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# STEREOCONTROLLED TOTAL SYNTHESIS OF (+)-ASTEROMURIN A, A PICROTOXANE SESQUITERPENE ISOLATED FROM THE SCALE INSECT ASTEROCOCCUS MURATAE KUWANA

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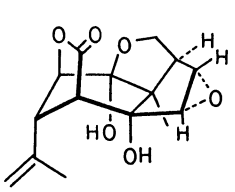
The first total synthesis of (+)-asteromurin A, a picrotoxane sesquiterpene isolated from the scale insect Asterococcus muratae KUWANA is described.

Asteromurin A (1) is the major component of the bitter principles isolated from the scale insect Asterococcus muratae KUWANA (fam. Asterolecaniidae)[1] and belongs to a picrotoxane group of sesquiterpenes. The structure of asteromurin A including the absolute stereochemistry has been established very recently by chemical and spectral means coupled with the X-ray crystallographic studies to be represented as the formula 1.[1,2] Asteromurin A (1) has been shown to be as toxic as the poisonous picrotoxane sesquiterpenes of plant origin (i.e., picrotoxinin (2), coriamyrtin (3), and tutin (4)).[1c] As part of our continuing efforts toward synthesis of the picrotoxane sesquiterpenes, we describe herein the first total synthesis of (+)-asteromurin A (1) in the stereocontrolled manner.



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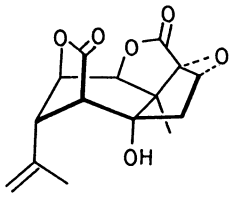

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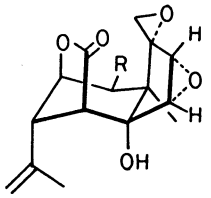
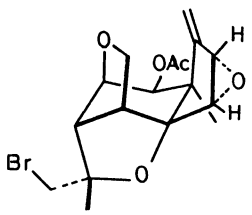


3 R = H
4 R = OH

We have chosen an epoxy olefin 5 as the starting material, which was employed in our synthesis of tutin (4)[3] previously.

Hydroboration of the epoxy olefin 5 [(1) $B_2H_6$, THF, room temp , 4 h; (2) 3 M NaOH, 30% aqueous $H_2O_2$, 55 °C, 1 h] provided the desired diol 6[4,6] [mp 202-204 °C (ether), $[\alpha]_D^{26}$ -73.4° (c 0.32, $CHCl_3$), 54%[5a]] together with the 1,4-reduction product 7[4] [colorless oil, $[\alpha]_D^{26}$ -58.4° (c 0.5, $CHCl_3$), 45%[5b]]. The high stereoselectivity in the formation of 6 may be due to preferred attack of diborane to the double bond from the less hindered face (i.e., syn to the epoxide ring) of the epoxy olefin 5. The primary hydroxyl group in the diol 6 was selectively esterified with 2,2,2-trichloethoxycarbonyl chloride (pyridine, -25 °C, 1.5 h) to afford the carbonate 8[4] [mp 187-188 °C (benzene-hexane), $[\alpha]_D^{25}$ -53.1° (c 0.52, $CHCl_3$), 60%[5c]]. Simultaneous oxidation of the secondary hydroxyl group and the O-methylene group in the carbonate 8 was achieved by the reaction with ruthenium

tetraoxide ($RuCl_3$-$NaIO_4$, pH 7 phosphate buffer-$CCl_4$-$CH_3CN$, 40 °C, 43 h)[7] to give the keto lactone 9[4] [mp 61-62 °C (hexane), $[\alpha]_D^{26}$ -46.6° (c 0.35, $CHCl_3$), 72%[5d]]. Finally, reduction of the keto lactone 9 with zinc powder ($NH_4Cl$, EtOH, reflux, 1 h) provided (+)-asteromurin A (1)[4] [mp 158-159 °C ($CHCl_3$-hexane), $[\alpha]_D^{26}$ +40.0° (c 0.23, MeOH), 94%[5c]].[8] The spectral (IR, $^1H$ NMR, and mass), chiroptical ($[\alpha]_D$), and chromatographic properties of synthetic 1 were identical with those of natural asteromurin A (1) in all respects.



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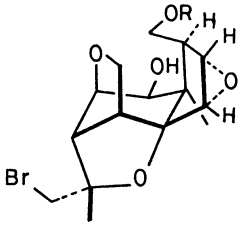
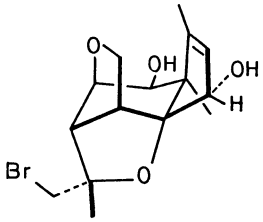


6 R = H
8 R = $CO_2CH_2CCl_3$



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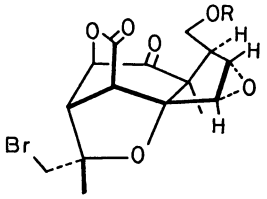


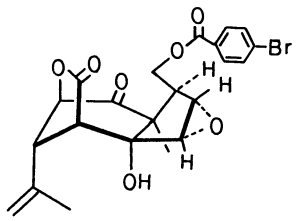
9 R = $CO_2CH_2CCl_3$

We express our cordial gratitudes to Prof. T. Tokuyama (Osaka City Univ.) for providing us with the reference sample and the spectral ($^1H$ NMR) and physical ($[\alpha]_D$ and mp) data of natural asteromurin A (1). We are also indebted to Prof. T. Tokuyama for informing us of the absolute stereochemistry of 1 prior to his publication. Financial support from the Ministry of Education, Science, and Culture (Grant-in-Aid for Special Project Research, Innovative Studies of Highly Selective Synthesis) is gratefully acknowledged.

References

1) a) T. Saika and T. Tokuyama, 41st National Meeting of the Chemical Society of Japan, Higashi-Osaka, April 1980, Abst., No. 1S14.
b) T. Saika and T. Tokuyama, 45th National Meeting of the Chemical Society of Japan, Tokyo, April 1982, Abst., No. 1E44.
c) T. Saika, T. Tokuyama, T. Higuchi, and K. Hirotsu, 47th National Meeting of the Chemical Society of Japan, Kyoto, April 1983, Abst., No. 1H30.

2) Based on the X-ray crystallographic studies of the compound 10[1c] the absolute stereochemistry of asteromurin A has been determined to be represented as the formula 1 (private communication from Prof. T. Tokuyama; T. Tokuyama, T. Saika, K. Hirotsu, and T. Higuchi, manuscript in preparation).



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3) K. Wakamatsu, H. Kigoshi, K. Niiyama, H. Niwa, and K. Yamada, Tetrahedron Letters, in press.

4) Satisfactory IR, $^1H$ NMR, mass, and high resolution mass spectral data were obtained for the purified, chromatographically homogeneous sample.

5) Yield after purification by preparative TLC on silica gel with: a) $CHCl_3$-EtOAc (1:3); b) $CCl_4$-acetone (4:1); c) hexane-EtOAc (1:1); d) hexane-EtOAc (2:1).

6) The yield of 6 was somewhat decreased when hydroboration was performed with $BH_3 \cdot Me_2S$ complex (6 43%; 7 53%). Hydroboration with 9-BBN or thexylborane has resulted in the exclusive formation of the undesired 1,4-reduction product 7.

7) P. H. Carlsen, T. Katsuki, U. S. Martin, and K. B. Sharpless, J. Org. Chem., 46, 3936 (1981).

8) Physical properties of natural asteromurin A (1): $[\alpha]_D^{16}$ +42.5° (c 1.23, MeOH); mp 163.5-165 °C (EtOAc-hexane) (private communication from Prof. T. Tokuyama).

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