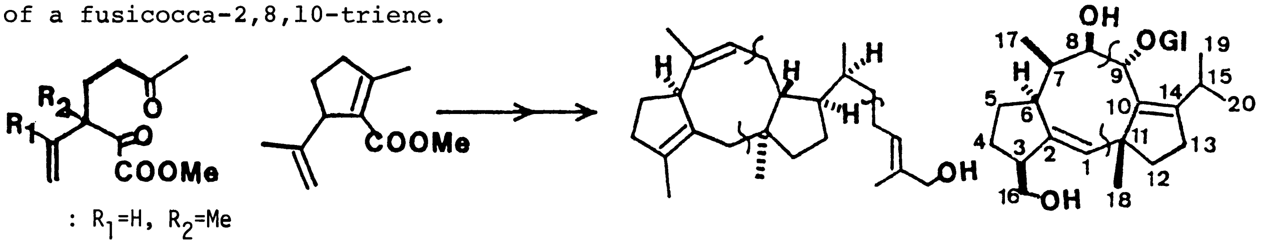
CHEMISTRY LETTERS, pp. 1495 - 1498, 1984.

SYNTHESIS OF FUSICOCCA-2,8,10-TRIENE, A BIOGENETIC MISSING LINK, STARTING FROM STEREOSPECIFIC CONDENSATION OF TWO IRIDOID SYNTHONS

Hitoshi TAKESHITA,* Nobuo KATO, Kohji NAKANISHI,
Hirotaka TAGOSHI, and Toshihide HATSUI
Research Institute of Industrial Science, 86, Kyushu University,
Kasuga-koen, Kasuga, Fukuoka 816

From two units of iridoid C_{10}-synthons which could be prepared from one of the photoadducts of isoprene and methyl 2,4-dioxopentanoate, the hydrocarbon which can be designated as fusicocca-2,8,10-triene, a missing link in the biogenesis, was stereospecifally synthesized.

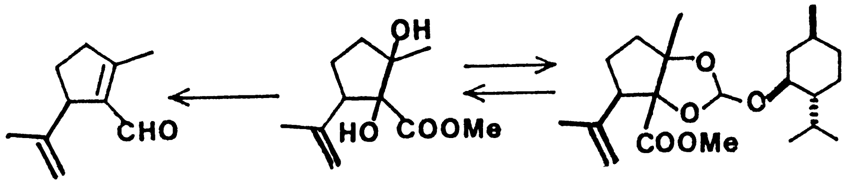
Previously, we have obtained two photoadducts (**1** and **2**) from iosprene and methyl 2,4-dioxopentanoate.$^{1)}$ The synthetic utility of **1** has been verified by conversion to geijerone$^{2)}$ and γ-elemene.$^{3)}$ We have also applied **2** for a synthesis of dehydroiridodial and chrysomelidial *via* 3-isopropenyl-2-methoxycarbonyl-1-methylcyclopentene (**3**).$^{4)}$ Based on this access of the C_{10}-units, we have thought that, from two units of **3**, fusicoccins$^{5)}$ and cotylenins,$^{6)}$ diterpenoid metabolites of microorganisms, or from **3** and a homologous C_{15}-unit, ophiobolins$^{7)}$ and ceroplastols,$^{8)}$ related sesterterpenoids isolated from several fungi and insects, could be prepared by suitable means. We wish herein to report the stereoselective synthesis of a fusicocca-2,8,10-triene.



: R_1=H, R_2=Me
: R_1=Me, R_2=H

Ceroplastol II   Fusicoccin H

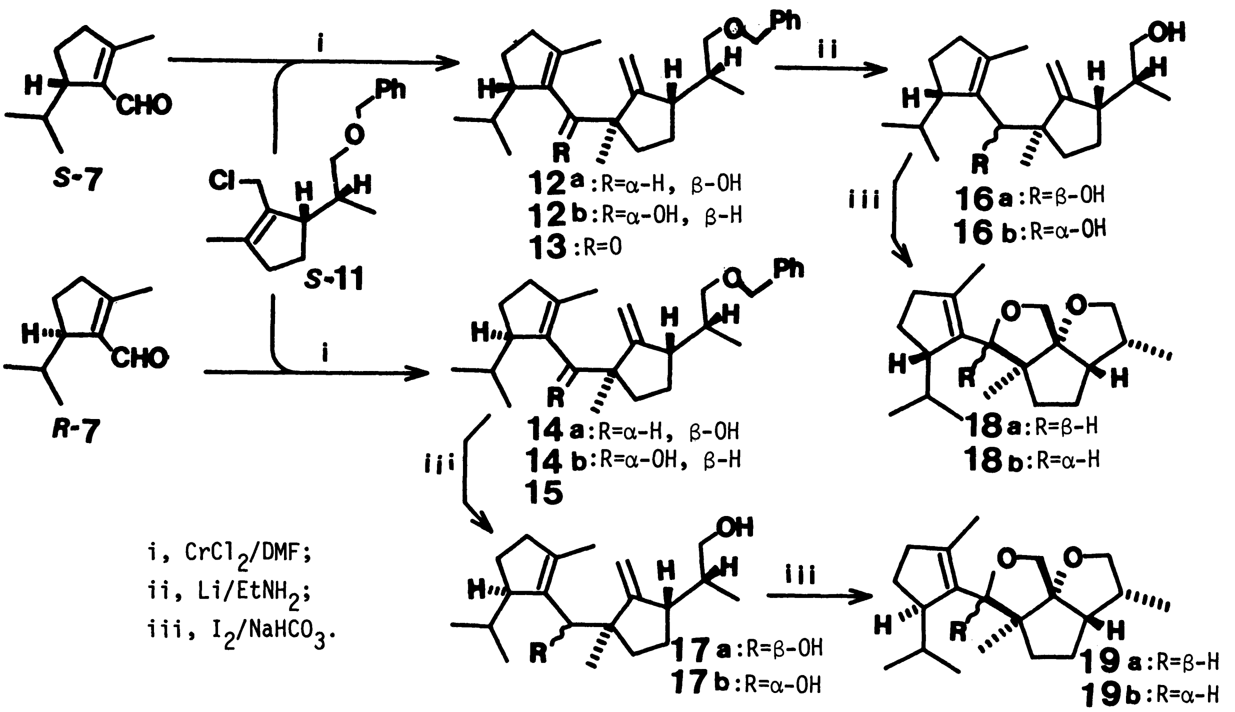
The starting material, **3**, was prepared from **2**, *via* the glycol (**4**),$^{9)}$ by $TiCl_2$-induced reductive cyclization and Zn-reduction as described previously.$^{4)}$



However, to avoid diastereomeric complication which should be faced in the later steps, the optically active **4**, which we obtained through resolution as menthyl orthoformates (**5a**', **5a**", **5b**', and **5b**")$^{10)}$ was employed. Consecutive LAH reduction and CrO_3 oxidation of *R*- or *S*-**3** gave the aldehyde (**6**). Its dihydro deriva-

tive (**7**) was prepared without difficulty. Conversion of **6** to the hydroxy acetal (**8**) was carried out as reported previously.[4] The benzyl ether of **8** (**9**) was hydrolyzed and reduced to an allyl alcohol (**10**), which upon treatment with oxalyl chloride and DMSO in CH_2Cl_2[11] yielded the primary allyl chloride (**11**).
#B4 By means of $CrCl_2$-induced coupling,[12] *S*-**7** and *S*-**11** gave two isomeric 1:1-condensates (**12a**, 64%, and **12b**, 18%) which gave the same dehydro derivative (**13**) by Collins oxidation; thus, **12a** and **12b** are epimers of the carbinyl carbon. Similarly, the reductive condensation of *R*-**7** and *S*-**11** gave also two epimeric condensates (**14a**, 76%, and **14b**, 4%) which could be oxidized to the same dehydro derivative (**15**) by the oxidation. LAH reduction of **15** regenerated **14a**, 71%, and **14b**, 24%, while the same treatment of **13** yielded **12a**, 38%, and **12b**, 57%.

Birch reduction of **12a** and **12b** gave dihydroxyl derivatives (**16a** and **16b**, respectively), and by the same reaction, **14a** and **14b** gave **17a** and **17b**. All the **16** and **17** formed bis-ether derivatives (**18a**, **18b**, **19a**, and **19b**) upon treatment with I_2 and $NaHCO_3$ in aqueous ether. Therefore, the oxygenated C_3-side chain of every condensate (**12a**, **12b**, **14a**, and **14b**) is *cis* to the tertiary methyl group.

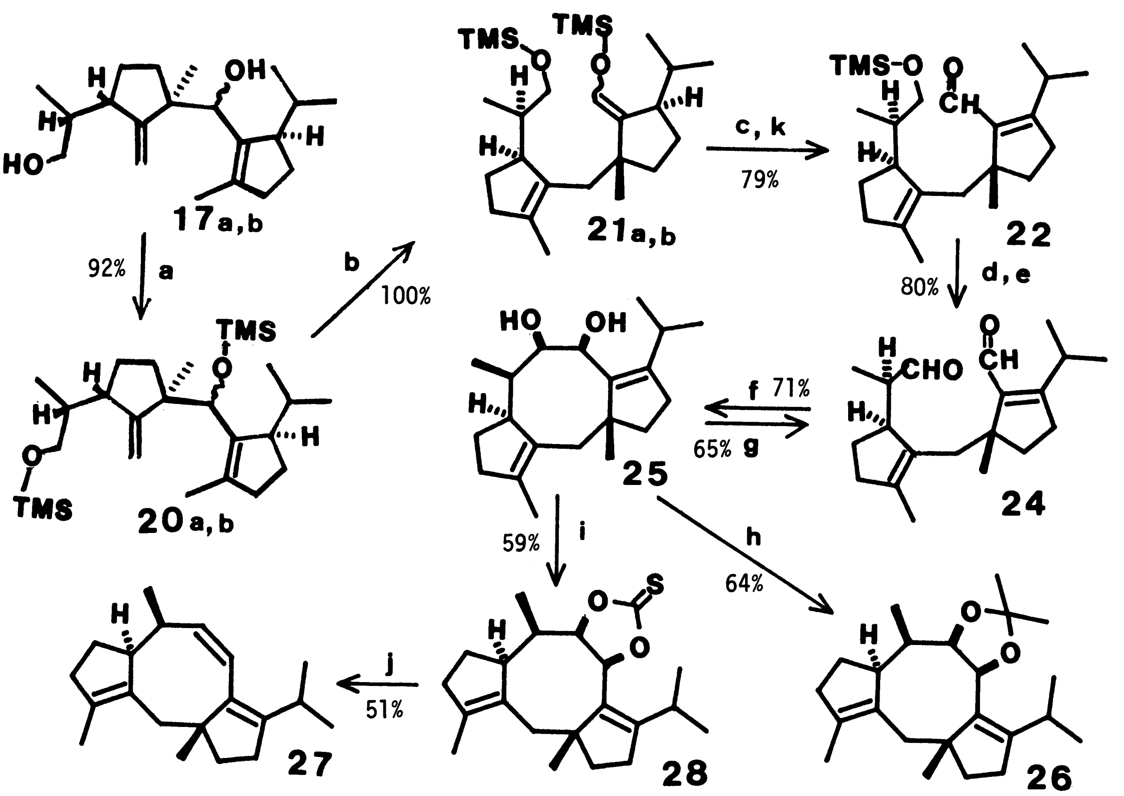


Cope rearrangement of di(trimethylsiloxyl) derivative (**20a**), prepared from **17a**, at 190 °C for 12 h gave the trimethylsilyl vinyl ether (**21a**). Its *meso*-tetraphenylporphin (TPP)-sensitized photooxygenation[13] yielded the α,β-unsaturated aldehyde (**22**). The $Pd(OAc)_2$ oxidation[14] of **21a** also produced **22** only with less satisfactory yield. By the same reaction sequence, **17b** was converted to **22** *via* **20b** and **21b**; separation of **17a** and **17b** is therefore unnecessary. A mild hydrolysis of residual trimethylsilyl ether of **22** afforded the hydroxy aldehyde (**23**), which was easily converted to the dialdehyde (**24**).

By treatment with $TiCl_2$ at 0 °C in THF, **24** was reduced to colorless-oily 1,2-glycol (**25**) [$\delta(CDCl_3)$=0.94(3H, d, J=7 Hz), 0.97(3H, d, J=7 Hz), 1.14(3H, d, J=7

Hz), 1.24(3H, s), 1.67(3H, br. s), 3.54(1H, br. t, J=5 Hz), and 4.87(1H, br. s)], 71%, from which the dioxolane (26), a colorless oil [δ(CDCl$_3$)=0.94(3H, d, J=7 Hz), 1.00(3H, d, J=7 Hz), 1.11(3H, d, J=7 Hz), 1.24(3H, s), 1.28(3H, s), 1.37(3H, s), 1.60(3H, br s), 2.52(1H, sept, J=7 Hz), 2.59(1H, br m), 4.20(1H, dd, J=9, 1 Hz), and 5.17(1H, br d, J=9 Hz)], was obtained by treatment with 2,2-dimethoxypropane and pyridinium *p*-toluenesulfonate (PPTS). NaIO$_4$-oxidation of 25 cleaved back to 24.

Since 25 was conformationally mobile, the stereochemistry of the tricyclic products was deduced from the NMR spectrum of 26 by the aids of coupling parameters and nuclear Overhauser effect as depicted.



a, TMSCl/Py; b, Δ; c, hν-O$_2$-TPP; d, 0.2 N HCl; e, (COCl)$_2$-DMSO, NEt$_3$; f, TiCl$_4$-Zn/THF(Py); g, NaIO$_4$; h, Me$_2$C(OMe)$_2$/PPTS; i, (C$_3$H$_3$N$_2$)$_2$CS/Toluene; j, (MeNCH$_2$)$_2$P-Ph/Benzene; k, PPh$_3$.

The glycol, 25, had closely resembled arrangements of oxygen and unsaturated functions to fusicoccins; one notable difference to the natural series was its *cis*-glycol function, and the inversion of the C-9 allylic hydroxyl was difficult indeed. Thus, as a target, we have chosen the triene, fusicocca-2,8,10-triene (27), which can be viewed as a member of the missing link in their biogenesis. The TiCl$_2$-reduction of 25 was not satisfctory to yield very trace amount of 27. Up to date, the most satisfactory results (30% yield) of 25 to 27, a colorless oil [δ(CDCl$_3$)=0.92(6H, d, J=7 Hz), 0.95(3H, s), 0.96(3H, d, J=7 Hz), 1.58(3H, br s), 2.51(1H, sept, J=7 Hz), 2.60(1H, br m), 5.40(1H, br. dd, J=11, 7 Hz), and 5.79(1H, br d, J=11 Hz)], were obtained by reduction of the thiocarbonate derivative of 25 (28), prepared by treatment with di(imidazolyl)thione at 110 °C in toluene, with

1,3-dimethyl-2-phenyl-1,3,2-diazaphosphoridine at 80 °C in benzene.[16]

Since there are several stereochemically different 5/8/5-membered-fused tricyclic higher terpenoids, the present method,[17] dimerization of two iridoid synthons, should be versatile; *i.e.*, i) availability of such an appropriate synthon by known stereoselective hydroboration of **3** to dehydroiridodial and its further conversion to chrysomelidial,[4] and ii) intentional transfer of absolute stereochemistry from one to the other cyclopentene *via* Cope rearrangement.

Further approach to the natural products will be reported in due course.

We are grateful to The Ministry of Education, Science and Culture of Japan for financial supports by Grant in Aid for Scientific Research to H.T. (No. 57218019) and to N.K. (No. 58740246).

References

1) H. Takeshita, T. Hatsui, and T. Masuda, *Kyushu Daigaku Sogo Rikogaku Kenkyuka Hokoku*, 1, 35(1979).

2) A. F. Thomas, *Helv. Chim. Acta*, 55, 2429(1972); S. D. Sharma, A. S. Sethi, and M. L. Sharma, *Indian J. Chem.*, 15B, 958(1977).

3) C. Ganter and B. K.-Wojtkiewicz, *Helv. Chim. Acta*, 54, 183(1971).

4) H. Takeshita, T. Hatsui, N. Kato, T. Masuda, and H. Tagoshi, *Chem. Lett.*, 1982, 1153.

5) A. Ballio, M. Brufani, C. G. Casinovi, S. Cerrini, W. Fedeli, R. Pellicciari, B. Santurbano, and A. Vaciago, *Experientia*, 24, 631(1968); K. D. Barrow, D. H. R. Barton, E. B. Chain, U. F. W. Ohnsorge, and R. Thomas, *Chem. Commun.*, 1968, 1198.

6) T. Sassa, *Nipon Nogei Kagaku Kaishi*, 49, R35(1975).

7) S. Nozoe, M. Morisaki, K. Tsuda, Y. Iitaka, N. Takahashi, S. Tamura, K. Ishibashi, and M. Shirasaka, *J. Am. Chem. Soc.*, 87, 4968(1965); L. Canonica, A. Fiecchi, M. G. Kienle, and A. Scala, *Tetrahedron Lett.*, 1966, 1211; S. Nozoe and M. Morisaki, *J. Chem. Soc., Chem. Commun.*, 1969, 1319.

8) Y. Iitaka, I. Watanabe, I. T. Harrison, and S. Harrison, *J. Am. Chem. Soc.*, 90, 1092(1968); T. Rios and L. Quijano, *Tetrahedron Lett.*, 1969, 1317; F. Miyamoto, H. Naoki, Y. Naya, and K. Nakanishi, *Tetrahedron*, 36, 3481(1980).

9) All the new compounds described in this paper have been fully characterized.

10) This will be a matter of independent paper.

11) A. J. Mancuso, S. -L. Huang, and D. Swern, *J. Org. Chem.*, 43, 2480(1978).

12) Y. Okude, S. Hirano, T. Hiyama, and H. Nozaki, *J. Am. Chem. Soc.*, 99, 3179 (1977).

13) G. Rousseau, P. Le Perchec, and J. M. Conia, *Synthesis*, 1978, 67.

14) Y. Ito, T. Hirao, and T. Saegusa, *J. Org. Chem.*, 43, 1011(1978).

15) These will be included in a full paper.

16) E. J. Corey and P. B. Hopkins, *Tetrahedron Lett.*, 1982, 1979.

17) Including the latest paper (L. A. Paquette, D. R. Andrews, and J. P. Springer, *J. Org. Chem.*, 48, 1147(1983)), several model syntheses of these 5/8/5-ring systems have been published.

(Received June 7, 1984)