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Sulfuric Acid-Catalyzed Cyclization of Germacrene-D to Eudesmane-4,6-diol Cyclic Sulfate

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Reaction of germacrene-D with sulfuric acid afforded a eudesmane-4,6-diol cyclic sulfate (**1**). The structure of **1** was determined by spectral analysis and chemical correlations.

Keywords——sesquiterpene; germacrene-D; eudesmane; cyclic sulfuric acid ester; cyclization; *Torilis japonica*; ^{1}H-NMR; ^{13}C-NMR

To facilitate the discussion, we present first the historical background of this work. In 1935, during work on the constituents of the fruits of *Torilis japonica* (HOUTT.) D.C., Kariyone and Majima[1] reported that a main sesquiterpene, named 'torilen,' gave an equimolar adduct of sulfuric acid, named 'torilensulfat' having the molecular formula, $C_{15}H_{24} \cdot H_2SO_4$, which afforded 'torilenhydrat,' $C_{15}H_{26}O$, on saponification with alcoholic KOH. However, the structure of torilen, torilensulfat and torilenhydrat were never solved.

In the course of our continuing work on *Torilis* species, which elaborate a number of sesquiterpenes,[2] germacrene-D has been isolated as a main sesquiterpene, and we found that germacrene-D (**1**) formed a sulfuric acid adduct, having the same molecular formula as torilensulfat, under the condition, reported by Kariyone and Majima.[1] Therefore, we assumed that torilen and torilensulfat are germacrene-D (**1**) and its sulfuric acid adduct (**2**), respectively, and the structure of **2** was clarified as follows.

Germacrene-D (**1**)[3] is considered to be a key intermediate for biosynthesis of several sesquiterpenes. Acid- or base-catalyzed reaction of germacrene-D and/or epoxygermacrene-D gives bi- or tricyclic sesquiterpenes, *e.g.* cadinanes, eudesmanes and oppositanes.[4] In this paper, we present the formation of an eudesmane-4,6-diol cyclic sulfate (**2**) from germacrene-D catalyzed by sulfuric acid.

Germacrene-D (**1**) was dropped into an ice-cooled mixture of ether and sulfuric acid, and the resulting precipitate was recrystallized from hexane–benzene to obtain compound **2** as colorless crystals having the molecular formula, $C_{15}H_{26}O_4S$, corresponding to an equimolar adduct of sulfuric acid and germacrene-D. The strong infrared (IR) absorption bands at 1395 and 1205 cm^{-1} showed the presence of sulfuric ester, but no other absorption due to hydroxyl, carbonyl or double bond was observed. In the proton nuclear magnetic resonance (^{1}H-NMR), four methyl signals at δ 0.89 (d, $J=7$ Hz), 0.89 (s), 0.95 (d, $J=7$ Hz) and 1.75 (s), and a pair of proton signals coupled to each other at δ 1.96 (1H, d, $J=11$ Hz) and 4.74 (1H, t, $J=11$ Hz) were seen. In the carbon-13 nuclear magnetic resonance (^{13}C-NMR), the signals due to four methyls, five methylenes, four methines and two quaternary carbons were observed. Among them, two signals at δ 82.99 (d), and 93.86 (s) were considered to be the carbons attached to the sulfuric ester group. These data suggested compound **2** to be an intramolecular cyclic sulfate of a bicyclic sesquiterpene, eudesmane.

Ester ring cleavage of **2** by KOH–EtOH afforded compound **3**, corresponding to

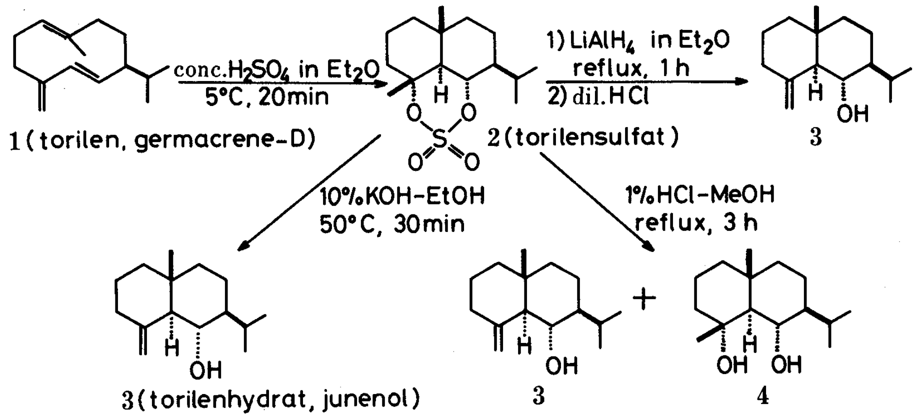


Chart 1

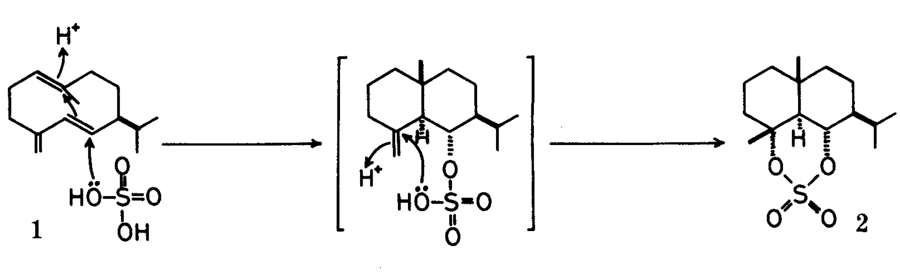
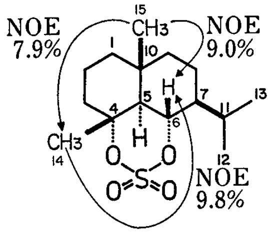


Chart 2



NOEs (%) in 1D-NOE experiments

Chart 3

torilenhydrat, which was identified as junenol.[5] The ester was also cleaved by 1% HCl to give **3** and **4**; the structure of **4** has also been reported by Niwa and co-workers[5] (Chart 1). The structure of **2** was deduced to be eudesmane cyclic sulfate linked at C4 and C6, and the reaction mechanism may be explained as shown in Chart 2.

The relative configuration of **2** was established as follows. As nuclear Overhauser effects (NOEs) were observed among protons on C6, C14 and C15, as shown in Chart 3, the C14-methyl configuration was concluded to be β-axial. Reduction of **2** with $LiAlH_4$ also afforded **3**. Since the attack of a hydride ion of $LiAlH_4$ at the S atom occurs with retention of the C6 configuration,[6] the hydroxyl group at C6 is α-equatorial. Accordingly, the structure of **2** was solved as shown in Chart 1.

Experimental

All melting points are uncorrected. Spectral data were obtained with the following machines: IR on a JASCO A-302, mass spectra (MS) on a Hitachi M-80, ^{1}H-NMR and ^{13}C-NMR on a Bruker AM-400.

Preparation of Germacrene-D(1)——Germacrene-D(1) was obtained from oil of *Solidago altissima* L. by the procedure reported by Niwa and co-workers, $[\alpha]_D$: $-111.0°$ ($c=0.53$, MeOH).[7]

Reaction of 1 with Sulfuric Acid——Compound **1** (10.0 g) was added dropwise to a solution of ether (8 ml) and sulfuric acid (3 ml) at 0 °C and allowed to react for 20 min. The resulting pale yellow precipitate was recrystallized from hexane–benzene to afford **2** (450 mg) as colorless plates; mp 144—147 °C[7]. $[\alpha]_D$: -23.0 °C ($c=0.1$, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{26}O_4S$: C, 59.57; H, 8.67; S, 10.67. Found: C, 59.34; H, 8.71; S, 10.31. MS *m/z* (%): 222 (M^+-80, 10), 204 (67), 161 (100), 105 (45), 81 (50). IR ν_{max}^{KBr} cm^{-1}: 3400, 2880, 1465, 1372, 1195, 1150. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, d, $J=7$ Hz), 0.89 (3H, s), 0.95 (3H, d, $J=7$ Hz), 1.75 (3H, s), 1.96 (1H, d, $J=11$ Hz), 2.14 (1H, d of septet, $J=2.5$, 7 Hz), 4.74 (1H, t, $J=11$ Hz). ^{13}C-NMR ($CDCl_3$) δ: 16.56 (q), 18.71 (t), 19.60 (q), 19.69 (t), 20.54 (q), 21.88 (q), 25.92 (d), 36.33 (s), 39.94 (t), 40.43 (t), 42.87 (t). 47.95 (d), 51.18 (d), 82.99 (d), 93.86 (s).

Reaction of 2 with Alcoholic KOH——A solution of **2** (400 mg) in 10% alcoholic KOH (15 ml) was reacted for 30 min at 50 °C. The reaction mixture was neutralized with 2 N HCl to pH 4.0 and partitioned between Et_2O and H_2O. The Et_2O layer was dried ($MgSO_4$) and evaporated. The crude product was recrystallized from hexane–AcOEt to give **3** (228.5 mg), mp 79—81 °C,[7] whose spectral data were identical with those of junenol.[5]

Reaction of 2 with HCl——A solution of **2** (51 mg) in a mixture of 1 N HCl (10 ml) and MeOH (10 ml) was refluxed for 3 h. The reaction mixture was neutralized with 1 N KOH to pH 5.0 and partitioned between H_2O and Et_2O. The Et_2O layer was dried ($MgSO_4$) and evaporated, and the residue was separated by high performance liquid chromatography (benzene : EtOAc (65 : 35)) to afford junenol (**3**) (17.8 mg) and **4** (13.0 mg), mp 144.0—146.0 °C (hexane–AcOEt), whose spectral data were identical with those of authentic specimens.

$LiAlH_4$ Reduction of 2——$LiAlH_4$ (10 mg) was added to a solution of **2** (53 mg) in ether (30 ml) and the mixture was refluxed for 1 h. The usual work-up of the reaction mixture afforded **3** (44.7 mg).

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References and Notes

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7) M. Niwa, M. Iguchi and S. Yamamura, *Chem. Pharm. Bull.*, **28**, 997 (1980); S. Fujita, Abstracts of Papers, The 27th Symposium on the Chemistry of Terpenes, Essential Oils and Aromatics, Nagasaki, October 1983, p. 40; Natural germacrene-D has usually been isolated in an optically impure state from many plants; (−)- and (+)-germacrene-D co-occur in different ratios in various plants. The optical rotation of pure (−)-germacrene-D was estimated to be −305°. Therefore germacrene-D and its derivatives in this paper are not optically pure and we can not employ on the values of optical rotation and the melting points for identification of the compounds. Incidentally, the melting point of **2**, 144.0—147.0 °C, was coincident with that of torilensulfat, 145 °C, reported by Kariyone and Majima.[1]