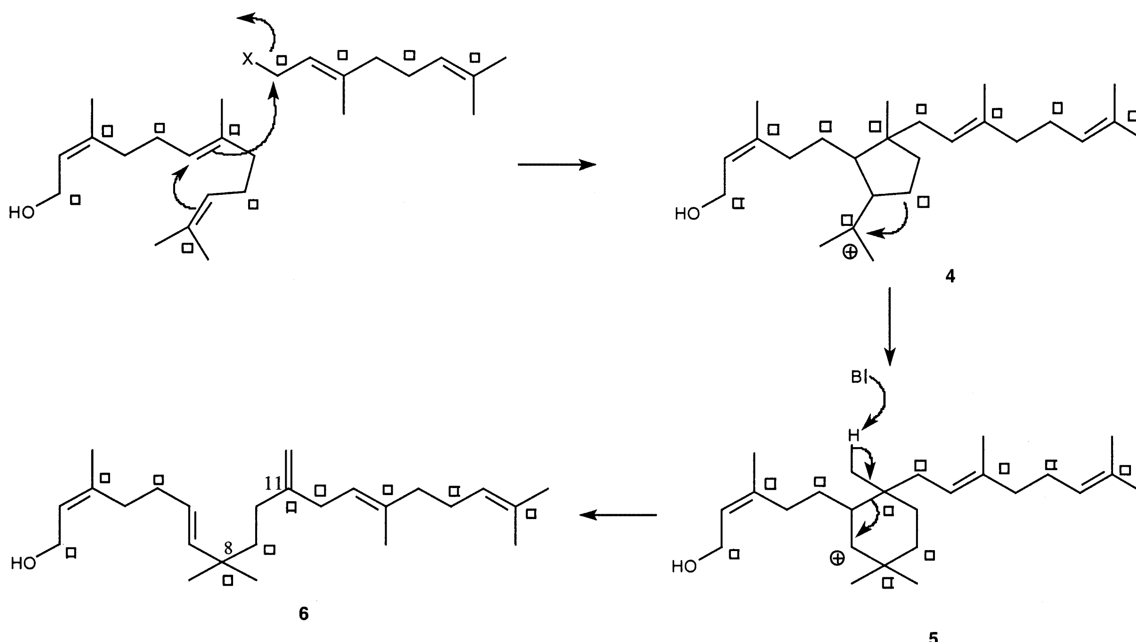
While the percent enrichments in all labeled positions were practically identical, the extent of $^{13}$C–$^{13}$C coupling between C-8 and C-9 (which stem from the same doubly labeled precursor unit) was ca. 2.2 times larger




**Scheme 2.**




**Scheme 3.**




**Scheme 4.**

than between C-11 and C-12 (which are linked in an intermolecular process involving two different precursor units). Such a difference is, of course, expected if in the course of the feeding experiment the administered precursor had suffered a ca. two-fold dilution with endogeneous material.

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## References

1. For leading references, see: Donnerstag, A.; Marzian, S.; Müller, D.; Welzel, P.; Böttger, D.; Stärk, A.; Fehlhaber, H.-W.; Markus, A.; van Heijenoort, Y.; van Heijenoort, J. *Tetrahedron* **1995**, *51*, 1931–1940.
2. Review: (a) Rohmer, M. *Nat. Prod. Rep.* **1999**, *16*, 565–574. For leading references on new work in this area, see: (b) Herz, S.; Wungsintaweekul, J.; Schuhr, C.; Hecht, S.; Lüttgen, H.; Sagner, S.; Fellermeier, M.; Eisenreich, W.; Zenk, M. H.; Bacher, H.; Rohdich, F. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 2486–2490; (c) Takagi, M.; Kuzuyama, T.; Kaneda, K.; Watanabe, H.; Dairi, T.; Seto, H. *Tetrahedron Lett.* **2000**, *41*, 3395–3398.
3. Kennedy, I. A.; Hemscheidt, T.; Britten, J. F.; Spenser, I. D. *Can. J. Chem.* **1995**, *73*, 1329–1337.
4. Giner, J.-L. *Tetrahedron Lett.* **1998**, *39*, 2479–2482.
5. Schuricht, U.; Hennig, L.; Findeisen, M.; Welzel, P. *Tetrahedron Lett.* **2000**, *41*, 3047–3051.
6. Schuricht, U.; Endler, K.; Hennig, L.; Findeisen, M.; Welzel, P. *J. Prakt. Chem.* **2000**, *342*, 761–772.
7. The experimental conditions are described in detail in Ref. 6.
8. BC Biochemie GmbH, Industriepark Höchst, 65929 Frankfurt/M.
9. See compound $M_A$ in: Kempin, U.; Hennig, L.; Welzel, P.; Marzian, S.; Müller, D.; Fehlhaber, H.-W.; Markus, A.; van Heijenoort, Y.; van Heijenoort, J. *Tetrahedron* **1995**, *51*, 8471–8482. The chemical shifts of C-19$^{I}$ and C-20$^{I}$ have to be reversed.
10. Scott, A. I.; Townsend, C. A.; Okada, K.; Kajiwara, M.; Crushley, R. J.; Whitman, P. J. *J. Am. Chem. Soc.* **1974**, *96*, 8069–8080.