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SYNROTOLIDE, AN α-PYRONE FROM *SYNCOLOSTEMON ROTUNDIFOLIUS*

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Key Word Index—*Syncolostemon rotundifolius*; *S. densiflorus*; Lamiaceae; α-pyrone; synrotolide; crystal structure.

Abstract—The structure of synrotolide, a new α-pyrone isolated from *Syncolostemon rotundifolius*, has been established as 6*R*-[3*R*,6*S*-(diacetyloxy)-4*R*,5*S*-(dihydroxy)-1-heptenyl]-5,6-dihydro-2H-pyran-2-one. Oleanolic acid is the major component of both *S. rotundifolius* and *S. densiflorus*.

INTRODUCTION

In continuation of our phytochemical studies of plants belonging to the Lamiaceae (formerly Labiatae), we have examined *Syncolostemon*, a Southern African genus of nine species [1], which has not been investigated before.

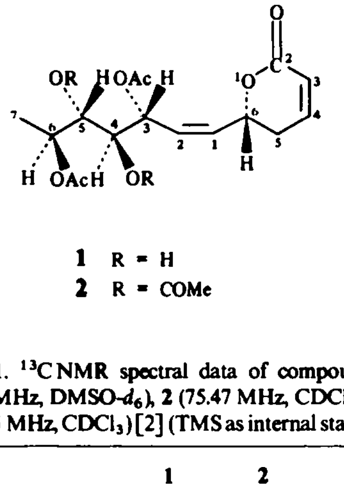
RESULTS AND DISCUSSION

The leaves and stems of two species, *S. rotundifolius* and *S. densiflorus*, have been examined. In addition to large amounts of oleanolic acid, we isolated from *S. rotundifolius* in 0.8 % yield a new α-pyrone, synrotolide (1), $C_{16}H_{22}O_8$, mp 168–170°, $[\alpha]_D^{24} - 29°$. The presence of an α,β-unsaturated δ-lactone was shown by the UV (λ_{max} 210 nm, log ε 4.013) and IR (ν_{max} 1710 and 1695 cm^{-1}) spectra. It also showed hydroxyl absorption at 3365 cm^{-1}, gave a positive test for a 1,2-diol and on acetylation formed a diacetate (2), mp 102–103°. The ^{1}H NMR spectrum indicated the presence of a secondary methyl group (δ 1.1), two acetoxy groups (δ 1.98 and 2.00), one methylene group (δ 2.4), four olefinic protons (3H complex at δ 5-6 and a *cis* 1H multiplet at 7.05, $J = 10$ Hz) and two hydroxyl protons at δ 3.3 and 3.5.

The ^{13}C NMR spectrum assisted by off-resonance and selective noise decoupling techniques indicated that one secondary methyl (δ 13), one methylene (δ 30), five oxymethine (δ 69–74), four olefinic (δ 120–147) and three carbonyl (δ 163–169) carbon atoms were present. This evidence suggested that synrotolide is a 6-substituted α-pyrone related to umuravumbolide (3) and deacetylumuravumbolide (4) isolated from *Iboza riparia* [2] and hyptolide (5) obtained from *Hyptis pectinata* [3]. Both plants belong to the Lamiaceae.

The ^{13}C NMR spectra of compounds 1, 2 and 3 are compared in Table 1. The proton signals of 2 were assigned by a COSY experiment [4]. These ^{1}H shifts were then used in a two-dimensional heteronuclear ^{1}H–^{13}C correlation experiment [5] to assign and confirm the otherwise ambiguous ^{13}C shifts.

As in the case of compound 3 [2], the mass spectrum of 1 showed no $[M]^+$. The only major peak was the base peak at m/z 43; no other peak exceeded 20 % on this peak's intensity. The most useful information came from the peaks at m/z 196, 97 and 68, which were interpreted as arising from a McLafferty-type rearrangement (Fig. 1). This placed one acetoxy group at C-3 in the side-chain and hence limited the 1,2-diol structure of synrotolide to two possibilities, with the second acetoxy group at either C-4



1 R = H
2 R = COMe

Table 1. ^{13}C NMR spectral data of compounds 1 (75.54 MHz, DMSO-d_6), 2 (75.47 MHz, $CDCl_3$) and 3 (25.15 MHz, $CDCl_3$) [2] (TMS as internal standard)

C	1	2	3
2	163.2	163.28	163.37
3	120.1	121.50	121.73
4	147.0	144.31	144.15
5	29.3	29.53	30.09
6	74.1	73.65	74.07
1 (side-chain)	132.9	132.96	131.72
2 (side-chain)	126.7	126.28	130.12
3	69.9	67.63	69.45
4	71.7*	71.50	34.32
5	71.6*	71.03	27.60
6	71.0	68.52	22.47
7	12.9	14.03	13.88

*Assignments interchangeable.

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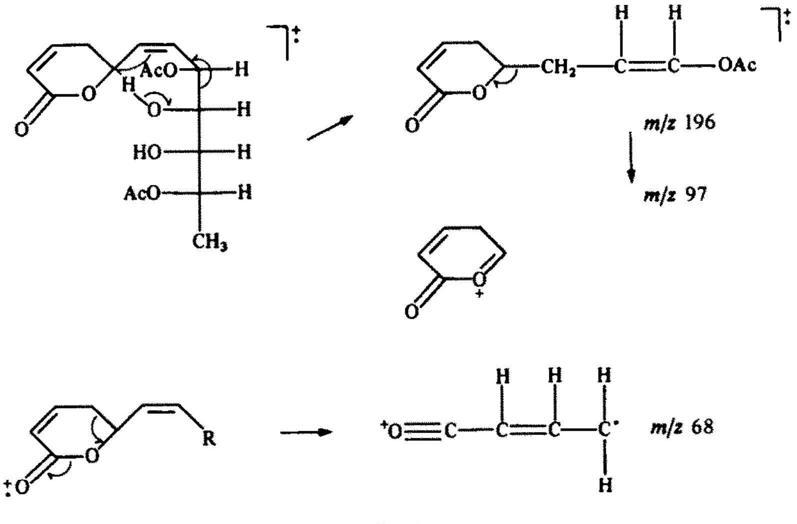
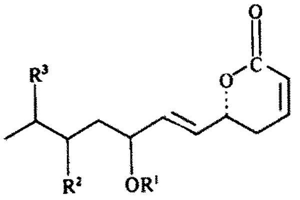


Fig. 1.

or C-6. In order to settle this uncertainty and also to determine the stereochemistry, an X-ray analysis was carried out. A stereoscopic drawing of synrotolide is shown in Fig. 2.

The double bond in the side-chain is *cis*, a result which is at variance with the *trans* structures proposed for compounds 3, 4 and 5 on the basis of their IR absorptions at 965 cm^{-1}. Synrotolide also has an absorption band at 950 cm^{-1} but this absorption is clearly not definitive for a *trans*-double bond in these instances and compounds 3–5 possibly also possess *cis* structures.

The absolute configuration of compound **1** was determined as follows. Reductive ozonolysis in acetic acid yielded two products which were separated by paper chromatography. The major product was saponified with aqueous trifluoroacetic acid to afford 6-deoxyallose, identified by GC comparison with the peracetylated aldononitrile derivative [6] of an authentic sample, thus providing chemical proof of the stereochemical structure of the acyclic portion of compound **1**. Glycosides formed from D- and L-monosaccharides and a chiral alcohol are diastereomeric and can be separated by GC of a suitable derivative [7]. Accordingly, the absolute configuration of the 6-deoxyallose derived from synrotolide (**1**) followed from conversion to the acetylated 2(−)-octyl glycoside and GC comparision with the acetylated 2(−)-octyl glycoside and 2(±)-octyl glycosides of 6-deoxy-D-allose. This method established an L-configuration for the derived 6-deoxyallose. Figure 2 corresponds to the absolute configuration of **1**.



3 R^1 = COMe, R^2 = R^3 = H
4 R^1 = R^2 = R^3 = H
5 R^1 = COMe, R^2 = R^3 = OCOMe

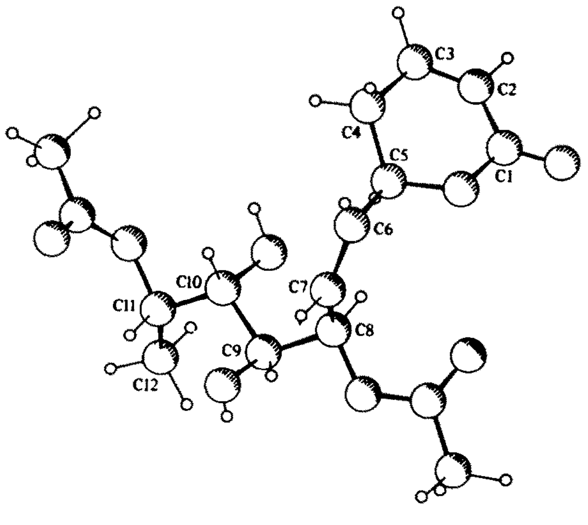


Fig. 2. A perspective view of the molecular structure of synrotolide.

EXPERIMENTAL

All GC experiments were performed with a Durabond fused silica capillary column coated with DB 225 and using an FID detector. Oven temp. 225°, injector temp. 250°; detector temp. 250°, He carrier at 1.5 ml/min, split ratio 1:63, injection volume 1 μl.

S. rotundifolius (Albany Museum, Grahamstown, Voucher No. A7335) was collected near Margate, Natal in June 1984, and *S. densiflorus* (Albany Museum, Voucher No. A7340) was collected near East London in May 1984.

Isolation. Air-dried leaves of *S. rotundifolius* (2.28 kg) were soaked in Me_2CO (80 l) for 4 days. The soln was concentrated by flash distillation, decolourized with activated charcoal (BDH) and filtered through a celite pad. The remaining Me_2CO was removed *in vacuo* to give a tan-coloured brittle solid (216 g). This solid (40 g) was chromatographed on silica gel (Merck No. 7734) (350 g) and eluted with hexane–EtOAc. The fractions eluted with hexane–EtOAc (5:2) yielded 5.8 g of crude oleanolic acid as the major component. The fractions eluted with hexane–EtOAc (1:2) showed four spots on TLC. The major component, compound **1**, (1.2 g) crystallized from EtOAc–hexane (3:1). Chromatography of the mother liquors on silica gel (Merck No. 9385) yielded a further 2.1 g **1**. Recrystallization of **1** from EtOAc gave colourless prisms, mp 168–170°; $[\alpha]_D^{24} -29°$ (MeOH; *c* 0.06); UV λ_{max}^{MeOH} nm: 208 (log ε 4.013); IR ν_{max}^{KBr} cm^{-1}: 3365 (OH), 1740 (ester carbonyl), 1710 (sh) 1695 (α,β-unsaturated δ-lactone), 1375, 1230, 1025, 950; EIMS (70 eV) *m/z* (rel. int.): No $[M]^+$, 196 (6), 165 (6), 154 (14), 136 (16), 135 (14), 107 (14), 97 (10), 91 (6), 81 (19), 68 (17), 43 (100); ^{1}H NMR (300 MHz, DMSO-d_6): δ1.08 (3H, *d*, $J_{6,1} = 6.5$ Hz, H-7 side-chain), 1.97 (3H, *s*, acetyl), 2.01 (3H, *s*, acetyl), 2.39 (2H, *m*, H-5,5′ ring), 3.28 (1H, *m*, H-4 side-chain), 3.49 (1H, *m*, H-5 side-chain), 5.01 (1H, *td*, H-6 side-chain), 5.05 (1H, *d*, $J = 6$ Hz, OH), 5.31 (1H, *m*, H-6 ring), 5.39 (1H, *d*, $J = 6$ Hz, OH), 5.60 (1H, *dd*, $J_{2,3} = 9$ Hz, H-3 side-chain), 5.72 (1H, *dd*, $J_{1,2} = 11$ Hz, H-2 side-chain), 5.82 (1H, *dd*, $J_{2,1} = 11$ Hz, H-1 side-chain), 5.97 (1H, *m*, $J_{4,3} = 10$ Hz, H-3 ring), 7.05 (1H, *m*, $J_{3,4} = 10$ Hz, H-4 ring). (Found: C, 56.06; H, 6.50. $C_{16}H_{22}O_8$ requires: C, 56.14; H, 6.48%.)

Acetylation of compound 1. Ac_2O–pyridine treatment of **1** overnight at room temp. gave **2**, mp 102–103° (EtOH); $[\alpha]_D^{24} -11°$ ($CHCl_3$; *c* 0.09); UV λ_{max}^{MeOH} nm: 208 (log ε 4.002); IR ν_{max}^{KBr} cm^{-1}: 1745, 1728 (sh), 1375, 1230, 1210, 1015, 960; EIMS (70 eV) *m/z* (rel. int.): 426 $[M]^+$ (0.8), 225 (8), 196 (16), 195 (15), 165 (49), 154 (39), 153 (100), 137 (43), 136 (100), 135 (100), 129 (100), 119 (26), 118 (47), 117 (21), 110 (24), 109 (23), 108 (61), 107 (100), 97 (48), 91 (26), 87 (21), 81 (85), 77 (21), 68 (100), 43 (100); ^{1}H NMR (500 MHz, $CDCl_3$): δ1.18 (3H, *d*, $J_{6,7} = 6.7$ Hz, H-7 side-chain), 1.97, 2.02, 2.04, 2.05 (4 × 3H, 4*s*, acetyl), 2.39 (2H, *m*, H-5,5′ ring), 5.07 (1H, *d* × *q*, $J_{5,6} = J_{7,6} = 6.7$ Hz, H-6 side-chain), 5.14 (1H, *dd*, $J_{5,4} = J_{3,4} = 6.7$ Hz, H-4 side-chain), 5.21 (1H, *dd*, $J_{6,5} = J_{4,5} = 6.7$ Hz, H-5 side-chain), 5.27 (1H, *ddd*, $J_{1,6} = 8.3$ Hz, H-6 ring), 5.61 (1H, *dd*, $J_{1,2} = 11.1$, $J_{3,2} = 9.6$ Hz, H-2 side-chain), 5.66 (1H, *dd*, $J_{2,3} = 9.6$, $J_{4,3} = 6.7$ Hz, H-3 side-chain), 5.81 (1H, *dd*, $J_{6,1} = 8.3$, $J_{1,2} = 11.1$ Hz, H-1 side-chain), 6.01 (1H, *ddd*, $J_{4,3} = 9.9$ Hz, H-3 ring), 6.85 (1H, *ddd*, $J_{3,4} = 9.9$ Hz, H-4 ring). (Found: C, 56.15; H, 6.16. $C_{20}H_{26}O_{10}$ requires: C, 56.33; H, 6.15%.)

Ozonolysis of compound 1. An excess of ozone was passed at 10° through a solution of **1** (150 mg) in HOAc (6 ml). Excess ozone was removed by stirring for 2 hr with dimethyl sulphide (0.4 ml). The soln was evaporated *in vacuo* to afford a pale yellow syrup. The two ozonolysis products were separated by preparative PC in EtOAc–HOAc–HCOOH–H_2O (18:3:1:4) soln. The section containing the side-chain residue was extracted with H_2O and the soln freeze-dried to afford 60 mg of a light brown solid which was hydrolysed by refluxing for 2 hr with 2 ml 1 M trifluoroacetic acid soln. Evaporation of the soln *in vacuo* gave 51 mg of a brown syrup, of which 3 mg was converted [6] to the peracetylated aldononitrile derivative. The product was compared by GC with the same derivative of 6-deoxyallose. An R_t of 6.22 min was obtained with both compounds.

The absolute stereochemistry of the derived 6-deoxyallose. The peracetylated 2(−)-octyl glycoside of 2 mg of an authentic sample of 6-deoxy-D-allose was prepared [7]. GC under the conditions stated (oven temp. 230°) gave three peaks, R_t 8.78, 9.26 and 9.53 min. The peracetylated 2(±)-octyl glycoside was similarly prepared and GC afforded 7 peaks, R_t 8.16, 8.34, 8.78, 9.24, 9.43, 9.53 and 10.09 min. The peracetylated 2(−)-octyl glycoside prepared from 3 mg of the crude 6-deoxyallose obtained from ozonolysis of **1** gave on GC four peaks, R_t 8.16, 8.35, 9.45 and 10.12 min, thus establishing an L-configuration for the derived 6-deoxyallose.

X-Ray crystallography. The crystallographic data for **1**, $C_{16}H_{22}O_8$, were collected on an Enraf-Nonius CAD-4F diffractometer. The space group was found to be $P2_12_12_1$ with cell constants $a = 8.858$ (3) Å, $b = 8.977$ (2) Å, $c = 21.741$ (3) Å, $z = 4$. The intensities of 1775 reflections were measured using graphite monochromated MoKα radiation. MULTAN was used to solve the structure and the refinement on *F* was carried out by full matrix least-squares analysis. The final *R* and R_w values were 0.1317 and 0.1083, respectively, for 1269 reflections and 153 least-squares variables with $|F_0| > \delta(F_0)$. The final *R* value based on 755 reflections with $|F_0| > 5\delta(F_0)$ was 0.0747 but the variable/parameter ratio was unacceptably low. The atomic coordinates are available on request from the Director of the Cambridge Crystallographic Data Centre.

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