Regioselective Total Synthesis of Furoventalene, a Marine Natural Benzofuran, via the β-Vinylbutenolide Annulation

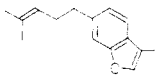
Fusao Kido,[1] Yoshihiro Noda,[1] Takao Maruyama,[1] Chizuko Kabuto,[2] and Akira Yoshikoshi*[1]

Chemical Research Institute of Non-Aqueous Solutions and Department of Chemistry, Tohoku University, Sendai 980, Japan

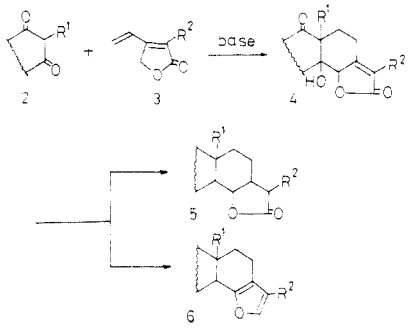
Received May 19, 1981

The framework of furoventalene (1) was regioselectively constructed from methyl 2-formyl-6-methyl-5-heptenoate (12) and 2,5-dihydro-3-methyl-4-vinyl-2-furanone (10) by consecutive 1,6 conjugate addition and aldol-type cyclization to lead to a diastereomeric mixture of bicyclic butenolides **13a** and **13b**. Both of the annulation products were transformed into 1 by a sequence of reactions: reduction, hydrolysis, dehydrative decarboxylation, and dehydrogenation via intermediates **14–16**. The stereochemistry of the annulation products **13a** and **13b** is also discussed.

Furoventalene (1) is an irregular isoprenoid benzofuran isolated from the sea fan *Gorgonia ventalina*.[3] This compound was first synthesized by Weinheimer and Washecheck in a nonregioselective manner.[3]



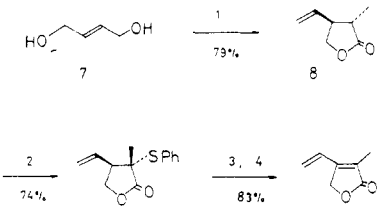
Recently, the new annulation reaction of 1,3-dicarbonyl compound **2** with β-vinylbutenolide (**3**), which is shown by the following equation (**2** + **3** → **4**), has been developed



in this laboratory.[4,5] Transformation of the annulated butenolide **4** into butyrolactone **5** and furan **6** would be feasible by conventional means, and oxacyclic structures in compounds **4–6** have frequently been found in natural products. The usefulness of this annulation reaction in natural product synthesis was recently illustrated by the total synthesis of frullanolide, an allergenic eudesmanolide, which was reported from this laboratory.[5] In this paper we describe the regioselective total synthesis of furoventalene (1), which exemplified a utility of our annulation in natural furanoid synthesis.[6]

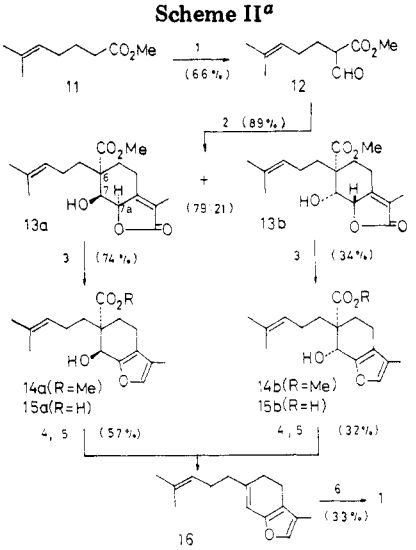
The requisite reagent α-methyl-β-vinylbutenolide (**10**) was prepared in good overall yield as shown in Scheme I. By employing reaction conditions analogous to those reported for β-vinylbutyrolactone,[7] a neat mixture of (*E*)-2-butene-1,4-diol (**7**) and ethyl orthopropionate was heated in the presence of a catalytic quantity of hydroquinone to give α-methyl-β-vinylbutyrolactone (**8**), and the product was then sulfenylated[8] to afford **9**. Although we have not attempted to obtain evidence for the stereochemical assignment of the substituents on the lactone rings in **8** and **9**, these lactones seemed to be homogeneous spectroscopically (^{1}H NMR) and chromatographically (TLC), and their stereochemistry would most likely be as depicted. Peracid oxidation of **9** followed by heating of the resulting

Scheme I[a]



[a] (1) EtC(OEt)$_3$, hydroquinone; (2) *i*-Pr$_2$NLi, Ph$_2$S$_2$, HMPA, THF; (3) MCPBA, CH$_2$Cl$_2$; (4) Δ, PhMe.

Scheme II[a]



[a] (1) *i*-Pr$_2$NLi, HCO$_2$Et, THF; (2) **10**, KF, Me$_2$SO; (3) *i*-Bu$_2$AlH and C$_6$H$_{14}$ and then aqueous H$_2$SO$_4$; (4) KOH, MeOH; (5) Me$_2$NCH(OMe)$_2$, CHCl$_3$; (6) DDQ, PhH.

(1) Chemical Research Institute of Non-Aqueous Solutions.
(2) Department of Chemistry.
(3) Weinheimer, A. J.; Washecheck, P. H. *Tetrahedron Lett.* **1969**, 3315.
(4) Kido, F.; Fujishita, T.; Tsutsumi, K.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1975**, 337.
(5) Kido, F.; Tsutsumi, K.; Maruta, R.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1979**, *101*, 6420.
(6) An interesting lactone annulation complementary to our approach has recently been developed: Schultz, A. G.; Godfrey, J. D. *J. Am. Chem. Soc.* **1980**, *102*, 2414 and references cited.
(7) Kondo, K.; Mori, F. *Chem. Lett.* **1974**, 741.
(8) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

0022-3263/81/1946-4264$01.25/0

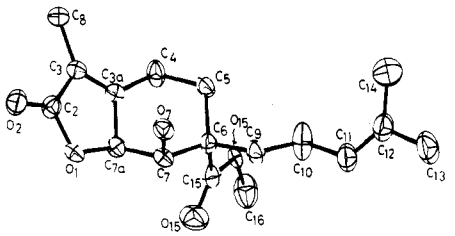
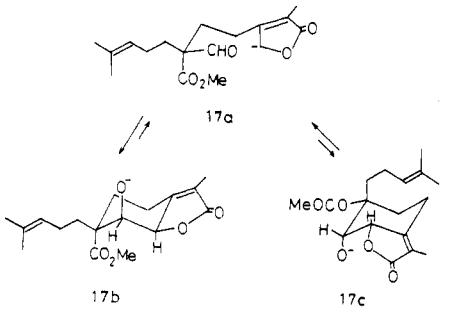


Figure 1. ORTEP drawing of the molecular structure of (**13a**). Hydrogen atoms are omitted for clarity. The ellipsoids of thermal motion for atoms are scaled to enclose 35% probability.

crude sulfoxide in toluene yielded the reagent **10**. Since this compound slowly changed into a polymeric substance on being allowed to stand, it was used in the next reaction immediately after purification.

The dicarbonyl compound **12** required for the key step in this synthesis was readily obtained as the enol form by formylation of the methyl ester of 6-methyl-5-heptenoic acid[9] with ethyl formate (Scheme II). When the formyl ester **12** was treated with the butenolide **10** in Me_2SO at room temperature in the presence of KF, the annulation product was obtained as a diastereomeric mixture in excellent yield. The mixture was separated by chromatography to give **13a** and **13b** (79:21) as crystalline compounds. In the ^1H NMR spectra of these butenolides possessing rigid structures, their C(7) protons (δ 4.58 and 4.47, respectively) were observed as triplets, which on addition of D_2O collapsed into doublets with coupling constants of 4 Hz. This fact demonstrated that these protons were both equatorial and cis to the respective C(7a) protons and that the diastereomers were epimeric with respect to their methoxycarbonyl groups. Since we could obtain no rigorous evidence of the stereochemistry at C(6) by chemical means, the major butenolide **13a** was submitted to X-ray crystallographic analysis, which revealed its crystal structure to be as shown in Figure 1; i.e., the methoxycarbonyl and hydroxyl groups in this compound were trans diaxial.

The predominant formation of **13a** over **13b** may be rationalized as follows; in an equilibrium between naked anions **17b** and **17c** through uncyclized anion **17a**, **17b** is favorable compared with **17c** in which unfavorable dipole repulsion can be anticipated between the negatively charged oxygen atom and methoxycarbonyl group.



Although our initial schedule was to derive hydroxy acids from **13a** and **13b** by selective hydrolysis of their ester groups followed by dehydrative decarboxylation with *N,N*-dimethylformamide dimethyl acetal[10] to lead to lactonic cyclohexadiene derivatives, some attempts failed to give satisfactory results for the selective hydrolysis. We thus turned to reduction of the butenolide rings in these annulation products prior to dehydrative decarboxylation.

The butenolide **13a** was treated with diisobutylaluminum hydride followed by acidic workup to afford furano ester **14a**, which was then hydrolyzed with alkali to afford hydroxy acid **15a**. The reaction with *N,N*-dimethylformamide dimethyl acetal produced dihydrobenzofuran **16** at room temperature in good overall yield from the ester **14a**. On the other hand, the minor butenolide **13b** was also transformed into **16** in a similar manner.

To complete our synthesis, **16** was dehydrogenated with DDQ at room temperature and the product was identified as furoventalene (**1**) by spectroscopic comparison (IR and ^1H NMR).

Experimental Section

Melting points were determined with a MRK melting point apparatus, Model No. 78, and are uncorrected. IR spectra were recorded on a JASCO A-3 spectrophotometer in $CHCl_3$. ^1H NMR spectra were recorded on a JEOL C-60HL (60 MHz) or JEOL PS-100 (100 MHz) instrument in $CDCl_3$, unless otherwise stated. Coupling constants (J) are given in hertz. Solvent systems that developed the major products in a moderate R_f range (0.4–0.6) are described for preparative, silica gel, thin-layer chromatography.

2,3,4,5-Tetrahydro-3-methyl-2-oxo-4-vinylfuran (8). A stirred mixture of (*E*)-2-butene-1,4-diol (2.0 g, 23 mmol), ethyl orthopropionate (8.0 g, 45 mmol), and hydroquinone (0.2 g) was heated at 140–150 °C for 14 h under continuous removal of ethanol by using a distillation apparatus. Fractional distillation [bp 75 °C (11 mmHg)] of the reaction mixture afforded **8**: 2.29 g (79%); IR 1777, 1647, 1174, 1012, 930 cm^{-1}; ^1H NMR[11] 1.26 (d, 3 H, J = 7), 2.41 (qd, 1 H, J = 11, 7), 2.84 (ddd, 2 H, J = 11, 9.5, 8), 3.98 (t, 1 H, J = 9.5), 4.47 (q, 1 H, J = 8, 9.5), 5.28–6.04 (ABX m, 3 H). Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.26; H, 8.15.

2,3,4,5-Tetrahydro-3-methyl-2-oxo-3-(phenylthio)-4-vinylfuran (9). To a stirred solution of LDA prepared from *n*-BuLi (3.82 mmol) in hexane and diisopropylamine (386 mg, 3.82 mmol) in THF was added dropwise a solution of **8** (400 mg, 3.17 mmol) in THF (2.4 mL) over a period of 7 min at −78 °C. After being gradually warmed to −50 °C over 1 h, the enolate solution was quenched with a solution of diphenyl disulfide (1.04 g, 4.77 mmol) and HMPA (850 mg, 4.75 mmol) in THF (2.5 mL). The mixture was stirred at 0 °C for 3 h and then acidified with dilute HCl. The product was extracted with ether, and the extract was washed with water and saturated brine and dried. Removal of the solvent left an oil (1.245 g), which was purified by silica gel column chromatography. CH_2Cl_2 eluted **9** (589 mg, 74%) as crystals: mp 52 °C (recrystallized from petroleum ether); IR 1770, 1642, 1586 cm^{-1}; ^1H NMR 1.35 (s, 3 H), 3.03 (br q, 1 H, J = 13.5, 6), 4.05 (q, 1 H, J = 5.5, 9), 4.45 (q, 1 H, J = 7, 9), 5.03–6.08 (ABX m, 3 H), 7.50 (m, 5 H). Anal. Calcd for $C_{13}H_{14}O_2S$: C, 66.64; H, 6.02; S, 13.68. Found: C, 66.88; H, 6.33; S, 13.42.

2,5-Dihydro-3-methyl-2-oxo-4-vinylfuran (10). To a stirred solution of **9** (180 mg, 0.77 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise a solution of MCPBA (assay 80%; 168 mg, 0.78 mmol) in the same solvent (2 mL) in an ice bath. After being stirred at the same temperature for 40 min, the mixture was filtered, and the filtrate was washed successively with aqueous K_2CO_3, water, and brine and then dried. The crude product obtained by evaporation was dissolved in toluene (3 mL) containing pyridine (2 drops) and heated at 110–115 °C for 1 h. The solvent was removed, and the residue was purified by TLC (CH_2Cl_2 as solvent) to give **10**: 79 mg (83%); IR 1753, 1664, 1600, 1082, 934 cm^{-1}; ^1H NMR[11] 1.94 (t, 3 H, J = 2), 4.90 (m, 2 H), 5.48–6.92 (ABX m, 3 H). No analytically pure sample was obtained owing to its instability.

Methyl 2-Formyl-6-methyl-5-heptenoate (12). 6-Methyl-5-heptenoic acid[6] was esterified with a slight excess of ethereal diazomethane in a conventional manner, and the product was distilled [bp 84–86 °C (31 mmHg)] to give **11** quantitatively: IR

(9) Mori, K.; Matsui, M. *Tetrahedron* **1969**, *25*, 5013.
(10) Hara, S.; Taguchi, T.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1975**, 1545. See also: Rittimann, A.; Wick, A.; Eschenmoser, A. *Helv. Chim. Acta* **1975**, *58*, 1450. Mulzer, J.; Brüntrup, G. *Tetrahdedron Lett.* **1979**, *21*, 1909. Fráter, G. *Helv. Chim. Acta* **1979**, *62*, 2825.

(11) Measured at 100 MHz.

1730, 906 cm^{-1}; ^1H NMR 1.58 (br s, 3 H), 1.68 (br s, 3 H), 3.63 (s, 3 H), 5.07 (m, 1 H).

A solution of **11** (468 mg, 3 mmol) in THF (1 mL) was added dropwise to a solution of LDA prepared from *n*-BuLi (4 mmol) in hexane and diisopropylamine (0.67 mL) in THF (8 mL) at −78 °C. The mixture was warmed to −50 °C over 1 h, and ethyl formate (370 mg, 5 mmol) was then added. After being stirred for an additional 1 h at the same temperature, the mixture was diluted with water and extracted with ether. The aqueous layer was acidified with dilute HCl at 0 °C and extracted with CH_2Cl_2. The extract was washed with water and brine and dried. Removal of the solvent afforded an oil (414 mg), which was distilled [bp 115–120 °C (bath temperature; 15 mmHg)] to give pure **12**: 366 mg (66%); IR 3400, 1725, 1667, 1601 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.08; H, 9.03.

2,4,5,6,7aα-Hexahydro-7β-hydroxy-6β-(methoxycarbonyl)-3-methyl-6α-(4-methyl-3-pentenyl)-2-oxo-1-benzofuran (13a) and Its C(6) Epimer (13b). To a stirred suspension of KF (238 mg, 4.1 mmol) and **12** (1.25 g, 6.8 mmol) in dry Me_2SO (18 mL) was added dropwise a solution of **10** (422 mg, 3.4 mmol) in the same solvent (5 mL) at room temperature. After being stirred overnight at the same temperature, the mixture was poured into ice–water and extracted with CH_2Cl_2. The extract was successively washed with aqueous K_2CO_3, water, and brine and dried. Removal of the solvent left crystals, which were separated by silica gel column chromatography. CH_2Cl_2–ether (5:1) eluted **13a** [736 mg (70%); mp 133–134 °C (recrystallized from ether–petroleum ether)] first and then **13b**: 194 mg (19%); mp 163–164 °C (recrystallized from petroleum ether–CH_2Cl_2). For **13a**: IR 3400, 1750, 1730, 1692 cm^{-1}; ^1H NMR[11] 1.55 (br s, 3 H), 1.65 (br s, 3 H), 1.79 (br s, 3 H), 3.73 (s, 3 H), 4.58 (t, 1 H, J = 4), 4.85 (br s, 1 H), 5.07 (m, 1 H). For **13b**: IR 3400, 1750, 1690 cm^{-1}; ^1H NMR[11] 1.59 (br s, 3 H), 1.69 (br s, 3 H), 1.82 (br s, 3 H), 3.70 (s, 3 H), 4.47 (t, 1 H, J = 4), 4.84 (br s, 1 H), 5.08 (m, 1 H). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found for **13a**: C, 65.97; H, 7.61. Found for **13b**: C, 66.32; H, 7.80.

4,5,6,7-Tetrahydro-7β-hydroxy-6β-(methoxycarbonyl)-3-methyl-6α-(4-methyl-3-pentenyl)-1-benzofuran (14a) and Its C(6) Epimer (14b). A hexane solution of diisobutylaluminum hydride (0.65 mmol) was added dropwise to a stirred solution of **13a** (100 mg, 0.32 mmol) in THF (2.5 mL) at −25 °C, and stirring was continued for an additional 1 h at −20 to −25 °C under N_2. Dilute H_2SO_4 (2 N, 3 mL) was added at 0 °C, and the mixture was stirred for 45 min at the same temperature. After dilution with water, the product was extracted with CH_2Cl_2, and the extract was washed with water and dried. Evaporation of the solvent afforded an oil, which was purified by TLC [CH_2Cl_2–ether (10:1) as solvent] to give **14a**: 70 mg (74%); IR 3560, 1721 cm^{-1}; ^1H NMR 1.67 (br s, 3 H), 1.76 (br s, 3 H), 1.96 (br s, 3 H), 3.73 (s, 3 H), 5.20 (br s, 1 H), 5.32 (m, 1 H), 7.31 (br s, 1 H).

In a similar manner, **14b** (20 mg, 34%) was obtained from **13b** (62 mg, 0.2 mmol) as an oil: IR 3600, 1732 cm^{-1}; ^1H NMR[11] 1.58 (br s, 3 H), 1.67 (br s, 3 H), 1.94 (br s, 3 H), 3.87 (s, 3 H), 4.70 (br s, 1 H), 5.05 (m, 1 H), 7.16 (br s, 1 H). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found for **14a**: C, 69.72; H, 8.53. Found for **14b**: C, 69.52; H, 8.47.

4,5-Dihydro-3-methyl-6-(4-methyl-3-pentenyl)-1-benzofuran (16). A solution of **14a** (96 mg) in excess 10% methanolic KOH was refluxed for 3 h and then diluted with water. After extraction with ether, the aqueous layer was acidified with 6 N HCl at 0 °C and extracted with CH_2Cl_2. The extract was washed with water and dried. Evaporation gave crude **15a**: 84 mg; IR 3600, ~2600, 1704, 1640 cm^{-1}; ^1H NMR 1.62 (br s, 3 H), 1.68 (br s, 3 H), 1.92 (d, 3 H, J = 1), 5.17 (m, 1 H), 5.03 (s, 1 H), 6.30 (br s, 1 H), 7.18 (br s, 1 H).

A mixture of crude **15a** (77 mg) and *N,N*-dimethylformamide dimethyl acetal (0.24 mL) in $CHCl_3$ (1 mL) was stirred at room temperature for 1 h. After removal of the solvent, the residue was passed through a short silica gel column with hexane to give **16**: 37 mg (57% from **14a**); IR 1092 cm^{-1}; ^1H NMR[11] 1.66 (br s, 3 H), 1.72 (br s, 3 H), 1.98 (br s, 3 H), 5.26 (m, 1 H), 6.22 (br s, 1 H), 7.18 (br s, 1 H). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 82.97; H, 9.46.

The same dihydrobenzofuran **16** (11 mg, 32% from **14b**) was also obtained from **14b** (47 mg) via **15b** by a similar treatment and was identified by IR and ^1H NMR.

Furoventalene (1). A solution of **16** (37 mg, 0.2 mmol) in benzene (0.6 mL) was added dropwise to a stirred solution of DDQ (46 mg, 0.2 mmol) in the same solvent (1.5 mL) at room temperature, and the mixture was further stirred for an additional 1 h at the same temperature. The solvent was removed in vacuo, and the residue was passed through a short silica gel column. Hexane eluted **1** (12 mg, 33%), which was identified with natural furoventalene by comparison of the IR and ^1H NMR spectra of the neat liquid.

The unreported spectral data of **1** in solutions are as follows: IR 1625, 1580, 862, 810 cm^{-1}; ^1H NMR 1.57 (br s, 3 H), 1.68 (br s, 3 H), 2.20 (d, 3 H, J = 1.5), 5.12 (m, 1 H), 6.97–7.47 (m, 4 H).

X-ray Diffraction Analysis of 13a. A suitably cut platelike crystal with the dimensions of 0.10 × 0.20 × 0.30 mm was mounted on a Rigaku Denki four-circle diffractometer for X-ray measurements with Zr-filtered Mo Kα radiation (λ = 0.71079 Å). The crystals belong to the space group $P2_1/c$, and the cell constants refined by the setting angles with $20° < 2\theta < 30°$ are a = 14.679 (2) Å, b = 13.323 (2) Å, c = 8.529 (1) Å, and β = 98.07 (1)°, and ρ_{calcd} = 1.240 g/cm^3 for Z = 4 (M_r = 308.38; $C_{17}H_{24}O_5$). A total of 1869 independent reflections within 2θ = 52° were measured by the 2θ–θ scan method with a scan rate of 4°/min. No significant decrease of intensity was shown in the periodic measurements of three check reflections during the data collection. The intensitites were corrected for the Lorenz and polarization effects but not for the absorption and extinction effects. The structure was solved by the direct method with the program MULTAN78.[12] Approximate coordinates of nonhydrogen atoms were refined by the block-diagonal least-squares method, at first with isotropic and then with anisotropic temperature factors. The hydrogen atoms were calculated in the expected geometry and then verified from the difference Fourier map. The hydroxyl hydrogen atom was found with a significant level, through a somewhat wide spread, of positive electron density toward formation of an intermolecular hydrogen bond.

The successive refinements with all hydrogen atoms converged to give isotropic temperature factors of 2.7 up to 6.0 $Å^2$. The final residual value is 0.09 for the 1756 nonzero reflections. The final difference map contained a few noise peaks of ca. 0.30 e/$Å^3$ with a general level of ±0.20 e/$Å^3$ (see supplementary material for additional crystallographic details).

As shown in the structure (Figure 1), the six-membered ring is in a chair conformation with 1,2-diaxial hydroxyl and methoxycarbonyl groups. Therefore there is no evidence for the intramolecular hydrogen bond between them, which would be possible geometry in a boat conformation. In the crystalline state, the hydroxyl group forms a normal intermolecular hydrogen bond to carbonyl oxygen (O···O, 2.730 Å; O···H, 2.03 Å) on the lactone ring in the adjacent molecule which is related to a center of symmetry.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Cooperative Research A (434027). We thank Professor A. J. Weinheimer for the spectra of furoventalene.

Registry No. **1**, 25074-12-8; **7**, 821-11-4; **8**, 78657-18-8; **9**, 78657-19-9; **10**, 78657-20-2; **11**, 33077-53-1; **12**, 78657-21-3; **13a**, 78657-22-4; **13b**, 78685-06-0; **14a**, 78657-23-5; **14b**, 78657-24-6; **15a**, 78657-25-7; **15b**, 78657-26-8; **16**, 78657-27-9; diphenyl disulfide, 882-33-7; 6-methyl-5-heptenoic acid, 24286-45-1.

Supplementary Material Available: Listings of final atomic coordinates and temperature factors (Table I), estimated standard deviations (Table II), and bond lengths and bond angles (Table III) (3 pages). Ordering information is given on any current masthead page.

(12) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. B*, **1970**, *B26*, 274. Lessinger, L; Margulis, T. N. *Ibid.* **1978**, *34*, 578.