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SYNTHESIS OF PLERAPLYSILLIN-1

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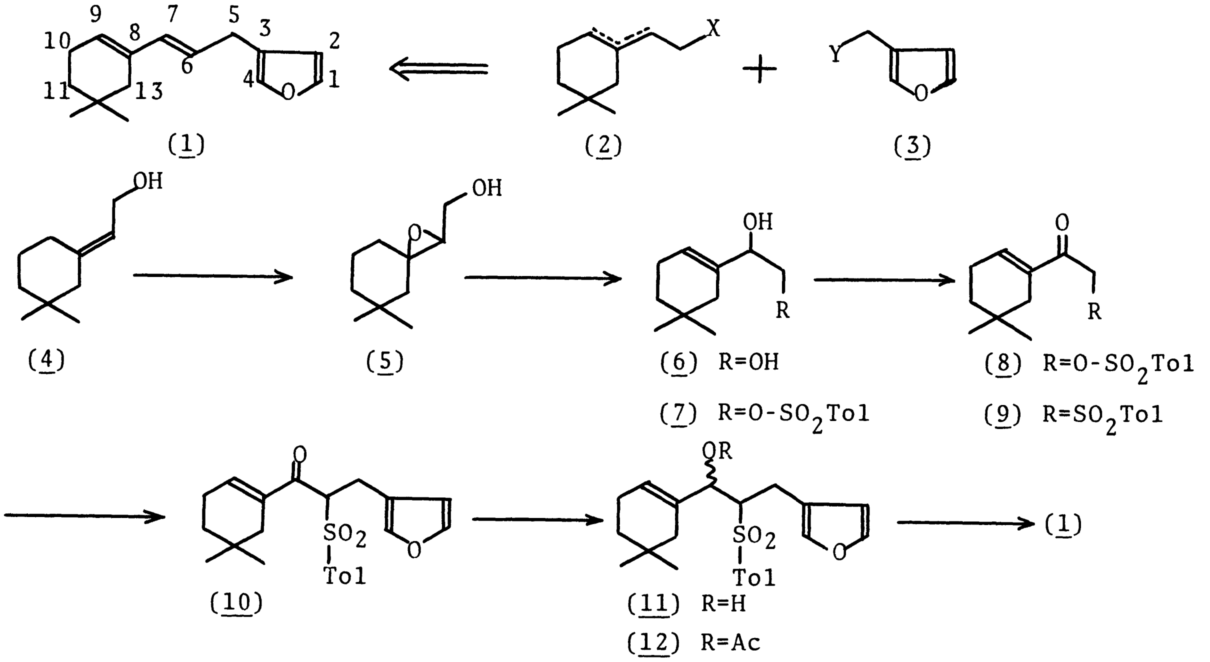
A marine sesquiterpene, pleraplysillin-1 was synthesized by way of coupling of an ochtodane derivative with 3-furfuryl bromide, and regio- and stereoselective olefinations.

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 $Ti(O-CH(CH_3)_2)_4$ and formation of the trans Δ^6-double bond was achieved by the reductive treatment of the β-acetoxy sulfone (12).



(1) (2) (3)

(4) (5) (6) R=OH (8) $R=O-SO_2Tol$

(7) $R=O-SO_2Tol$ (9) $R=SO_2Tol$

(10) (11) R=H

(12) R=Ac

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 $Ti(O-CH(CH_3)_2)_4$ 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

1) G. Cimino, S. De Stefano, L. Minale, and E. Trivellone, Tetrahedron, 28, 4761 (1972). 2) The carbon framework, 1,1-dimethyl-3-ethylcyclohexane was named ochtodane by Fenical: V.J. Paul, O.J. McConnell, and W. Fenical, J. Org. Chem., 45, 3401 (1980). 3) Y. Masaki, K. Hashimoto, K. Sakuma, and K. Kaji, Tetrahedron Lett., 23, 1481 (1982). 4) D.J. Morgans,Jr., K.B. Sharpless, and S.G. Traynor, J. Am. Chem. Soc., 103, 462 (1981). 5) P.J. Kocienski, B. Lythgoe, and S. Ruston, J. Chem. Soc. Perkin I, 1978, 829. 6) The $AgNO_3$-impregnated silica gel for HPLC was prepared by drying the slurry of LiChrosorb Si 60 (MERCK)(10g.) and $AgNO_3$(0.5g.) in 40ml. of water at 100-110°C for 20 h, and HPLC was performed by elution with hexane.

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