Tetrahedron Vol. 42, No. 20, pp. 5551 to 5558, 1986
Printed in Great Britain.

0040-4020/86 $5.00+.00
Pergamon Journals Ltd.

STEREOCONTROLLED TOTAL SYNTHESIS OF (+)-TUTIN AND (+)-ASTEROMURIN A, TOXIC PICROTOXANE SESQUITERPENES

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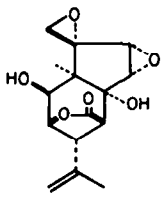
(*Received in Japan* 24 *July* 1986)

Abstract - The first total synthesis of (+)-tutin (1), a toxic principle of the plants of the Coriaria species and (+)-asteromurin A (2), a bitter principle of the scale insect Asterococcus muratae KUWANA in the stereocontrolled manner is described, utilizing the epoxy olefin 10 as the common intermediate.

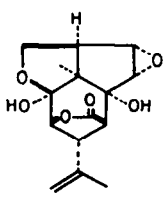
Tutin (1), one of the representative members of the picrotoxane sesquiterpenes was first isolated in 1901 as the poisonous principle from the three New Zealand Coriaria species ("tutu" or "toitoi" in Maori)[1] and later from the same species native in Japan.[2,3] The structure (1) of tutin including absolute stereochemistry was elucidated by the X-ray crystallographic analysis[4a,b] together with chemical and chiroptical means.[4c,d] The biological activities of tutin (1) have been reported to be nearly identical with those of the representative picrotoxane sesquiterpenes, picrotoxinin (3) and coriamyrtin (4).[5] Tutin (1) has recently been found to be the specific antagonist of γ-aminobutyric acid (GABA).[6] Asteromurin A (2) is the major component of the bitter principles isolated from the scale insect Asterococcus muratae KUWANA (family Asterolecaniidae),[7] and has been proved as toxic as the poisonous picrotoxane sesquiterpenes of plant origin such as picrotoxinin (3) and coriamyrtin (4). The X-ray crystallographic studies in conjunction with chemical and spectral investigation have elucidated the absolute structure of asteromurin A to be 2.[7,8]

From the viewpoints of the intriguing structures and prominent biological activities, we have carried out the synthetic studies on the picrotoxane sesquiterpenes, resulting in the synthesis of (-)-picrotoxinin (3) and (+)-coriamyrtin (4).[9,10] As part of our continuing studies in this field we wish to report in details the first total synthesis of (+)-tutin (1) and (+)-asteromurin A (2) in the stereocontrolled manner.[11]



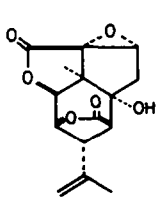
1

tutin



2

asteromurin A



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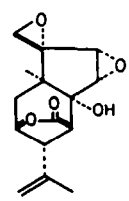
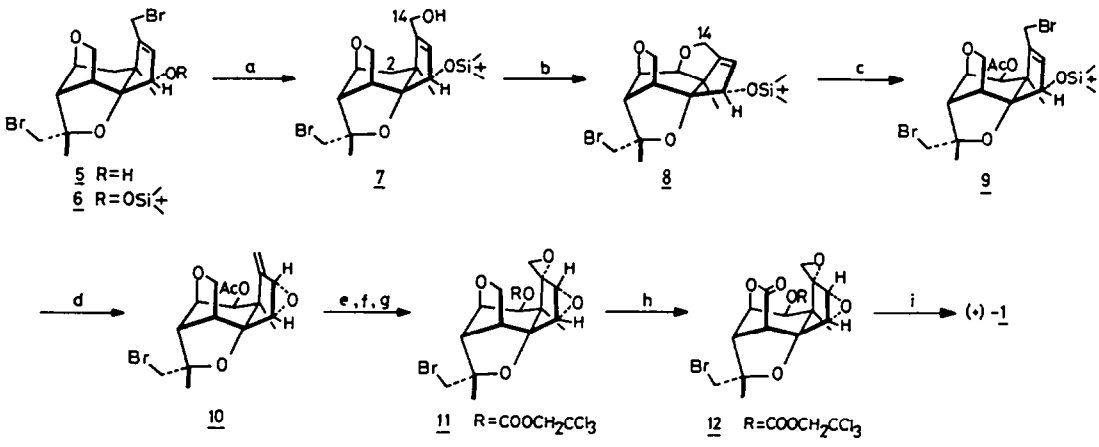


4

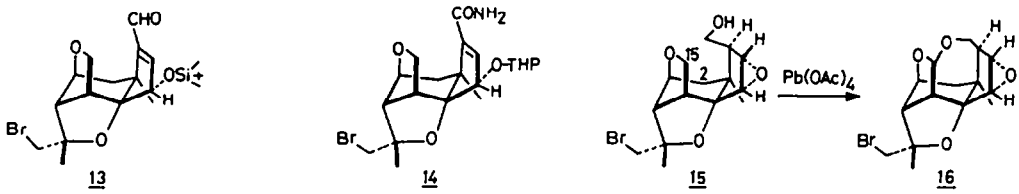
For the synthesis of tutin (1), the (-)-bromo alcohol 5 was chosen as the starting compound, which was employed in the synthesis of (+)-coriamyrtin (4).[9] Protection of the hydroxyl group in 5 by silylation provided the silyl ether 6 (96%). Although conversion of the allylic bromide moiety in 6 into the allylic alcohol grouping could not be effected under ordinary conditions (e.g., K_2CO_3-aqueous THF; KOH-MeOH), it was achieved by treating 6 with potassium superoxide under the Corey's conditions[12] to give the allylic alcohol 7 (76%) (Scheme I). In order to introduce the hydroxyl group at C-2 of 7 regio- and stereoselectively by virtue of the intramolecular reaction making use of the C-14 hydroxyl function, the allylic alcohol 7 was reacted with $Pb(OAc)_4$ in benzene under reflux to afford the desired cyclic ether 8 (57%) and the aldehyde 13 (29%), the latter 13 being able to be reduced to the starting alcohol 7. Attempts to introduce the oxygen function at C-2 utilizing other derivatives

Scheme I

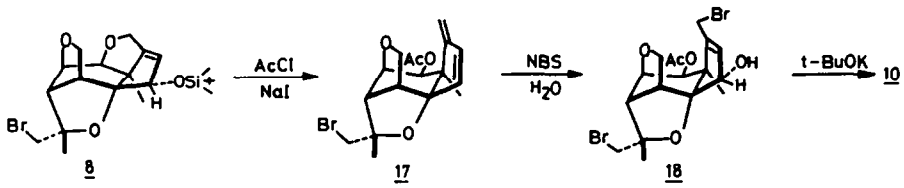


(a) KO_2, dicyclohexyl-18-crown-6, DMSO-DMF. (b) $Pb(OAc)_4$, benzene.
(c) AcBr-Bu_4NBr-CaH_2, MeCN. (d) Bu_4NF, THF. (e) K_2CO_3, MeOH.
(f) $ClCOOCH_2CCl_3$, pyridine. (g) CF_3CO_3H-Na_2HPO_4, CH_2Cl_2.
(h) $RuCl_3$-$NaIO_4$, buffer (pH 6.9)-MeCN-CCl_4. (i) Zn-NH_4Cl, EtOH.

such as the amide 14[13] and the alcohol 15[14] failed: when the amide 14 was photolyzed[15] in the presence of $Pb(OAc)_4$ and I_2 in benzene or was treated with $Pb(OAc)_4$ in benzene under reflux, complex mixtures resulted; on treatment of the alcohol 15 with $Pb(OAc)_4$ in benzene under reflux there was obtained the acetal 16, the product resulting from the oxygenation at the undesired C-15 site, together with recovery of 15. Next, conditions for the cleavage of the allylic ethereal linkage at C-



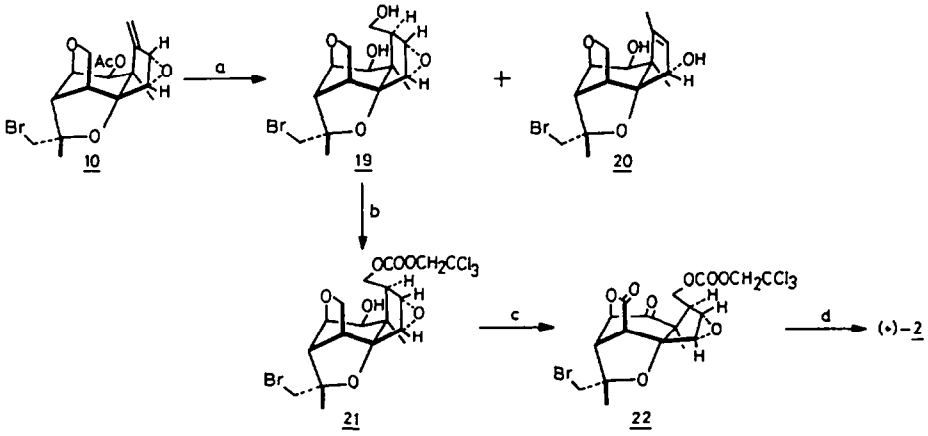
14 in 8 were extensively examined. The reaction of 8 with AcCl and NaI in acetonitrile afforded the conjugated diene 17 (63%), which on treatment with NBS in aqueous THF was led to the desired bromo alcohol 18 (32%). Further, action of t-BuOK on 18 provided the epoxy olefin 10 (38%). More efficiently the ethereal bond in question in 8 was cleaved by treating 8 with AcBr, Bu_4NBr, and CaH_2 in acetonitrile, affording the allylic bromide 9 in 94% yield (Scheme I). The presence of CaH_2 in this reaction was shown to be crucial for the success of the conversion of 8 into 9. Under the conditions of removing the silyl protecting group in 9 (Bu_4NF-THF), the intramolecular S_N2' reaction at



the allylic bromide moiety took place to give the epoxy olefin 10 (99%) (Scheme I). In this stage the replacement of the protecting group of the hydroxyl function at C-2 from the acetate to the group that can be deprotected under neutral conditions was made, because in the final stage of the synthesis of tutin (1) the protecting group in question must be removed in the presence of the functional groups (a γ-lactone and two epoxides) in the molecule which are sensitive to both acidic and basic conditions. Thus, the epoxy olefin 10 was transformed into the bisepoxide 11 in 38% overall yield by the following sequence of the reactions: (1) alkaline hydrolysis (K_2CO_3-MeOH) to afford the alcohol; (2) esterification ($ClCOOCH_2CCl_3$-pyridine) to form the 2,2,2-trichloroethyl carbonate; and (3) epoxidation (CF_3CO_3H-Na_2HPO_4-CH_2Cl_2). Oxidation of 11 with RuO_4 ($RuCl_3$-$NaIO_4$, pH 6.9 phosphate buffer-MeCN-CCl_4)[16] provided 2,2,2-trichloroethoxycarbonyl α-bromotutin (12) (73%), which was identical with the authentic specimen prepared from natural tutin (1) by spectral (IR, ^1H NMR, and mass) and chromatographic comparison. Finally reduction of 12 with zinc (NH_4Cl, EtOH) afforded (+)-tutin (1) in 99% yield. The spectral (IR, ^1H NMR, and mass), physical (mp and $[\alpha]_D$), and chromatographic properties of synthetic 1 were completely identical with those of natural tutin (1) in all respects.

For the synthesis of (+)-asteromurin A (2), the epoxy olefin 10 was subjected to hydroboration (B_2H_6, THF) followed by oxidation (H_2O_2-NaOH, H_2O) to give the desired diol 19 (54%) and the 1,4-reduction product 20 (45%) (Scheme II). The high stereoselectivity in the formation of 19 may be due to the preferred attack of B_2H_6 to the double bond from the less hindered side (i.e., syn to the epoxide ring) of 10. The yield of 19 was somewhat decreased when hydroboration was performed with the BH_3·Me_2S complex (19, 43%; 20, 53%). Hydroboration of 10 with thexylborane and 9-BBN resulted in the exclusive formation of the undesired 1,4-reduction product 20. The primary hydroxyl group in 19 was selectively protected by esterification ($ClCOOCH_2CCl_3$, pyridine) to obtain the 2,2,2-trichloroethyl carbonate 21 (60%). Simultaneous oxidation of the secondary hydroxyl group and the O-methylene group in 21 was executed by RuO_4 ($RuCl_3$-$NaIO_4$, pH 6.9 phosphate buffer-MeCN-CCl_4), affording the keto lactone 22 (72%). Reduction of 22 with zinc (NH_4Cl, EtOH) provided (+)-asteromurin A (2) in 94% yield, which was proved to be identical with natural 2 by spectral (IR, ^1H NMR, and mass), physical (mp and $[\alpha]_D$), and chromatographic comparison.

Scheme II



(a) B_2H_6, THF; H_2O_2-NaOH, H_2O. (b) $ClCOOCH_2CCl_3$, pyridine.
(c) $RuCl_3$-$NaIO_4$, buffer (pH 6.9)-MeCN-CCl_4. (d) Zn-NH_4Cl, EtOH.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were obtained with a JASCO Model IRS spectrophotometer in $CHCl_3$ solution. ^1H NMR spectra were recorded on a JEOL FX-90QE (90 MHz) spectrometer in $CDCl_3$: chemical shifts (δ) are reported in ppm downfield from internal TMS and coupling constants in Hz. Mass spectra were recorded on Hitachi RMU-6C and JEOL JMS-DX300 instruments. Optical rotations were measured on a JASCO DIP-181 polarimeter. Fuji-Davison silica gel BW-80 was used for column chromatography. Merck precoated silica gel $60F_{254}$ plates were employed for analytical thin layer chromatography (TLC) and Merck silica gel PF_{254} for preparative TLC. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated by vacuum rotary evaporator.

Silyl ether 6. A solution of t-butyldimethylsilyl triflate (35 mg, 0.13 mmol) in pyridine (40 µl) - MeCN (0.5 ml) was added slowly under nitrogen to a stirred solution of 5[9] (12.3 mg, 0.030 mmol) in MeCN (0.2 ml) cooled at 0 °C. The mixture was stirred at 0 °C for 40 min, diluted with saturated $NaHCO_3$ solution (2 ml), and extracted with EtOAc (4 x 5 ml). The combined organic extracts were washed with saturated KBr solution, dried, and concentrated to give a crystalline solid (27 mg), which was purified by preparative TLC on silica gel (4:1 hexane-EtOAc), yielding 6 (15.1 mg, 96%) as colorless crystals : mp 86-87 °C (MeOH); $[\alpha]_D^{25}$ -17.9° (c 0.69, $CHCl_3$); IR 1248, 1078, 1030, 832 cm^{-1}; ^1H NMR (90 MHz) δ 0.05 (3H, s), 0.09 (3H, s), 0.87 (9H, s), 1.35 (3H, s), 1.55 (1H, dd, J = 17, 4), 1.56 (3H, s), 2.22 (1H, br d, J = 17), 2.5-2.8 (2H, m), 3.46 (1H, d, J = 10), 3.71 (1H, d, J = 10), 3.72 (2H, m), 4.03 (2H, br s), 4.15 (1H, d, J = 3), 4.41 (1H, m), 5.86 (1H, m); MS m/z 509 (M^+ + 4 - Me), 507 (M^+ + 2 - Me), 505 (M^+ - Me), 467, 465, 463, 437, 435, 433, 385, 383 [HREIMS. Found: 462.9943 (M^+ - t-Bu). $C_{17}H_{25}O_3{}^{79}Br_2Si$ requires: 462.9940].

Allylic alcohol 7. To a stirred solution of 6 (7.6 mg, 0.015 mmol) in DMSO (0.2 ml) - DMF (0.2 ml) cooled at 0 °C under nitrogen were added KO_2 (5.0 mg, 0.070 mmol) and dicyclohexyl-18-crown-6 (27 mg, 0.072 mmol). The mixture was stirred at 0 °C for 15 min, diluted with H_2O (1 ml), and extracted with EtOAc (4 x 3 ml). The combined organic extracts were washed with saturated NaCl solution, dried, and concentrated. The crude oily product (36 mg) was purified twice by preparative TLC on silica gel (1:4 hexane-Et_2O and 2:3 hexane-EtOAc) to give 7 (5.1 mg, 76%) as colorless crystals: mp 87-88 °C (hexane-Et_2O); $[\alpha]_D^{17}$ -12.6° (c 1.23, $CHCl_3$); IR 3640, 3420, 1640, 1248, 1075, 1030 cm^{-1}; ^1H NMR (90 MHz) δ 0.06 (3H, s), 0.09 (3H, s), 0.87 (9H, s), 1.31 (3H, s), 1.54 (1H, dd, J = 17, 4), 1.57 (3H, s), 2.08 (1H, br d, J = 17), 2.5-2.8 (2H, m), 3.46 (1H, d, J = 10), 3.71 (1H, d, J = 10), 3.77 (2H, m), 4.17 (1H, d, J = 3), 4.26 (2H, br s), 4.39 (1H, m), 5.70 (1H, m); MS m/z 445 (M^+ + 2 - Me), 443 (M^+ - Me), 427, 425, 403, 401, 385, 383, 373, 371 [HREIMS. Found: 401.0787 (M^+ - t-Bu). $C_{17}H_{26}O_4{}^{79}BrSi$ requires: 401.0784].

Cyclic ether 8 and aldehyde 13. A mixture of 7 (26 mg, 0.057 mmol) and $Pb(OAc)_4$ (102 mg, 0.22 mmol) in benzene (4.2 ml) was refluxed for 7 h under nitrogen, cooled to room temperature, and diluted with ether. The mixture was passed through a short column of Florisil with EtOAc. The organic solution was concentrated and the crude oily product was purified by preparative TLC on silica gel (3:1 benzene-EtOAc) to afford 8 (14.8 mg, 57%) as crystals and 13 (7.6 mg, 29%) as an oil, respectively. 8: mp 87-88 °C (hexane); $[\alpha]_D^{13}$ +35.7° (c 1.45, $CHCl_3$); IR 1650, 1249, 1158, 1078 cm^{-1}; ^1H NMR (90 MHz) δ 0.07 (3H, s), 0.10 (3H, s), 0.89 (9H, s), 1.54 (6H, s), 2.5-2.8 (2H, m), 3.44 (2H, br s), 3.77 (2H, m), 3.84 (1H, d, J = 5), 4.3-4.5 (3H, m), 4.64 (1H, d, J = 3), 5.47 (1H, m); MS m/z 458 (M^+ + 2), 456 (M^+), 443, 441, 417, 415, 401, 399, 377 [HREIMS. Found: 399.0652 (M^+ - t-Bu). $C_{17}H_{24}O_4{}^{79}BrSi$ requires: 399.0627]. 13: IR 1685, 1600, 1465, 1380, 1250, 1080 cm^{-1}; ^1H NMR (90 MHz) δ 0.09 (3H, s), 0.12 (3H, s), 0.87 (9H, s), 1.34 (3H, s), 1.58 (3H, s), 1.66 (1H, dd, J = 18, 4), 2.4-2.8 (2H, m), 2.80 (1H, br d, J = 18), 3.4-3.8 (4H, m), 4.35 (1H, d, J = 3), 4.37 (1H, m), 6.63 (1H, d, J = 3), 9.75 (1H, s); MS m/z 458 (M^+ + 2), 456 (M^+), 443 (M^+ + 2 - Me), 441 (M^+ - Me), 401 (M^+ + 2 - t-Bu), 399 (M^+ - t-Bu) [HREIMS. Found: 399.0605 (M^+ - t-Bu). $C_{17}H_{24}O_4{}^{79}BrSi$ requires: 399.0627].

Reduction of aldehyde 13. A mixture of 13 (18.9 mg, 0.041 mmol) and $NaBH_4$ (8.8 mg, 0.23 mmol) in MeOH (3.1 ml) was stirred at room temperature, concentrated, diluted with H_2O, and extracted with EtOAc (4 x 10 ml). The combined organic extracts were washed with saturated NaCl solution, dried, and concentrated. Purification by preparative TLC on silica gel (3:1 benzene-EtOAc) afforded 7 (11.0 mg, 58%) as crystals: mp 87-88 °C (hexane-Et_2O).

Alcohol 15. A 10 M solution of $B_2H_6{\cdot}Me_2S$ in THF (5 µl, 0.055 mmol) was added under nitrogen to a stirred solution of 24[9] (5 mg, 0.015 mmol) cooled at 0 °C. The mixture was stirred at room temperature for 3 h under nitrogen. To the mixture cooled at 0 °C were added EtOH (0.1 ml), 3 M NaOH (5 µl), and 30% H_2O_2 solution (10 µl) successively, and the mixture was stirred at 55 °C for 1 h. After cooling the mixture was diluted with H_2O (0.5 ml) and extracted with ether (4 x 10 ml). The combined organic extracts were washed with H_2O (2 x 1 ml) and saturated NaCl solution (2 ml), dried, and concentrated to give an oily material. Purification by preparative TLC on silica gel (1:3 $CHCl_3$-EtOAc) provided 15 (2.0 mg, 38%) as a solid: ^1H NMR (90 MHz) δ 1.26 (3H, s), 1.40 (1H, dd, J = 18, 4), 1.60 (3H, s), 2.26 (1H, br d, J = 18), 2.28 (1H, dd, J = 7, 7), 2.60 (1H, dd, J = 5, 5), 2.88 (1H, dd, J = 5, 5), 3.30 (1H, d, J = 4), 3.46 (1H, d, J = 10), 3.50 (1H, d, J = 4), 3.6-4.1 (5H, m), 4.44 (1H, m).

Acetal 16. A mixture of 15 (2.0 mg, 0.006 mmol) and $Pb(OAc)_4$ (2.8 mg, 0.0063 mmol) in benzene (0.5 ml) was refluxed for 1 h under nitrogen, cooled to room temperature, diluted with ether, and passed through a short column of Florisil with EtOAc. The organic solution was concentrated to give a solid. Purification by preparative TLC on silica gel (1:4 $CHCl_3$-EtOAc) afforded 16 (0.3 mg, 15%) as an amorphous powder and 15 (0.6 mg, 30%) as a solid. 16: IR 1380, 1150, 1030 cm^{-1}; ^1H NMR (90 MHz) δ 1.26 (3H, s), 1.56 (3H, s), 2.7-2.9 (2H, m), 3.34 (1H, d, J = 4), 3.42 (1H, d, J = 10), 3.54 (1H, d, J = 4), 3.72 (1H, d, J = 10), 3.75 (1H, dd, J = 12, 4), 4.22 (1H, d, J = 12), 4.52 (1H, m),

5.52 (1H, d, J = 5); MS m/z 344 (M^+ + 2), 342 (M^+), 329, 327, 299, 297, 263 [HREIMS. Found: 342.0441 (M^+). $C_{15}H_{19}O_4{}^{79}Br$ requires: 342.0467].

Allylic bromide 9. A mixture of AcBr (0.1 ml) and CaH_2 (250 mg) in MeCN (1.0 ml) was stirred at room temperature for 30 min under nitrogen and the supernatant solution (0.34 ml, 0.47 mmol as AcBr) was added to a mixture of 8 (9.5 mg, 0.021 mmol), Bu_4NBr (66.9 mg, 0.20 mmol), and CaH_2 (113 mg, 2.78 mmol) in MeCN (1.6 ml) under nitrogen. The mixture was stirred at 40 °C for 4 h and cooled to room temperature. The solution obtained from the mixture by decantation was poured into H_2O (1 ml). The resulting mixture was extracted with Et_2O (4 x 10 ml). The combined organic extracts were washed with saturated KBr solution, dried, and concentrated to give an oily residue. Purification by column chromatography on silica gel (20:1 benzene-EtOAc) gave 9 (11.3 mg, 94%) as a colorless oil: $[\alpha]_D^{13}$ -62° (c 0.80, $CHCl_3$); IR 1740, 1375, 1240, 1160, 1080, 1040, 1025 cm^{-1}; ^1H NMR (90 MHz) δ 0.06 (3H, s), 0.09 (3H, s), 0.87 (9H, s), 1.51 (3H, s), 1.57 (3H, s), 2.20 (3H, s), 2.6-2.8 (2H, m), 3.56 (1H, d, J = 11), 3.67 (1H, d, J = 11), 3.78 (2H, br s), 4.21 (1H, d, J = 4), 4.26 (2H, br s), 4.41 (1H, m), 5.08 (1H, d, J = 4), 5.92 (1H, m); MS m/z 582 (M^+ + 4), 580 (M^+ + 2), 578 (M^+), 525, 523, 521, 483, 481, 479, 465, 463, 461, 383, 381 [HREIMS. Found: 521.0009 (M^+ - t-Bu). $C_{19}H_{27}O_5{}^{79}Br_2Si$ requires: 520.9995].

Epoxy olefin 10. A 1.0 M solution of Bu_4NF in THF (0.078 ml, 0.078 mmol) was added to a solution of 9 (6.2 mg, 0.011 mmol) in THF (0.78 ml). The mixture was stirred at room temperature for 1.5 h, concentrated, diluted with H_2O, and extracted with EtOAc (3 x 10 ml). The combined organic extracts were washed with saturated NaCl solution, dried, and concentrated to give an oily residue. Purification by preparative TLC (3:1 benzene-EtOAc) afforded 10 (4.0 mg, 99%) as a colorless oil: $[\alpha]_D^{12}$ -158° (c 0.53, $CHCl_3$); IR 1740, 1655, 1385, 1375, 1250, 1155, 1040 cm^{-1}; ^1H NMR (90 MHz) δ 1.36 (3H, s), 1.63 (3H, s), 2.20 (3H, s), 2.71 (1H, dd, J = 5, 5), 2.96 (1H, br dd, J = 5, 5), 3.52 (1H, d, J = 10), 3.56 (1H, d, J = 3), 3.73 (1H, d, J = 3), 3.73 (1H, d, J = 10), 3.83 (1H, dd, J = 10, 5), 4.01 (1H, dd, J = 10, 1), 4.45 (1H, dd, J = 5, 3), 5.03 (1H, d, J = 3), 5.36 (1H, s), 5.74 (1H, s); MS m/z 386 (M^+ + 2), 384 (M^+), 344, 342, 326, 324, 305 [HRCIMS. Found: 385.0675 (M^+ + 1). $C_{17}H_{22}O_5{}^{79}Br$ requires: 385.0651].

Epoxy olefin 10 via conjugated diene 17 and bromo alcohol 18. To a stirred mixture of 8 (2.0 mg, 0.004 mmol) and NaI (6.0 mg, 0.04 mmol) in MeCN (0.6 ml) was added a 0.90 M solution of AcCl in MeCN (0.1 ml, 0.09 mmol) under nitrogen at room temperature. The mixture was stirred at room temperature for 9 h, diluted with saturated $NaHCO_3$ solution (0.3 ml), and extracted with Et_2O (3 x 10 ml). The combined organic extracts were washed with saturated $NaHSO_3$ solution and saturated NaCl solution, dried, and concentrated to give an oily residue. Purification by preparative TLC on silica gel (3:1 benzene-EtOAc) afforded 17 (1.0 mg, 63%) as a colorless oil: ^1H NMR (90 MHz) δ 1.28 (3H, s), 1.56 (3H, s), 2.20 (3H, s), 2.6-2.9 (2H, m), 3.52 (1H, d, J = 11), 3.72 (1H, d, J = 11), 3.80 (2H, m), 4.42 (1H, m), 4.88 (1H, br s), 5.22 (1H, br s), 5.24 (1H, d, J = 5), 5.80 (1H, br d, J = 7), 6.18 (1H, d, J = 7); MS m/z 370 (M^+ + 2), 368 (M^+), 328, 326, 310, 308, 300, 298, 247. A mixture of 17 (2.0 mg, 0.0054 mmol) and NBS (4.0 mg, 0.022 mmol) in THF - H_2O (10:1, 0.3 ml) was stirred at room temperature for 40 min. To the mixture was added $Na_2S_2O_3$ (4 mg). The mixture was stirred for 30 min, diluted with H_2O (0.5 ml), and extracted with $CHCl_3$ (4 x 10 ml). The combined organic extracts were washed with saturated KBr solution, dried, and concentrated to give an oily material. Purification by preparative TLC on silica gel (1:1 benzene-EtOAc) gave 18 (0.8 mg, 32%) as a colorless oil: ^1H NMR (90 MHz) δ 1.28 (3H, s), 1.58 (3H, s), 2.22 (3H, s), 2.76 (2H, m), 3.54 (1H, d, J = 11), 3.74 (1H, d, J = 11), 3.80 (2H, br s), 4.1-4.4 (3H, m), 4.42 (1H, m), 5.08 (1H, d, J = 4), 6.04 (1H, m); MS m/z 468 (M^+ + 4), 466 (M^+ + 2), 464 (M^+), 426, 424, 422. A mixture of 18 (1.0 mg, 0.0022 mmol) and t-BuOK (1.0 mg, 0.0090 mmol) in benzene (0.5 ml) was stirred at 50 °C for 30 min. After cooling, ion-exchange resin Amberlite IRC-50 (acid form, 200 mg) was added to the mixture. The mixture was stirred at room temperature for 10 min and passed through a column of Amberlite IRC-50 (acid form, 200 mg) with benzene. The resulting organic solution was concentrated to give an oily residue. Purification by preparative TLC (2:1 benzene-EtOAc) afforded 10 (0.3 mg, 38%) as a colorless oil, the spectral (IR, ^1H NMR, and MS) properties of which were identical with those of the authentic 10.

Bisepoxide 11. A mixture of 10 (5.6 mg, 0.015 mmol) and K_2CO_3 (6.4 mg, 0.046 mmol) in MeOH (0.5 ml) was stirred at 0 °C for 3.5 h, neutralized by adding Amberlite IRC-50 (acid form, 700 mg), then stirred for 15 min, and passed through a column of Amberlite IRC-50 (acid form, 700 mg) with MeOH. The resulting methanolic solution was concentrated to give an oily residue. Purification by column chromatography on silica gel (2:1 hexane-EtOAc) afforded the alcohol (4.5 mg, 90%) as a colorless oil: $[\alpha]_D^{12}$ -154° (c 0.34, $CHCl_3$); IR 3550, 1653, 1380, 1260, 1160, 1035 cm^{-1}; ^1H NMR (90 MHz) δ 1.43 (3H, s), 1.61 (3H, s), 2.65 (1H, d, J = 12, OH), 2.73 (1H, dd, J = 5, 5), 2.91 (1H, ddd, J = 5, 5, 3), 3.42 (1H, d, J = 10), 3.49 (1H, d, J = 3), 3.57 (1H, d, J = 10), 3.68 (1H, d, J = 3), 3.72 (1H, dd, J = 12, 3), 3.81 (2H, m), 4.30 (1H, dd, J = 5, 3), 5.36 (1H, br s), 5.80 (1H, s); MS m/z 344 (M^+ + 2), 342 (M^+), 329, 328, 327, 326, 263 [HRCIMS. Found: 343.0558 (M^+ + 1). $C_{15}H_{20}O_4{}^{79}Br$ requires: 343.0545]. A mixture of the alcohol (4.5 mg, 0.013 mmol) and $ClCOOCH_2CCl_3$ (59 l, 0.41 mmol) in pyridine (0.6 ml) was stirred at room temperature for 1.5 h under nitrogen. Ice (ca. 1 g) was added to the mixture. The mixture was kept with stirring for 5 min at room temperature and extracted with ether (4 x 10 ml). The combined ethereal extracts were washed with 1 M HCl (2 ml), saturated $NaHCO_3$ solution (2 ml), and saturated NaCl solution (2 ml) successively, dried, and concentrated. Toluene (ca. 1 ml) was added to the residue and the toluene solution was concentrated, and this procedure was repeated three times in order to remove pyridine in the residue. Purification of the oily residue by preparative TLC on silica gel (1:1 hexane-EtOAc) afforded the 2,2,2-trichloroethyl carbonate (6.7 mg, 99%) as a colorless oil: $[\alpha]_D^{12}$ -159° (c 0.38, $CHCl_3$); IR 1760, 1650, 1380, 1285, 1245, 1155 cm^{-1}; ^1H NMR (90 MHz) δ 1.44 (3H, s), 1.63 (3H, s), 2.76 (1H, dd, J = 6, 6), 2.99 (1H, ddd, J = 6, 6, 1), 3.49 (1H, d, J = 11), 3.56 (1H, d, J = 3), 3.65 (1H, d, J = 11), 3.73 (1H, d, J = 3), 3.84 (1H, dd, J = 10, 6), 4.00 (1H, dd, J = 10, 1), 4.58

(1H, dd, J = 6, 3), 4.70 (1H, d, J = 12), 4.89 (1H, d, J = 3), 4.95 (1H, d, J = 12), 5.40 (1H, s), 5.82 (1H, s); MS m/z 520 (M^+ + 4), 518 (M^+ + 2), 516 (M^+), 491, 489, 487, 441, 439, 437 [HREIMS. Found: 437.0297 (M^+ - ^{79}Br). $C_{18}H_{20}O_6{}^{35}Cl_3$ requires: 437.0326]. To a mixture of the 2,2,2-trichloroethyl carbonate (7.0 mg, 0.014 mmol) and $Na_2HPO_4 \cdot 12H_2O$ (425 mg, 1.19 mmol) in CH_2Cl_2 (1.1 ml) was added a 1.0 M solution of CF_3CO_3H in CH_2Cl_2 (1.0 ml, 1.0 mmol). After the mixture was stirred at 35 °C for 7 h, a 1.0 M solution of CF_3CO_3H in CH_2Cl_2 (0.5 ml, 0.5 mmol) and $Na_2HPO_4 \cdot 12H_2O$ (215 mg, 0.60 mmol) were added, and the stirring was continued for additional 7 h. Subsequently, a 1.0 M solution of CF_3CO_3H in CH_2Cl_2 (1.5 ml, 1.5 mmol) and $Na_2HPO_4 \cdot 12H_2O$ (420 mg, 1.19 mmol) were again added, and the mixture was stirred for further 6 h and diluted with saturated $NaHCO_3$ solution (2 ml). Then, $Na_2S_2O_3 \cdot 5H_2O$ (ca. 200 mg) was added to the mixture. The mixture was stirred at room temperature for 10 min and extracted with CH_2Cl_2 (4 x 25 ml). The combined organic extracts were washed with saturated NaCl solution (2 ml), dried, and concentrated to give an oily residue. Separation and purification by preparative TLC on silica gel (1:1 hexane-EtOAc) afforded 11 (colorless oil, 3.1 mg, 43%) and the diastereomer (colorless oil, 1.3 mg, 18%), respectively. 11: $[\alpha]_D^{18}$ -107° (c 0.56, $CHCl_3$); IR 1762, 1382, 1284, 1247, 1160 cm^{-1}; ^1H NMR (90 MHz) δ 1.50 (3H, s), 1.65 (3H, s), 2.80 (1H, dd, J = 5, 5), 2.85 (1H, d, J = 5), 2.98 (1H, m), 3.22 (1H, d, J = 3), 3.54 (1H, d, J = 3), 3.56 (2H, m), 3.96 (1H, d, J = 5), 3.99 (2H, m), 4.52 (1H, dd, J = 5, 3), 4.67 (1H, d, J = 3), 4.69 (1H, d, J = 12), 4.81 (1H, d, J = 12); MS m/z 540 (M^+ + 8), 538 (M^+ + 6), 536 (M^+ + 4), 534 (M^+ + 2), 532 (M^+), 511, 509, 507, 505, 503, 457, 455, 453, 443, 441, 439, [HRCIMS. Found: 532.9517 (M^+ + 1). $C_{18}H_{21}O_7{}^{79}Br^{35}Cl_3$ requires: 532.9536]. Diastereomer: $[\alpha]_D^{18}$ -136° (c 0.40, $CHCl_3$); IR 1760, 1382, 1282, 1248, 1156 cm^{-1}; ^1H NMR (90 MHz) δ 1.43 (3H, s), 1.64 (3H, s), 2.79 (1H, dd, J = 6, 6), 2.92 (1H, d, J = 5), 3.03 (1H, dd, J = 6, 6), 3.09 (1H, d, J = 5), 3.14 (1H, d, J = 3), 3.47 (1H, d, J = 11), 3.50 (1H, d, J = 3), 3.58 (1H, d, J = 11), 3.93 (1H, dd, J = 10, 6), 4.48 (1H, d, J = 10), 4.52 (1H, d, J = 12), 4.53 (1H, dd, J = 6, 4), 4.66 (1H, d, J = 4), 4.98 (1H, d, J = 12); MS m/z 511, 509, 507, 505, 503, 457, 455, 453, 443, 441, 439.

2,2,2-Trichloroethoxycarbonyl α-bromotutin 12. A mixture of 11 (6.1 mg, 0.011 mmol), $RuCl_3 \cdot H_2O$ (42 mg, 0.19 mmol), and $NaIO_4$ (197 mg, 0.91 mmol) in CCl_4 (1.5 ml), MeCN (1.5 ml), and phosphate buffer (0.05 M, pH 6.9; 2.3 ml) was stirred for 12 h at 40 °C. Additional $RuCl_3 \cdot H_2O$ (40 mg, 0.18 mmol) and $NaIO_4$ (200 mg, 0.94 mmol) were added and the stirring was continued for further 12 h at 40 °C. The mixture was diluted with H_2O and extracted with CH_2Cl_2 (4 x 25 ml). The combined organic extracts were washed with saturated $NaHCO_3$ solution (1.5 ml), saturated $Na_2S_2O_3$ solution (1 ml), and saturated NaCl solution (2 ml), dried, and concentrated to give an oily residue, which was dissolved in $CHCl_3$. The solution was passed through a short column of Florisil and concentrated to afford a crude product. Purification by preparative TLC on silica gel (1:1 hexane-EtOAc) provided 12 (4.6 mg, 73%) as a colorless oil: $[\alpha]_D^{19}$ -124° (c 0.60, $CHCl_3$); IR 1791, 1766, 1388, 1285, 1245, 1155 cm^{-1}; ^1H NMR (90 MHz) δ 1.56 (3H, s), 1.60 (3H, s), 2.75 (1H, d, J = 5), 3.21 (1H, dd, J = 5, 1), 3.22 (1H, d, J = 3), 3.37 (1H, dd, J = 5, 5), 3.50 (1H, d, J = 11), 3.65 (1H, d, J = 11), 3.71 (1H, d, J = 3), 3.77 (1H, d, J = 5), 4.71 (1H, d, J = 12), 4.85 (1H, d, J = 3), 4.87 (1H, d, J = 12), 5.05 (1H, ddd, J = 5, 3, 1); MS m/z 554 (M^+ + 8), 552 (M^+ + 6), 550 (M^+ + 4), 548 (M^+ + 2), 546 (M^+), 473, 471, 469, 467 [HRCIMS. Found: 546.9332 (M^+ + 1). $C_{18}H_{19}O_8{}^{79}Br^{35}Cl_3$ requires: 546.9329].

(+)-Tutin 1. To a solution of 12 (18.0 mg, 0.033 mmol) in EtOH (2.3 ml) were added Zn powder (200 mg) and NH_4Cl (200 mg). The mixture was refluxed for 1.5 h under nitrogen, cooled to room temperature, diluted with EtOAc, and filtered through a pad of Celite. The filtrate was concentrated to give a solid, which was purified by preparative TLC (4:1 $CHCl_3$-EtOAc) to afford (+)-1 (9.6 mg, 99%) as colorless crystals: mp 204-205 °C ($CHCl_3$-hexane); $[\alpha]_D^{17}$ +13.9° (c 0.75, MeOH). The natural sample gave mp 204-205 °C and $[\alpha]_D^{16}$ +14.1° (c 1.10, MeOH). The IR, ^1H NMR, and mass spectra and the TLC behaviors (several solvent systems) of synthetic (+)-1 proved identical in all respects with those of natural tutin.

Preparation of 2,2,2-trichloroethoxycarbonyl α-bromotutin 12 from natural tutin 1. A mixture of natural 1 (10.0 mg, 0.034 mmol) and $ClCOOCH_2CCl_3$ (0.15 ml, 1.06 mmol) in pyridine (1.6 ml) was stirred at room temperature for 14 h under nitrogen and then, ice (ca. 2 g) was added. After stirring for 5 min, the mixture was diluted with H_2O (0.5 ml) and extracted with EtOAc (4 x 20 ml). The combined organic extracts were washed with saturated NaCl solution (2 ml), dried, and concentrated. Toluene (ca. 3 ml) was added to the residue and the toluene solution was concentrated, and this procedure was repeated three times for the removal of pyridine in the residue. Purification of the residue obtained by preparative TLC (2:1 $CHCl_3$-EtOAc) provided 2,2,2-trichloroethoxycarbonyl tutin (16.0 mg, quantitative) as a colorless oil: ^1H NMR (90 MHz) δ 1.38 (3H, s), 1.96 (3H, br s), 2.57 (1H, br s), 2.85 (1H, d, J = 4), 3.20 (1H, d, J = 4), 3.1-3.4 (2H, m), 3.76 (1H, d, J = 4), 3.78 (1H, d, J = 4), 4.68 (1H, d, J = 12), 4.86 (1H, d, J = 12), 4.94 (1H, m), 5.20 (1H, br s), 5.24 (1H, br s). To a stirred solution of 2,2,2-trichloroethoxycarbonyl tutin (16.0 mg, 0.034 mmol) in THF (2.0 ml) and H_2O (0.2 ml) was added NBS (7.0 mg, 0.038 mmol) under nitrogen. The mixture was stirred at room temperature for 30 min, and then $Na_2S_2O_3 \cdot 5H_2O$ (10 mg) was added. After stirring for 5 min, the mixture was diluted with saturated $NaHCO_3$ solution (1 ml) and extracted with EtOAc (4 x 10 ml). The combined organic extracts were washed with saturated NaCl solution, dried, and concentrated to give an oily residue. Purification by preparative TLC (1:2 hexane-Et_2O) provided 12 (13.3 mg, 71%) as a colorless oil and the diastereomer (2.7 mg, 14%) as a solid. 12: $[\alpha]_D^{18}$ -122° (c 1.00, $CHCl_3$).

Diol 19. A 1.0 M solution of B_2H_6 in THF (0.086 ml, 0.086 mmol) was added under nitrogen to a stirred solution of 10 (6.5 mg, 0.017 mmol) in THF (1.0 ml) cooled at 0 °C. The mixture was stirred at room temperature for 4 h under nitrogen. To the mixture cooled at 0 °C were added EtOH (0.5 ml), 3 M NaOH (0.2 ml), and 30% H_2O_2 solution (0.3 ml) successively, and the mixture was stirred at 55 °C for 1 h. After cooling the mixture was concentrated, diluted with H_2O (1 ml), and extracted with EtOAc (4 x 10 ml). The combined organic extracts were washed with saturated NaCl solution (1 ml), dried, and concentrated to give an oily residue. Separation by preparative TLC on

silica gel (1:3 $CHCl_3$-EtOAc) afforded 19 (3.3 mg, 54%) as crystals and crude 20 as an oil, and the latter was further purified by preparative TLC on silica gel (4:1 CCl_4-acetone) to yield 20 (2.7 mg, 45%) as a colorless oil. 19: mp 202-204 °C (Et_2O); $[\alpha]_D^{26}$ -73.4° (c 0.32, $CHCl_3$); IR 3400, 1380, 1160, 1030 cm^{-1}; ^1H NMR (90 MHz) δ 1.43 (3H, s), 1.61 (3H, s), 2.54 (1H, dd, J = 3, 9), 2.74 (1H, dd, J = 6, 6), 2.94 (1H, dd, J = 6, 5), 3.34 (1H, d, J = 3), 3.41 (1H, d, J = 3), 3.44 (1H, d, J = 11), 3.54 (1H, dd, J = 13, 3), 3.60 (1H, d, J = 11), 3.72 (1H, d, J = 10), 3.92 (1H, dd, J = 10, 5), 4.12 (1H, dd, J = 13, 9), 4.37 (1H, dd, J = 6, 4); MS m/z 362 (M^+ + 2), 360 (M^+), 344, 342, 333, 331, 329 [HRCIMS. Found: 361.0655 (M^+ + 1). $C_{15}H_{22}O_5{}^{79}Br$ requires: 361.0651]. 20: $[\alpha]_D^{26}$ -58.4° (c 0.50, $CHCl_3$); IR 3580, 1627, 1380, 1155, 1040 cm^{-1}; ^1H NMR (90 MHz) δ 1.50 (3H, s), 1.60 (3H, s), 1.97 (3H, m), 2.34 (1H, d, J = 11, OH), 2.6-2.8 (2H, m), 3.46 (1H, d, J = 10), 3.60 (1H, d, J = 10), 3.6-4.0 (3H, m), 4.16 (1H, m), 4.32 (1H, m), 5.52 (1H, m); MS m/z 346 (M^+ + 2), 344 (M^+), 331, 329, 328, 326, 317, 315, 265.

2,2,2-Trichloroethyl carbonate 21. To a stirred solution of 19 (7.1 mg, 0.020 mmol) in pyridine (0.3 ml) cooled at -25 °C was added $ClCOOCH_2CCl_3$ (12 μl, 0.084mmol) under nitrogen. The mixture was stirred at -25 °C for 1.5 h. Ice (ca. 1 g) was added to the mixture. The mixture was stirred for 5 min and extracted with ether (4 x 10 ml). The combined ethereal extracts were washed with saturated NaCl solution (1 ml), dried, and concentrated. Toluene (ca. 1 ml) was added to the residue and the toluene solution was concentrated, and this procedure was repeated twice for removal of pyridine in the residue. Purification by preparative TLC on silica gel (1:1 hexane-EtOAc) afforded 21 (6.2 mg, 59%) as crystals: mp 187-188 °C (benzene-hexane); $[\alpha]_D^{25}$ -53.1° (c 0.52, $CHCl_3$); IR 3540, 1760, 1380, 1160, 1030 cm^{-1}; ^1H NMR (90 MHz) δ 1.44 (3H, s), 1.61 (3H, s), 2.22 (1H, br d, J = 8, OH), 2.69 (1H, dd, J = 10, 6), 2.74 (1H, t, J = 6), 2.92 (1H, dd, J = 4, 6), 3.36 (1H, d, J = 3), 3.41 (1H, d, J = 11), 3.59 (1H, d, J = 3), 3.60 (1H, d, J = 11), 3.73 (1H, dd, J = 8, 3), 3.92 (2H, m), 4.31 (1H, dd, J = 11, 10), 4.36 (1H, dd, J = 6, 3), 4.78 (2H, s), 5.22 (1H, dd, J = 6, 11); MS m/z 542 (M^+ + 8), 540 (M^+ + 6), 5.38 (M^+ + 4), 536 (M^+ + 2), 534 (M^+), 513, 511, 509, 507, 505, 459, 457, 455, 445, 443, 441, 345, 343 [HRCIMS. Found: 343.0517 (M^+ - $OCOOCH_2C^{35}Cl_3$). $C_{15}H_{20}O_4{}^{79}Br$ requires: 343.0545].

Keto lactone 22. A mixture of 21 (5.7 mg, 0.011 mmol), $RuCl_3 \cdot H_2O$ (59 mg, 0.26 mmol), and $NaIO_4$ (185 mg, 0.85 mmol) in CCl_4 (1.5 ml), MeCN (1.5 ml), and phosphate buffer (0.05 M, pH 6.9, 2.2 ml) was stirred for 43 h at 40 °C. During the reaction $RuCl_3 \cdot H_2O$ (2 x 60 mg) and $NaIO_4$ (2 x 120 mg) were twice added, respectively. After cooling the mixture was diluted with H_2O and extracted with CH_2Cl_2 (4 x 25 ml). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 ml), saturated $Na_2S_2O_3$ solution (2 ml), and saturated NaCl solution (2 ml), dried, and concentrated to give an oily material. Purification by preparative TLC on silica gel (2:1 hexane-EtOAc) afforded 22 (4.2 mg, 72%) as crystals: mp 61-62 °C (hexane); $[\alpha]_D^{26}$ -46.6° (c 0.35, $CHCl_3$); IR 1800, 1770, 1730, 1380, 1240, 1045 cm^{-1}; ^1H NMR (90 MHz) δ 1.60 (3H, s), 1.63 (3H, s), 2.84 (1H, dd, J = 7, 8), 3.35 (2H, br s), 3.38 (1H, dd, J = 8, 5), 3.58 (1H, dd, J = 5, 5), 3.67 (2H, s), 4.14 (2H, m), 4.76 (2H, s), 4.79 (1H, dd, J = 5, 1); MS m/z 554 (M^+ + 8), 552 (M^+ + 6), 550 (M^+ + 4), 548 (M^+ + 2), 546 (M^+), 473, 471, 469, 467, 357, 355 [HREIMS. Found: 545.9246 (M^+). $C_{18}H_{18}O_8{}^{79}Br^{35}Cl_3$ requires: 545.9251].

(+)-Asteromurin A 2. Zinc powder (74 mg) and NH_4Cl (74 mg) were added to a solution of 22 (5.8 mg, 0.011 mmol) in EtOH (1.2 ml) under nitrogen. The mixture was refluxed for 1 h under nitrogen, cooled to room temperature, diluted with EtOAc, and filtered through a pad of Celite. The filtrate was concentrated to give an oily residue, which was purified by preparative TLC on silica gel (1:1 hexane-EtOAc) to give (+)-2 (2.9 mg, 94%) as colorless crystals: mp 158-159 °C ($CHCl_3$-hexane); mixed mp 158-159 °C; $[\alpha]_D^{26}$ +40.0° (c 0.23, MeOH). Physical properties of natural asteromurin A: mp 158-159 °C ($CHCl_3$-hexane); $[\alpha]_D^{16}$ +42.5° (c 1.26, MeOH).[17] The IR, ^1H NMR, and mass spectra and the TLC behaviors (several solvent systems) of synthetic (+)-2 proved identical with those of natural asteromurin A.

Acknowledgments - We are grateful to Professor D. Arigoni (E.T.H.) for providing us with the reference sample of natural tutin. We thank Professor T. Tokuyama (Osaka City University) for providing us with the reference sample and the spectral data of natural asteromurin A. We are also indebted to Professor T. Tokuyama for informing us of the absolute stereochemistry of asteromurin A prior to his publication. Financial support from the Ministry of Education, Science, and Culture (Grant-in-Aid for Special Project Research, Innovative Studies on Highly Selective Synthesis) is gratefully acknowledged.

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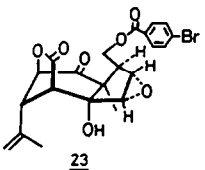

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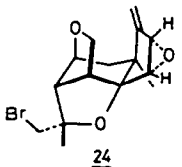
11. Preliminary communications: K. Wakamatsu, H. Kigoshi, K. Niiyama, H. Niwa, and K. Yamada, Tetrahedron Lett., **25**, 3873 (1984); K. Wakamatsu, K. Niiyama, H. Niwa, and K. Yamada, Chemistry Lett., 1763 (1984).
12. E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, Tetrahedron lett., 3183 (1975).
13. The amide 14 was prepared from 7 by the sequence: (i) PDC oxidation to form the carboxylic acid; (ii) reaction with carbonyl diimidazole and subsequent treatment with aqueous ammonia.
14. The alcohol 15 was prepared from 24[9] employed in the synthesis of (-)-coriamyrtin by hydroboration followed by alkaline H_2O_2 oxidation.
15. D. H. R. Barton, A. L. J. Beckwith, and A. Goosen, J. Chem. Soc., 181 (1965).
16. P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, J. Org. Chem., **46**, 3936 (1981).
17. Private communication from Prof. T. Tokuyama, Osaka City University.



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