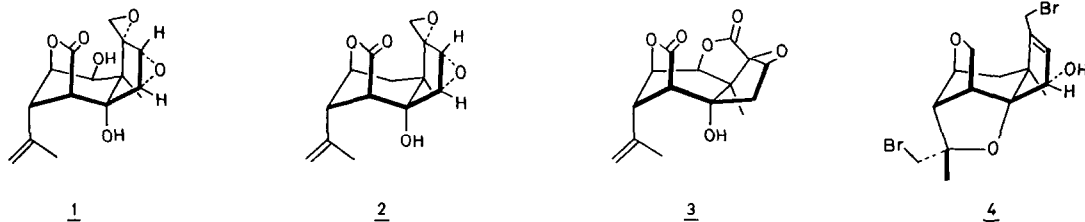


STEREOCONTROLLED TOTAL SYNTHESIS OF (+)-TUTIN, A TOXIC SESQUITERPENE OF PICROTOXANE-TYPE

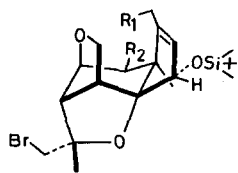
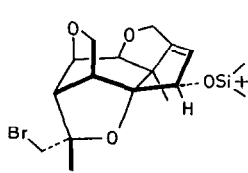
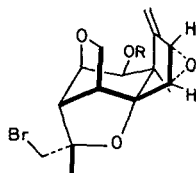
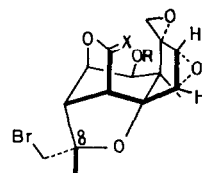
Kazumasa Wakamatsu, Hideo Kigoshi, Kenji Niiyama, Haruki Niwa, and Kiyoyuki Yamada*
Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464, Japan

Abstract. The first total synthesis of (+)-tutin (1), a toxic sesquiterpene of picROTOXANE-type isolated from the poisonous plants of the *Coriaria* species is described.

Tutin (1), the poisonous principle isolated first in 1901 from the three New Zealand *Coriaria* species ("tutu" or "toitoti" in Maori)¹ and later from the same species native in Japan,² is one of the representative members of the picROTOXANE sesquiterpenes. The structure of tutin including the absolute stereochemistry has been established by the X-ray crystallographic studies^{3a,b} coupled with chemical and chiroptical means^{3c,d} to be represented as the formula 1. The biological activities of tutin (1) have been known to be nearly identical with those of the representative picROTOXANE sesquiterpenes, coriamyrtin (2) and picROTOXININ (3).^{4a} Recent neuropharmacological studies have shown tutin (1) to be the specific antagonist of γ -aminobutyric acid (GABA).^{4b} We have been engaged in the synthetic studies on the picROTOXANE sesquiterpenes, resulting in the total synthesis of (+)-coriamyrtin (2) and (-)-picROTOXININ (3) very recently.⁵ As part of our continuing studies in this field, we describe herein the first total synthesis of (+)-tutin (1) in the stereocontrolled manner.



The present synthesis started from the (-)-bromo alcohol 4 which was employed in our synthesis of (+)-coriamyrtin (2).⁵ Silylation (t -BuMe₂SiOSO₂CF₃, Py, CH₃CN, 0 °C, 30 min) of 4 and treatment of the resulting silyl ether with potassium superoxide under the Corey's conditions⁶ (DMSO-DMF, 0 °C, 20 min) gave the allylic alcohol 5⁷ [mp 87-88 °C (ether-hexane), $[\alpha]_D^{17}$ -12.6° (c 1.23, CHCl₃), 73%^{8a}] from 4. Treatment of 5 with lead tetraacetate (benzene, reflux, 7 h) yielded the desired cyclic ether 6⁷ [mp 87-88.5 °C (hexane), $[\alpha]_D^{13}$ +35.7° (c 1.45, CHCl₃), 57%^{8b}]. Selective cleavage of the allylic ether linkage in 6 was executed by reaction with acetyl bromide in the presence of CaH₂⁹ (Bu₄NBr, CH₃CN, 40 °C, 4 h) to afford the acetoxy bromide 7⁷ [colorless oil, $[\alpha]_D^{13}$ -62.3° (c 0.8, CHCl₃), 94%¹⁰], desilylation (Bu₄NF, THF, room temp., 1.5 h) of which gave the epoxy olefin 8⁷ [colorless oil, $[\alpha]_D^{12}$ -158° (c 0.53, CHCl₃), 99%^{8b}]. Conversion of 8 into the carbonate 9⁷ [colorless oil, $[\alpha]_D^{12}$ -159° (c 0.38, CHCl₃)] was performed in 89% overall yield^{8c} by alkaline hydrolysis (K₂CO₃, MeOH, 0 °C, 3.5 h) and

**5** R₁=OH, R₂=H**7** R₁=Br, R₂=OCOCH₃**6****8** R=COCH₃**9** R=CO₂CH₂CCl₃**10** X=H₂, R=CO₂CH₂CCl₃**11** X=O, R=CO₂CH₂CCl₃

subsequent esterification (ClCO₂CH₂CCl₃, Py, room temp., 1.5 h). Epoxidation of **9** with peroxytrifluoroacetic acid (Na₂HPO₄·12H₂O, CH₂Cl₂, 35 °C, 4 h) yielded the desired bisepoxide **10**⁷⁾ [colorless oil, [α]_D¹⁸ -107° (c 0.56, CHCl₃), 43%^{8c}]. Oxidation of **10** with ruthenium tetroxide (RuCl₃-NaIO₄, pH 7 phosphate buffer-CH₃CN-CCl₄, 40 °C, 24 h)¹¹⁾ gave 2,2,2-trichloroethoxycarbonyl α-bromotutin (**11**)⁷⁾ [colorless oil, [α]_D¹⁹ -124° (c 0.6, CHCl₃), 73%^{8c}], the spectral (IR, ¹H NMR and mass), optical and chromatographical properties of which were identical with those of the authentic sample¹²⁾ derived from natural tutin (**1**) in all respects. Finally, reduction of **11** with zinc powder (NH₄Cl, EtOH, reflux, 1.5 h) provided (+)-tutin (**1**) [mp 204-205 °C (hexane-CHCl₃), mmp 203-205 °C, [α]_D¹⁷ +13.9° (c 0.75, MeOH), 99%^{8d}].¹³⁾ The spectral (IR, ¹H NMR and mass), physical (mp and [α]_D) and chromatographical properties of synthetic **1** were completely identical with those of natural tutin (**1**) in all respects.

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- Satisfactory spectral (IR, ¹H NMR and mass spectra) and analytical (microanalysis or high resolution mass spectra) data were obtained for this compound.
- Yield after purification by preparative TLC with; (a) 1:4 hexane-ether; (b) 3:1 benzene-EtOAc; (c) 1:1 hexane-EtOAc; (d) 4:1 CHCl₃-EtOAc.
- When this reaction was carried out in the absence of CaH₂, the yield of the desired **7** was dramatically decreased owing to the formation of the undesired products.
- Yield after purification by column chromatography on silica gel with 20:1 benzene-EtOAc.
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- Prepared from natural **1** by the following procedure: (1) ClCO₂CH₂CCl₃, Py; (2) NBS, THF; (3) separation of the resulting epimeric mixture at C-8 with preparative TLC.
- Physical properties of natural tutin (**1**): mp 204-205 °C (hexane-CHCl₃); [α]_D¹⁶ +14.1° (c 1.1, MeOH).

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