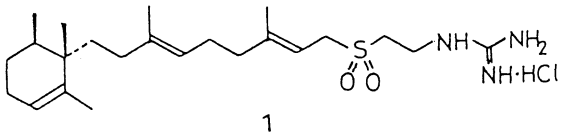
CHEMISTRY LETTERS, pp. 1813-1814, 1989.

Total Synthesis of (+)-Agelasidine C, a Physiologically Active Marine Diterpenoid with Hypotaurocyamine Group[1)]

Kazuhiko ASAO, Hideo IIO, and Takashi TOKOROYAMA*
Faculty of Science, Osaka City University, Sumiyoshi-ku, Osaka 558

The introduction of hypotaurocyamine unit to terpenic chain was examined using farnesyl bromide as a model compound and this was feasible by chemoselective oxidation of the derived sulfide by peracid. By the application of the method thus established, a total synthesis of agelasidine C has been accomplished.

Agelasidines are a group of physiologically active constituents found in marine sponges of *Agelas* species and structurally characterized by the presence of novel hypotaurocyamine unit as a polar functionality.[2)] In continuation of the synthetic studies on *Agelas* terpenoids,[3)] we investigated the synthesis of agelasidine C (**1**), of which monocyclic diterpenoid moiety was recently synthesized by us.[4)]



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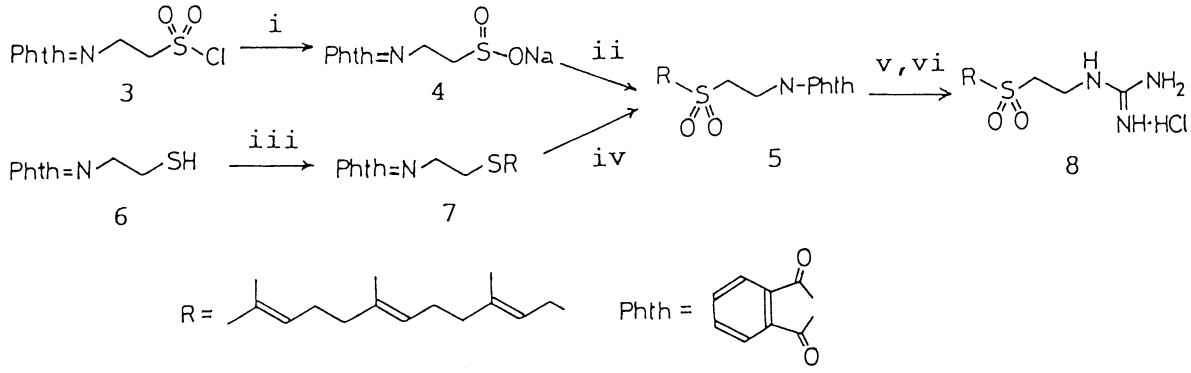
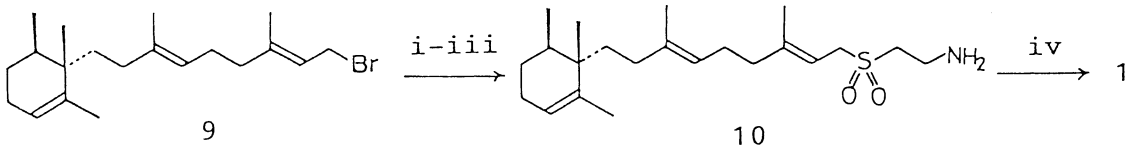
The installation of the hypotaurocyamine group to the terpenic unit was studied using farnesyl bromide (**2**) as a model compound (Scheme 1). The first approach was the substitution reaction of **2** with sodium phthalimidoethanesulfinate (**4**) to give the sulfone directly. The reaction of **2** with the crude sulfinate salt **4**, prepared by the reduction of the corresponding sulfonyl chloride,[5)] afforded **5** in 23% yield. The low yield and the lack of reproducibility in this procedure, mainly attributable to the problems associated in purification of **4**, led us to the examination of second approach. Namely, we investigated a route *via* sulfide **7**, where the chemoselective oxidation to the sulfone **5** was mandatory. The compound **7** was prepared by the alkylation of the thiol **6** with **2**. Of the several methods examined for the oxidation of **7** to **5**, the satisfactory result was obtained by the oxidation with *m*-chloroperbenzoic acid (MCPBA), in which the solvent effect was remarkable. Whereas the reaction with MCPBA (2 equiv) in CH_2Cl_2 afforded **5** in 16% yield after removal of the epoxidized products, the reactions in etheric solvents gave **5** in higher yields (Et_2O, 54%; THF, 66%).[6)] The sulfone **5** was deprotected and the guanylation of the product amine by treatment with 2-methyl-2-pseudothiourea sulfate gave the hypotaurocyamine derivative **8** in 85% yield.

Having established the route to introduce the hypotaurocyamine unit on a terpenic chain, we proceeded to the synthesis of agelasidine C starting from the diterpenic bromide **9**[4,7)] (Scheme 2). The peracid oxidation of the derived sulfide



Scheme 1. i) Zn, H_2O, then NaOH, Na_2CO_3; ii) **2**, DMF; iii) **2**, Et_3N, THF; iv) MCPBA, THF; v) NH_2NH_2, EtOH; vi) $NH_2C(=NH)SMe \cdot \frac{1}{2}H_2SO_4$, H_2O

afforded the corresponding sulfone in a yield higher than in the model case, of which deprotection provided the hypotaurin derivative **10**. The reaction of **10** with 2-methyl-2-pseudothiourea resulted in the formation of the hypotaurocyamine compound only in low yield (10-18%), probably due to the low solubility of the substrate **10** in water. However when the reaction performed with the use of 3,5-dimethylpyrazole-1-carboxamidine nitrate,[8] the aimed product was obtained in an acceptable yield. The spectral data (IR, ^1H and ^{13}C NMR) of the synthetic product[9] were identical with those of the natural product and thus the total synthesis of agelasidine C has been accomplished.[10]



Scheme 2. i) **6**, Et_3N, THF (51%); ii) MCPBA, THF (82%); iii) NH_2NH_2, EtOH (93%); iv) 3,5-dimethylpyrazole-1-carboxamidine nitrate, MeOH (65%)

References

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3) H. Iio, K. Asao, and T. Tokoroyama, J. Chem. Soc., Chem. Commun., 1985, 774.
4) K. Asao, H. Iio, and T. Tokoroyama, in preparation.
5) D. A. Baeyer, C. W. Chan, T. J. Polansky, J. J. Taggart, and G. L. Dunn, J. Heterocycl. Chem., 15, 981 (1981).
6) For similar example see: B. M. Trost, J. Org. Chem., 38, 3438 (1978). The selectivities may be ascribed to the higher rate of the sulfoxide group oxidation in more basic etheric solvents, whereas the oxidation of the olefinic bonds and the sulfide group is known to be supressed greatly in the same solvents: R. Curci, R. A. Diprete, J. O. Edwards, and G. Mondena, J. Org. Chem., 35, 741 (1970).
7) The structure denotes arbitarily one enantiomer.
8) F. L. Scott, D. G. O'Donovan, and J. Reilly, J. Am. Chem. Soc., 75, 4053 (1952).
9) IR($CHCl_3$): νmax 3400, 2975, 2940, 2845, 1715, 1680, 1660, 1620, 1450, 1405, 1375, 1300, 1190, 1120, 870, 850 cm^{-1}; ^1H NMR(CD_3OD, 400 MHz): δ 0.86(3H, s), 0.87(3H, d, J = 7.3 Hz), 1.60(3H, br s), 1.62(3H, br s), 1.78(3H, br s), 1.2-2.4(13H, m), 3.31(2H, t, J = 5.5 Hz), 3.72(2H, t, J = 5.5 Hz), 3.90(2H, d, J = 7.9 Hz), 5.11(1H, br s), 5.31(1H, t, J = 7.9 Hz), 5.42(1H, brs); ^{13}C NMR(CD_3OD, 100 MHz): δ 16.2, 16.4, 17.1, 19.5, 21.5, 26.5, 27.3, 28.2, 34.6, 35.4, 36.0, 36.5, 40.8, 41.6, 51.3, 54.6, 110.7, 124.0, 125.2, 137.8, 140.7, 148.3, 158.7.
10) Recently a report dealing with the synthesis of a related sesquiterpene, agelasidine A, appeared: Y. Ichikawa, Tetrahedron Lett., 29, 4957 (1988).

(Received July 10, 1989)