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SYNTHESIS OF PLERAPLYSILLIN-1

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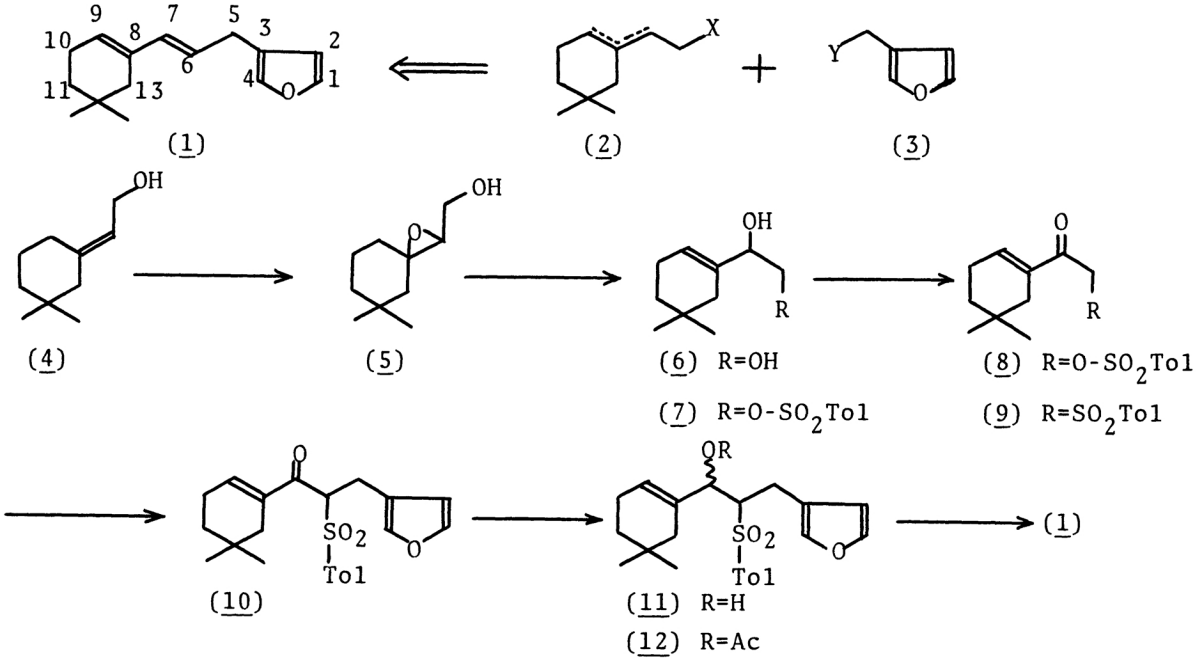
A marine sesquiterpene, pleraplysillin-1 was synthesized by way of coupling of an ochtodane derivative with 3-furfuryl bromide, and regio- and stereoselective olefinations.

Pleraplysillin-1 (1) is a sesquiterpene isolated from a marine sponge, Pleraplysilla spinifera, possessing a unique carbon skeleton which would seem to arise by carbon-carbon cyclization involving a lateral methyl group of the presumed farnesyl precursor and terminal oxidation forming the furan portion.[1] The structural elucidation of (1) has been done by spectral studies of itself and the hydrogenated product.[1] Now we wish to report the first synthesis of the sesquiterpene (1), verifying the structure. At a glance, it is expected that the carbon skeleton of (1) would be constructed by coupling between an ochtodane[2] derivative (2) and a 3-furylmethyl derivative (3). The synthetic problems lie in how to construct the conjugated diene system in the molecule (1) regio- and stereoselectively. We have solved the problems by the combination of devices in which the endocyclic Δ^8-double bond was furnished by the regioselective epoxide-ring opening of β,γ-epoxy alcohol (5) assisted by $Ti(O\text{-}CH(CH_3)_2)_4$ and formation of the trans Δ^6-double bond was achieved by the reductive treatment of the β-acetoxy sulfone (12).



We have reported recently the stereoselective synthesis of the ochtodane skeleton (4) from myrcene.[3] Effectively utilizing the trans geometry of the allylic alcohol (4), an application of the regioselective epoxide-ring opening developed by Sharpless[4] to the β,γ-epoxy alcohol (5) prepared from (4) would be the method of choice for the preparation of the desirably functionalized cyclohexene (2). Oxidation of (4) with m-Cl-perbenzoic acid (CH_2Cl_2/0°C/1 h) gave the β,γ-epoxy alcohol (5)(91%). Treatment of (5) with 1.2 equiv. of $Ti(O\text{-}CH(CH_3)_2)_4$ in CH_2Cl_2 at 15 °C for 20 h afforded regioselectively the ene-diol (6) in 77% yield. The monotosylate (7) was obtained in 76% yield on treatment of (6) with 1.3 equiv. of p-TsCl (Py./15°C/20 h). After several attempts for the carbon-carbon bond formation with furan derivatives, the coupling of the keto-sulfone (9) with 3-furfuryl bromide (3: Y=Br) proved to proceed excellently constructing the carbon skeleton of (1). Oxidation of (7) with active MnO_2 (CH_2Cl_2/15°C/3 h/86%) providing the keto-tosylate (8) followed by sulfonation of (8) with p-Tol-SO_2Na (DMF/15°C/20 h) furnished the keto-sulfone (9)(82%) as a crystalline compound. A small amount of the contaminating regioisomer as to the endocyclic olefin bond which would be ascribed to the presence of the cis-stereoisomer (ca. 6%) in the starting material (4),[3] and to the undesirable olefination which might take place slightly in the epoxide-ring opening reaction (5→6), was removed by recrystallization from hexane-Et_2O to give homogeneous keto-sulfone (9), mp. 111-113 °C. The carbon-carbon bond formation between (9) and 3-furfuryl bromide (3: Y:Br) proceeded smoothly in the presence of 1.2 equiv. of NaH in DMF-THF(1:1) at 15 °C for 20 h to give the crystalline sulfone (10), mp. 136–140 °C, in 92% yield.

Kocienski reported that treatment either of erythro or threo β-acetoxy-sulfones with sodium amalgam effected reductive elimination to afford exclusively trans olefins.[5] We tried to apply these conditions for the formation of the trans Δ^6-olefinic portion of (1). Reduction of (10) to a diastereomeric mixture of β-hydroxy-sulfone (11) with $NaBH_4$ (EtOH/0°C/30 min) followed by acetylation (Ac_2O/Py./15°C/20 h) afforded the β-acetoxy-sulfone (12) in nearly quantitative yield. Unfortunately, application of Kocienski's conditions (5% Na-Hg/MeOH/AcOEt/-20°C/2.5 h) to (12) resulted in preponderant formation of the β-hydroxy-sulfone (11) with a small amount of the conjugated diene (1)(7%) which was contaminated with Δ^6-cis olefin to some extent (ca. 20%) in HPLC[6] and ^1H NMR analyses. The desired reductive elimination producing (1) was accomplished by treatment of (12) with Na and EtOH in THF at -78 °C for 1 h in 65% yield. Analysis by HPLC using silica gel impregnated with $AgNO_3$(5%)[6] and ^1H NMR proved the product containing ca. 11% of the cis-isomer. Usual column chromatography of the product on the same absorbent afforded the pure trans olefin (1) as an oil, which was identical with authentic pleraplysillin-1 (1) in the spectral comparison.[1]

References

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