Selective Total Synthesis of (±)-α- and γ-Polypodatetraene

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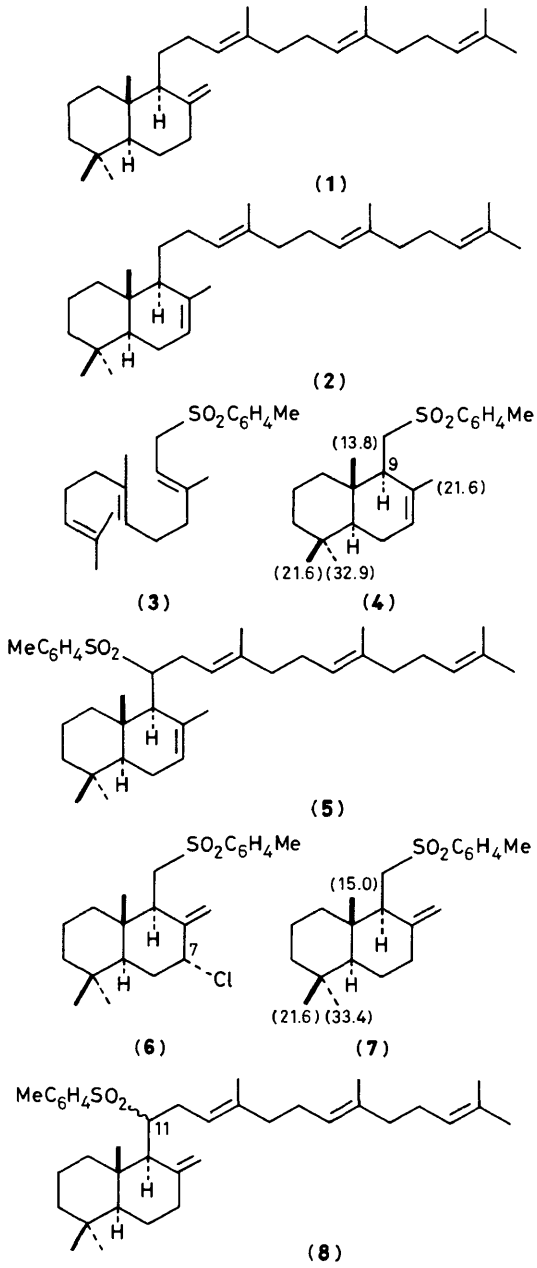
The fern metabolites, α- and γ-polypodatetraene, possible biosynthetic intermediates of onocerane type triterpenoids, are selectively synthesized by mercury(II) trifluoromethanesulphonate–amine complex-induced olefin cyclization followed by simple chemical transformations.

The isolation of the oily triterpene hydrocarbons, α- and γ-polypodatetraene [(**1**) and (**2**), respectively], from species of Polypodaceous and Aspidiaceous ferns has recently been reported by Ageta and his co-workers.[1] These compounds are regarded as the first biosynthetic intermediates of onocerane type triterpenes. Described herein is the simple selective total synthesis of these novel triterpenes by mercury(II) trifluoromethanesulphonate–amine complex-induced olefin cyclization, developed in this laboratory,[2] followed by alkylation. The major cyclization product (**4**) of the farnesyl sulphone (**3**) was effectively transformed into the *exo*-olefin (**7**), and the bicyclic sulphones (**4**) and (**7**) were smoothly converted into (**2**) and (**1**), respectively.

(*E,E*)-Farnesyl bromide was quantitatively transformed

into the sulphone (**3**) by the treatment with toluene-*p*-sulphinate in the presence of 0.05 equiv. of tetrabutylammonium bromide in tetrahydrofuran (THF) at room temperature for 10 h.[3] The cyclization of (**3**) was achieved by exposure to the mercury(II) trifluoromethanesulphonate–*N*,*N*-dimethylaniline complex (1.2 equiv., −20 °C, 2 h) in nitromethane, giving the bicyclic products (**4**) (74%) and (**7**) (5%) after treatment with aqueous NaCl and subsequent demercuration with $NaBH_4$ in aqueous NaOH. The stereochemistry of the substitution at C-9 in these products was found to be β by ^{13}C n.m.r. analysis.[4] The major product (**4**) was lithiated with butyl-lithium (2.2 equiv.) in THF–hexamethylphosphoramide (7 : 1) at −78 °C[5] and the resulting lithio-derivative was treated with (*E*,*E*)-farnesyl bromide at the same temperature for 30 min to give a single alkylation product (**5**) in 72% yield after silica gel column chromatography. The sulphone (**5**) was smoothly reduced with lithium in ethylamine to give (**2**) in 72% yield. Compound (**2**) was identical to natural γ-polypodatetraene in all respects.[1]



Numbers in parentheses are ^{13}C n.m.r. chemical shifts (δ, p.p.m.) in $CDCl_3$.

When the bicyclic sulphone (**4**) was treated with hypochlorous acid according to Wolinsky's procedure [$Ca(OCl)_2$, CO_2,CH_2Cl_2–H_2O, 10 °C, 30 min],[6] the 7α-chlorinated derivative (**6**) was obtained in 76% yield together with the 7β-chloro-isomer (20%). The 7α-chloro product (**6**) was smoothly converted into the required olefin (**7**) in 80% yield (Zn–AcOH–THF, room temp., 10 h) together with some of the starting material (**4**) (16%). In contrast, the 7β-chloro derivative resisted reductive dechlorination under the same conditions, probably owing to stereoelectronic effects.[7] The *exo*-olefin (**7**) was then converted into the alkylation product (**8**), by the procedure described above, in 71% yield. Compound (**8**) exists as a diastereoisomeric mixture at the newly formed chiral centre (C-11). Subsequent reduction (Li–ethylamine) of both diastereoisomers afforded (**1**) in 76% yield. This product was identical to natural α-polypodatetraene.[1]

We thank Professor H. Ageta of Shôwa College of Pharmaceutical Sciences for valuable results prior to publication and spectra of α- and γ-polypodatetraene, and Dr. Y. Fujita of Kuraray Co. Ltd. for a generous gift of (*E*,*E*)-farnesol. This work was partly supported by a Grant-in-Aid for Special Project Research from The Ministry of Education, Science and Culture of the Japanese Government.

Received, 19th December 1983; Com. 1671

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