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NEW OCHTODANE SYNTHESES FROM MYRCENE

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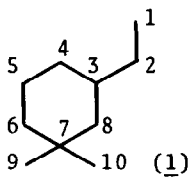
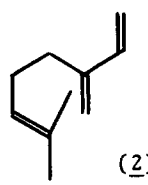
Summary: The ochtodane skeleton is formed stereoselectively from myrcene via acid-catalyzed cyclization of the benzenesulfenyl chloride adduct and the epoxide in a biogenetic type fashion. Its application to the syntheses of two ochtodane-type monoterpenes, an aldehyde component of the boll weevil pheromone and a diol found in the red alga Ochtodes crockeri, is reported.

Red seaweeds (Rhodophyta) of the genera Chondrococcus and Ochtodes (Rhizophyllidaceae) are known to contain a group of polyhalogenated and/or oxygenated cyclic monoterpenes possessing a ring system of 1,1-dimethyl-3-ethylcyclohexane (1) which is named ochtodane.[1] Interestingly, the same carbon skeleton has been found also in the pheromone of the insect, boll weevil.[2] These terpenes have been suggested to be the metabolites from myrcene (2) via the corresponding oxygenated or halogenated intermediates in organisms.[3]



(1)


(2)

Among the syntheses of the ochtodane-type monoterpenes,[4] attention has been focused on the biogenetic type cyclizations[4b,c] of acyclic monoterpenes including myrcene (2). In this paper we present new biogenetic type and stereoselective cyclizations of myrcene (2) assisted by sulfur or oxygen via the benzenesulfenyl chloride adduct (3) or the epoxide (9) effectively affording the functionalized ochtodane skeleton (1).

Myrcene (2) was treated with an equimolar amount of benzenesulfenyl chloride in CH_2Cl_2 at -20 °C to give the adduct (3).[5] The desired cyclization was achieved by the treatment of the crude adduct (3) with 0.2 equiv. $SnCl_4$ in CH_2Cl_2 at -78 °C for 30 min to furnish the chloride (4), which without purification was acetoxylated (NaOAc/DMF/60 °C/20 h) to give the acetate (5) in 48% overall yield from (2). The E/Z-ratio of the acetate (5) was tentatively estimated as 85:15 by its ^{1}H NMR analysis of two pairs of gem-dimethyl signals which appeared at δ 0.92, 1.14 (major) and 0.92, 1.18 (minor), and finally confirmed by ^{1}H NMR analysis of the

aldehyde (8) derived from (5), vide infra. Alkaline hydrolysis (3% NaOH/EtOH/ 15°C/20 h) of (5) followed by the Birch's reduction of the alcohol (6) with lithium in liq. NH_3 provided the desulfurized alcohol (7) in 65% overall yield from (5). Oxidation of the alcohol (7) with active manganese dioxide (n-hexane/ 0°C/30 min) gave the aldehyde (8) (85%), which is a component of the male boll weevil pheromone.[2] The E/Z-ratio of the aldehyde (8) was determined as 85:15 by ^1H NMR analysis; the diagnostic allylic C-8 methylene protons of each component were clearly observed as singlet at δ 2.05 (major) and 2.47 (minor) which were assigned to that of E- and Z-component respectively.[4b)]

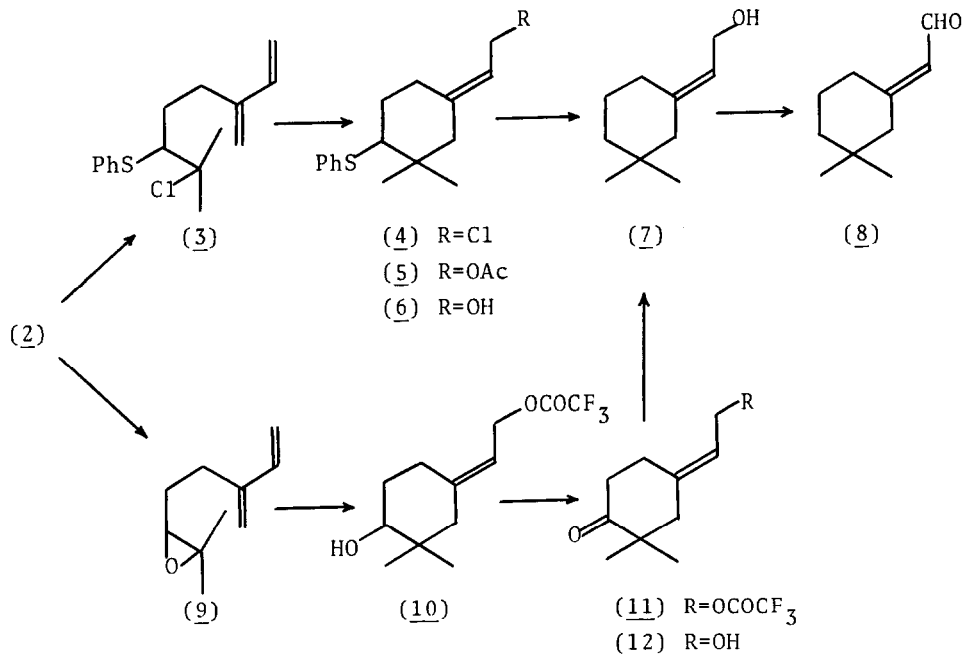


Table Cyclization Reaction[a] of Myrcene Derivatives (3) and (9)

Substrate	Acid	Reaction Temp. (°C)	Product	Yield (%)	E:Z-Ratio
(3)	0.2 equiv. $SnCl_4$	0	(5)[b]	56	59:41
		-20		58	75:25
		-78		48	85:15
(9)	5.0 equiv. CF_3CO_2H	-5	(10)	53	83:17
		-20		54	87:13
		-78		43	94:6

[a] Reactions were conducted in CH_2Cl_2 for 30 min.

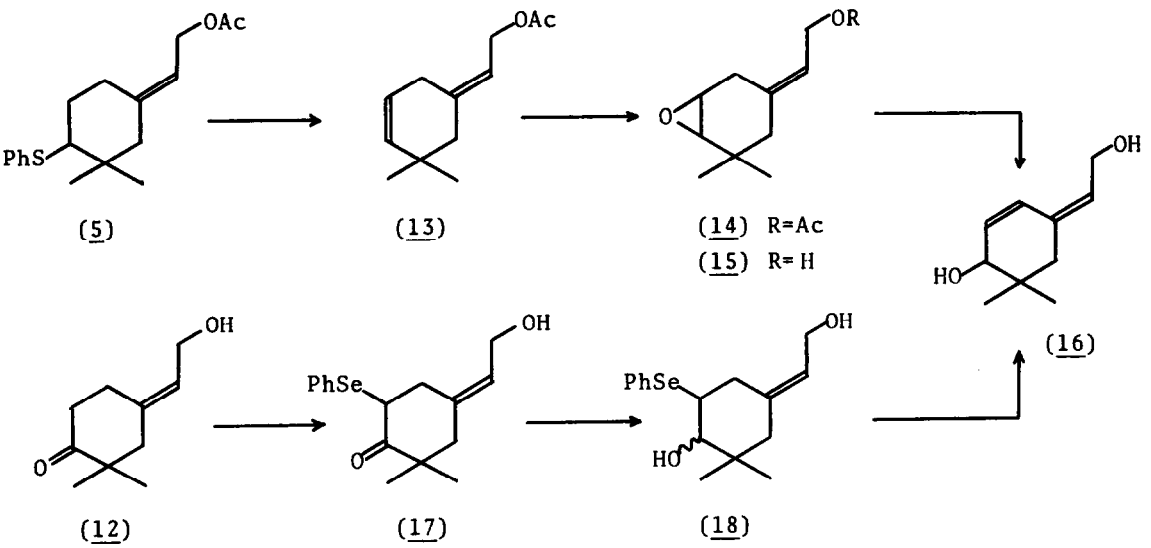
[b] The primary product (4) was not isolated and directly led to (5).

Analogous cyclization was realized on treatment of myrcene epoxide (9) with trifluoroacetic acid (5 equiv.) in CH_2Cl_2 at -78°C for 30 min to give the trifluoroacetate (10) in 54% yield. Oxidation of (10) with pyridinium chlorochromate (CH_2Cl_2/15°C/2 h) gave the ketone (11) (87%) which was observed to contain a minor amount of Z-component (E:Z=94:6) by ^1H NMR analysis; the gem-dimethyl signals of each component appeared at δ 1.05 (major) and 1.08 (minor) as singlet respectively. The structure and the E/Z-ratio were verified by conversion of (11) to the aldehyde (8) via deoxygenation of the derivative (12). Thus the ketone (11) was hydrolyzed (3% NaOH/EtOH/15°C/10 min) to give the ketol (12) (92%). Deoxygenation was carried out by reduction of the corresponding tosylhydrazone prepared quantitatively from (12) with $NaBH_4$ (MeOH/65°C/2 h) to give the alcohol (7) (65%).

It should be worth noting that the stereoselectivity of the concomitant formation of double bond in the present cyclization reactions was dependent upon the reaction temperature. As shown in the Table, the lower reaction temperature resulted in the formation of the E-component in higher proportion.

Ochtodanes (5) and (12) thus obtained were utilized for synthesis of a diol component (16) isolated from the red alga Ochtodes crockeri.[1] Oxidation of (5) with 30% aqueous H_2O_2 (AcOH/15°C/20 h) followed by heating the sulfoxide with $NaHCO_3$ in xylene at 140°C for 4 h gave the diene acetate (13) (79%). Selective epoxidation was carried out by m-chloroperbenzoic acid (CH_2Cl_2/$NaHCO_3$/-20°C/3 h) to lead to the epoxyacetate (14) in 59% yield. After alkaline hydrolysis (3% NaOH/15°C/20 h) of (14), the epoxyalcohol (15) was treated with 2.5 equiv. lithium diisopropylamide (LDA) in THF at -78 ~ -20°C for 2 h to furnish the diol (16)[6] in 73% yield. The diol (16) was also obtained from the ketol (12). The dianion of the ketol (12) prepared in THF with 2.5 equiv. LDA at -78 ~ 0°C for 1 h, was selenylated on treatment with diphenyldiselenide at 0 ~ 15°C for 1 h to give the seleno-ketol (17) (70%). Reduction of (17) with $LiAlH_4$ (Et_2O/-20 ~ 15°C/2 h/76%) followed by elimination of benzeneselenenic acid on treatment of the seleno-diol (18) with $NaIO_4$ in MeOH-H_2O (3:1) at 15°C for 7 h afforded the diol (16) (55%).

The products in the present cyclization possess the functional groups on the C-6 position of the ochtodane skeleton (1) and are claimed to be the promising intermediates for the syntheses not only of various natural ochtodane-type monoterpenes but also of pleraplysillin-1,[7] an unique sesquiterpene in which structurally ochtodane is coupled at the C-1 position with furfuryl moiety.



(5) (13) (14) R=Ac (15) R=H (16)

(12) (17) (18)

References and notes

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6) Nmr spectrum was completely identical to that reported (ref. 1). We have observed a kinetic stereoselection of Z-epoxyalcohol in the base-catalyzed epoxide opening reaction [(15) ⟶ (16)]: the reaction of (15) (Z:E=85:15) under the described condition gave pure Z-diol (16) and a small amount of recovery (less than 10%) of the starting epoxyalcohol which was consisted mainly of the E-isomer.

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