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Absolute Stereochemistry of Cacalol

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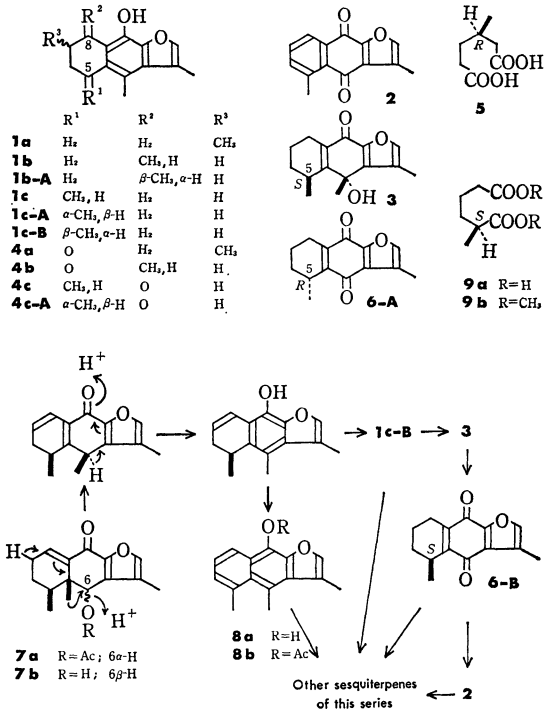
Synopsis. Descriptions on the absolute configuration at C-5 of cacalol have been confused. Ozonolysis of cacalol afforded (*S*)-(+)-2-methylhexanedioic acid. The asymmetric center at C-5 of cacalol, cacalone, and of sesquiterpenes related to these compounds was therefore established to be (*S*)-configuration.

Since cacalol and cacalone were isolated from *Cacalia decomposita* A. Gray,[1] a number of sesquiterpenes related to these compounds have been isolated from plants of the genus *Cacalia*.[2–7] Among these sesquiterpenes, cacalone,[1] maturinone,[2–8] and decompostin[3,9,10] have been chemically correlated with cacalol. Through a series of revisions (**1a**,[1] **1b**,[8] and **1c**), the structure of cacalol was established to be 5,6,7,8-tetrahydro-3,4,5-trimethylnaphtho[2,3-*b*]furan-9-ol (**1c**)[9,11–15] by unambiguous syntheses of maturinone (**2**)[9,11–13] and (±)-cacalol (**1c**).[12,14,15] Based on conversion of cacalol into cacalone,[16,17] a *p*-quinol structure (**3**)[16–18] was recently shown for cacalone, and previously presented formulas (**4a**,[1] **4b**,[8] and **4c**[9,11,13]) were excluded.

Descriptions on the absolute configuration at C-5 hitherto reported for cacalol have been confused. In the present paper, we wish to report evidence leading to a (5*S*)-configuration for cacalol (**1c-B**).

In early studies on cacalol and cacalone, a stereostructure (**1b-A**) with 8β-methyl group was proposed for cacalol because of the formation of (*R*)-(+)-β-methyladipic acid [**5**; (*R*)-(+)-3-methylhexanedioic acid] on ozonolysis of cacalol.[8] However, the formation of **5** from cacalol can not be explained by the present structure (**1c**) for cacalol. The stereostructures (**1c-A**, **4c-A**, and **6A**) with (5*R*)-configuration were then suggested[19] for cacalol, cacalone, and for a nor-*p*-quinone,[1,7,20] respectively, based on an interpretation of their anomalous ORD curves by means of the presence of inherently dissymmetric chromophores.[19] This result[19] seems to be inconvincing, as the reference compounds cited therein[19] are inadequate for the arguments, and the structure of cacalone was later revised from **4c** to **3**.[16,17]

Decompostin is a natural eremophilane derivertive coexisting with cacalol, cacalone, and maturinone in *C. decomposita*.[3] Biogenetic considerations that cacalol and its related compounds are derived from sesquiterpenes of eremophilane type such as decompostin have been proposed.[13,21] As an absolute configuration of decompostin was determined to be **7a**,[3,22] the biogenetic pathway is shown as in Scheme 1, suggesting a (5*S*)-configuration for cacalol (**1c**) and for its related sesquiterpenes (**3**, **6**, *etc.*).[20] It was reported that deacetyl-6-epidecompostin (**7b**)[9] [or its mesylate[10]] was converted chemically into naphthofuran derivertive (**8b**)[9,10] which was derived from cacalol.[1] However, no information on the stereochemistry at C-5 of cacalol can be



Scheme 1.

drawn from the above result, as **8b** bears no asymmetric center. Therefore, the ozonolysis of cacalol (**1c**) was reexamined.

Cacalol was ozonized in acetic acid and treated successively with hydrogen peroxide and with palladium on charcoal. The major component of acidic products was shown to be 2-methylhexanedioic acid by PMR examination. Purification of the acid fraction using an ion-exchange resin column and then by recrystallization gave (*S*)-(+)-2-methylhexanedioic acid (**9a**),[23,24] mp 76.5—77.5 °C, $[\alpha]_D$ +12° (EtOH), whose IR ($CHCl_3$) and PMR ($CDCl_3$) spectra were found to be identical with those of authentic (±)-**9a** prepared from 2-methyl-1-cyclohexanone. This led to a (5*S*)-configuration for cacalol and for its related sesquiterpenes in accordance with the biogenetic considerations (Scheme 1).

Experimental

Melting points were determined on a Mel-temp capillary melting point apparatus (Laboratory Devices) and are uncorrected. IR and UV spectra were measured on a Hitachi EPI-G2 spectrometer and a Hitachi EPS-3 spectrometer, respectively. Optical rotations were measured on a JASCO DIP-SL polarimeter. Mass spectra were taken on a Hitachi RMU-6-Tokugata mass spectrometer operating at 70 eV. PMR spectra were taken on a Hitachi R-20 spectrometer using TMS as internal standard. For column chromatography

Wakogel C-200 (Wako Pure Chem. Ind.) was used.

*Isolation of Cacalol (**1c-B**).* Cacalol was isolated from *Cacalia delphiniifolia* Sieb. et Zucc. according to the descriptions reported by Naya *et al.*[7] Crystallization from ether–hexane gave pure cacalol (**1c-B**), mp 92—93 °C (lit,[1] 92—94 °C), $[\alpha]_D^{24}$ +6° (*c* 1.0, $CHCl_3$) [lit,[1] +10° ($CHCl_3$)]. For an identification purpose, this natural product was acetylated (acetic anhydride, pyridine, at room temperature) to give cacalol acetate, mp 104—105 °C (lit,[1] 103—104 °C; lit,[7] 103.5—104.5 °C), $[\alpha]_D^{20}$ −10° (*c* 1.0, $CHCl_3$) [lit,[1] −9° ($CHCl_3$); lit,[7] −96.5° ($CHCl_3$)[25]]. Spectral data (IR, UV, and PMR) of cacalol and of its acetate were identical with the reported values.[1]

*Ozonolysis of Cacalol (**1c-B**).* Oxygen containing ozone (*ca.* 3%) was passed through the solution of cacalol (500 mg) in acetic acid (20 ml) at room temperature for 12 h. To this solution was added 30% hydrogen peroxide (2.5 ml), and the mixture was stirred at room temperature for 2 h and then at 60 °C for 2.5 h. After addition of water (10 ml) and 10% palladium–charcoal (100 mg), the reaction mixture was stirred at room temperature for 17 h to complete decomposition of the peracid. The catalyst was filtered off and the solution was evaporated to give an oil, which was dissolved in ether, washed with saturated aqueous sodium chloride solution, and extracted with 5% sodium hydrogencarbonate. The aqueous layer was acidified (pH 1) with concentrated hydrochloric acid and extracted with ether. The ethereal solution was dried over anhydrous sodium sulfate and evaporated to give an oil (174 mg). This oil was shown to consist mainly of 2-methylhexanedioic acid by PMR ($CDCl_3$) examination [δ 1.21 (3H, d, J=7 Hz), 1.70 (4H, m), 2.42 (3H, m), and 9.41 (2H, br s)]. The oil was dissolved in water (2 ml), neutralized with 1 M sodium hydroxide, and chromatographed on an Amberlite IR-120 cation exchange resin column (50 g; elution with water). Several fractions gave crystals [$[\alpha]_D^{20}$ +18° (*c* 0.5, EtOH)] on removal of water. These were combined and recrystallized from ether–hexane to afford (*S*)-(+)-2-methylhexanedioic acid (**9a**), mp 76.5—77.5 °C (lit,[23] 81—83 °C; lit,[24] 81—82 °C), $[\alpha]_D^{25}$ +12° (*c* 0.2, EtOH) [lit,[23] +13.8° (*c* 1.91, EtOH); lit,[24] −13.4° (*c* 2.15, EtOH)]; IR ($CHCl_3$) 3100, 2940, 2890, and 1700 cm^{-1}; PMR ($CDCl_3$) δ 1.20 (3H, d, J=7 Hz), 1.68 (4H, m), 2.36 (3H, m), and 8.9 (2H, br s) [lit,[24] PMR ($CDCl_3$) δ 1.22 (3H, d, J=7 Hz), 1.67 (4H, m), 2.38 (3H, m), and 11.6 (2H, s)]. The IR and PMR spectra were identical with those [IR ($CHCl_3$) and PMR ($CDCl_3$)] of authentic (±)-2-methylhexanedioic acid, respectively.

The acid (**9a**) was treated with diazomethane in ether to give a dimethyl ester (**9b**), an oil, IR (neat) 2960, 1735, 1435, and 1165 cm^{-1}; PMR (CCl_4) δ 1.15 (3H, d, J=7 Hz), *ca.* 1.5 (4H, m), 2.23 (3H, m), and 3.62 (6H, s) [lit,[26] PMR (CCl_4) δ 1.13 (3H, d, J=7 Hz), 1.57 (4H, m), *ca.* 2.30 (1H, m), 2.25 (2H, m), and 3.62 (6H, s)]; mass spectrum *m/e* 157 [$(M-OCH_3)^+$], *m/e* 129 [$(M-CO_2CH_3)^+$], *m/e* 128, *m/e* 88, and *m/e* 74. The IR, PMR, and mass spectra were found to be identical with those [IR (neat), PMR (CCl_4), and mass spectra)] of authentic dimethyl (±)-2-methylhexanedioate, respectively.

(±)-2-Methylhexanedioic Acid from 2-Methyl-1-cyclohexanone. 2-Formyl-6-methyl-1-cyclohexanone was prepared from 2-methyl-1-cyclohexanone according to the procedures described by Dallacker *et al.*[27] The formylated ketone in acetone was oxidized with potassium permanganate in a usual manner to give (±)-2-methylhexanedioic acid [(±)-**9a**].[28] This acid was esterified with diazomethane in ether to afford dimethyl (±)-2-methylhexanedioate [(±)-**9b**].[26]

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