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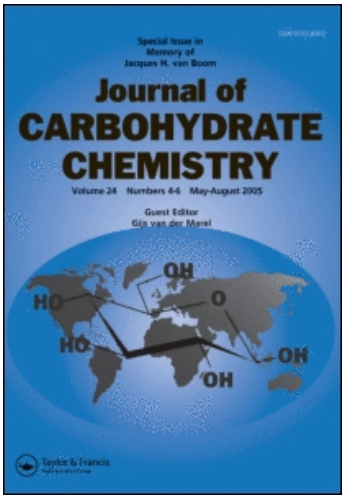

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Synthetic Approach Toward Antibiotic Tunicamycins, 4. X-Ray Crystal Structure Analysis of a Higher-Carbon Nitro Sugar

Tetsuo Suami[a]; Yoshimasa Fukuda[a]; Junji Yamamoto[a]; Yoshihiko Saito[a]; Masatoki Ito[a]; Shigeru Ohba[a]
[a] Department of Applied Chemistry, Faculty of Science and Technology Keio University, Hiyoshi, Yokohama, Japan

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J. CARBOHYDRATE CHEMISTRY, 1(1), 9-19 (1982)

SYNTHETIC APPROACH TOWARD ANTIBIOTIC TUNICAMYCINS, 4.†

X-RAY CRYSTAL STRUCTURE ANALYSIS OF A HIGHER-CARBON NITRO SUGAR

Tetsuo Suami*, Yoshimasa Fukuda, Junji Yamamoto,
Yoshihiko Saito, Masatoki Ito, and Shigeru Ohba

Department of Applied Chemistry
Faculty of Science and Technology
Keio University, Hiyoshi, Yokohama 223, Japan

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ABSTRACT

A higher-carbon carbohydrate, a derivative of undecose has been synthesized by the potassium fluoride-catalyzed addition of a nitro sugar to a sugar aldehyde. The addition of methyl 5-deoxy-2,3-O-isopropylidene-5-nitro-β-D-ribofuranoside to methyl 2-benzyloxycarbonylamino-2-deoxy-3,4-O-isopropylidene-α-D-galactodialdopyranoside-(1,5) yielded a single diastereomer of the nitro undecose derivative. The absolute configuration of two chiral centers of the derivative has been established by the X-ray crystal structure analysis.

INTRODUCTION

Nucleoside antibiotic tunicamycins, produced by a fermentation of *Streptomyces lysosuperficus*,[1] are highly active against tumors in mice.[2] Their common structure consists of uracil, fatty acids, N-acetyl-D-glucosamine and a higher-carbon carbohydrate named tunicamine,[3] as shown in Scheme 1.

† Part 3: reference 6.

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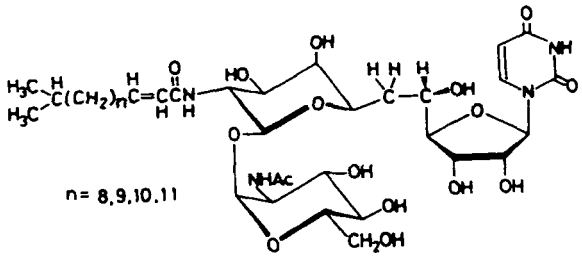
SCHEME 1



As a part of a program directed toward the total synthesis of tunicamycins, we have studied a general method for a synthesis of higher-carbon carbohydrates.[4-6] We have recently developed the facile synthesis of the carbohydrate, an undecose derivative, which is an important, intermediary compound for a synthesis of tunicamine, by the addition of methyl 5-deoxy-2,3-O-isopropylidene-5-nitro-β-D-ribofuranoside (2) to methyl 2-(benzyloxycarbonyl)amino-2-deoxy-3,4-O-isopropylidene-α-D-galactodialdopyranoside-(1,5)[6] (7) in the presence of potassium fluoride as the catalyst.[7] The reaction proceeded smoothly and a single diastereomer of the nitro undecose derivative (8) was obtained in a fairly good yield (61%). The configurations of the newly introduced chiral centers of 8 have been established by means of X-rays.

RESULTS AND DISCUSSION

Treatment of methyl 5-deoxy-5-iodo-2,3-O-isopropylidene-β-D-ribofuranoside[8] (1) with sodium nitrite in N,N-dimethylformamide gave an approximately 10:1 mixture of two products: 2 and the corresponding α-L-lyxofuranoside (3) in a yield of 44%. From the mixture, 2 was isolated as homogeneous crystals in 29% yield by a column chromatography (Scheme 2). During the course of the reaction, an inversion of the configuration on C-4 (from the β-D-ribo to the α-L-lyxo) occurred partially. The fact was rationalized by the base-catalyzed epimerization as shown in Scheme 3. The analogous

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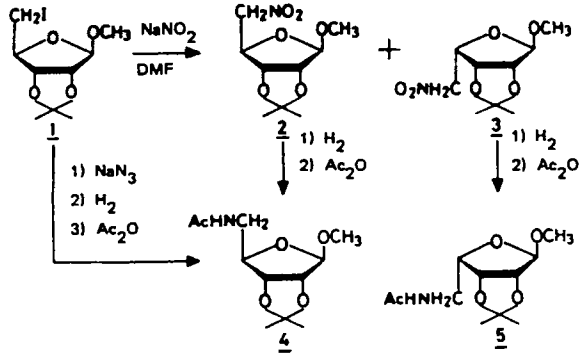
SCHEME 2



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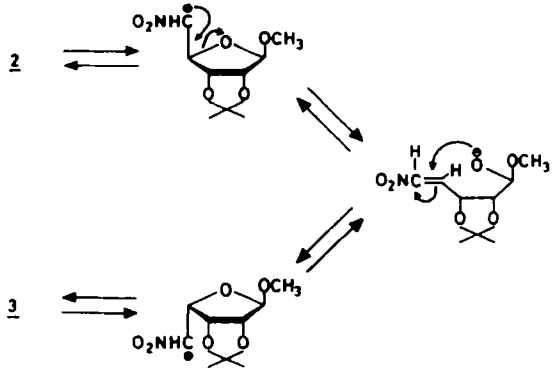
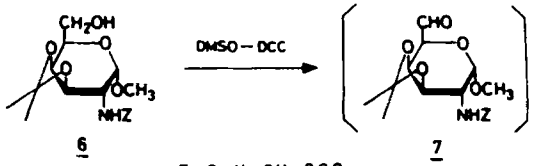
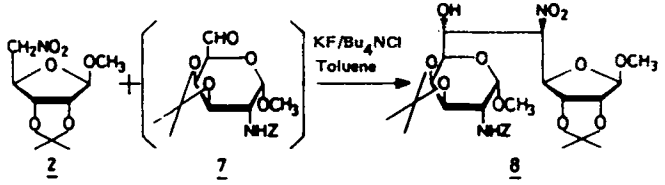


SCHEME 4



Z=$C_6H_5CH_2OCO$



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epimerization of 2,3-O-isopropylidene-D-furanosyl-C-glycosides has been described.[9]

The structures of 2 and 3 have been established as follows. Catalytic hydrogenation of 2 in the presence of Raney nickel, followed by a conventional acetylation yielded compound (4), which was identical with a sample prepared from 1 by the alternative reaction route shown in Scheme 2. The analogous hydrogenation of 3, and subsequent acetylation afforded another isomer (5). The structures of 4 and 5 have been established by means of proton NMR spectroscopy.

The oxidation of methyl 2-(benzyloxycarbonyl)amino-2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside (6) by the Pfitzner-Moffatt method[10] gave the sugar aldehyde 7.

When the nitro sugar 2 reacted with the sugar aldehyde 7 in the presence of methanolic sodium methoxide, a complex mixture of reaction products was obtained and a column chromatography did not yield a satisfactory result.

On the other hand, when the reaction was carried out in the presence of potassium fluoride and tetrabutylammonium chloride in a toluene solution, the reaction progressed smoothly and stereoselectively, and the nitro undecose derivative 8 was obtained as nice crystals in 61% yield (Scheme 4).

It is of interest to establish absolute configurations of the newly introduced chiral centers on C-6 and C-7 of 8, since these configurations have never been determined in this series of the reactions. The absolute configurations have been established by means of X-ray crystal structure analysis. In the crystalline state, the molecules are packed along the a axis, mainly with van der Waals forces. The shortest intermolecular approach of 2.719 Å is found between the carbonyl O-2 of the molecule and the hydroxyl O-7 of the other molecule related to the first by two fold axis of rotation. A perspective drawing of the molecule is provided in Fig. 1, which also presents the absolute configuration. The whole molecule is in a highly extended conformation with an end-to-end distance of 19 Å. The bond distances and angles are quite normal.

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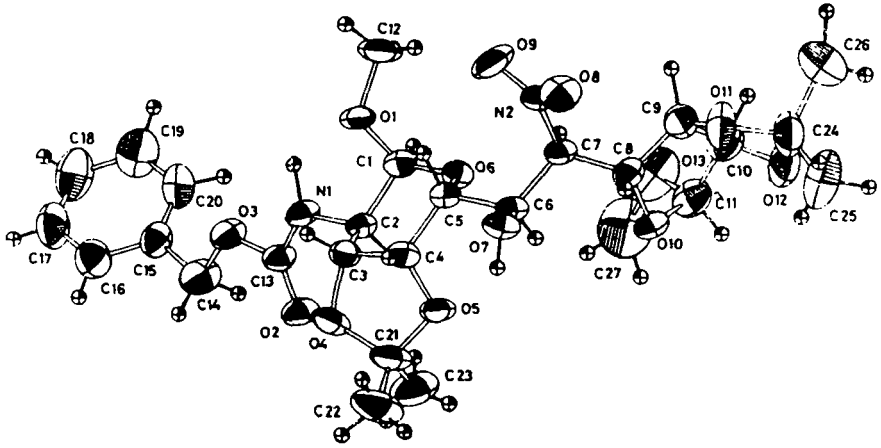

FIG. 1. ORTEP[13] Drawing of 8 with 50% Probability Ellipsoids, Indicating Numbering of Atoms.

These observations suggest that the molecular conformation does not seem to be much affected by particular intra- and intermolecular interactions.

Considering from the configurations of C-6 and C-7 of 8, the carbonyl group and the ring oxygen of 7 seem to be in an anti-conformation, owing to the electronic repulsion. And the approaching reagent 2 comes from the less hindered side to generate the R-configuration of C-6. The R-configuration of C-7 seems to be directed by a conformation of the reagent 2 which has been controlled by the electronic repulsion of the ring oxygen of the furanose.

EXPERIMENTAL

General Procedures. Melting points were determined in capillary tubes and uncorrected. Solutions were concentrated under reduced pressure below 40°C. Optical rotations were measured with a Japan Spectroscopic DIS-SL polarimeter. ^{1}H NMR spectra were recorded with a Varian EM-390 spectrometer at 90 MHz or a JEOL FX-200 spectrometer at 200 MHz. IR spectra were recorded with a

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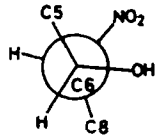

FIG. 2. Newman Projections along C6-C7 Bond.

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Hitachi 225 spectrophotometer. A chromatography was performed on a column of silica gel (Wakogel C-200, Wako Pure Chemical Co. Ltd.).

Methyl 5-Deoxy-2,3-O-isopropylidene-5-nitro-β-D-ribofuranoside (2) and Methyl 5-Deoxy-2,3-O-isopropylidene-5-nitro-α-L-lyxofuranoside (3). To a solution of methyl 5-deoxy-5-iodo-2,3-O-isopropylidene-β-D-ribofuranoside[8] (1, 4.0 g) in N,N-dimethylformamide (50 ml) was added a mixture of sodium nitrite (3.5 g) and phloroglucinol dihydrate (4.1 g). After 3 days at 30°C, water (50 ml) was added to the reaction solution, and the mixture was extracted with $CHCl_3$ (2 x 50 ml). The combined $CHCl_3$ layer was washed with water, dried over Na_2SO_4 and concentrated. The residue was chromatographed using toluene as the eluant to give 439 mg (15%) of a mixture of 2 and 3, and 821 mg (29%) of 2: R_f 0.61 on TLC (1:3 ethyl acetate-toluene); mp 44-46°C; $[\alpha]_D^{26}$ -64.5° (*c* 0.6, chloroform); IR (KBr) 1390, 1560 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28, 1.45 (2s, 6H, CMe_2), 3.28 (s, 3H, OMe), 4.83 (s, 1H, H-1).

Anal. Calcd for $C_9H_{15}NO_6$: C, 46.35; H, 6.48; N, 6.01. Found: C, 46.39; H, 6.32; N, 6.07.

The mixture of 2 and 3 was chromatographed using the same solvent to give 370 mg of the mixture and 38 mg (1%) of 3: R_f 0.64 on TLC (1:3 ethyl acetate-toluene); mp 89-90°C; $[\alpha]_D^{26}$ -96.1° (*c* 0.85, chloroform); IR (KBr) 1370, 1385, 1560 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25, 1.40 (2s, 6H, CMe_2), 3.20 (s, 3H, OMe), 4.73 (s, 1H, H-1).

Anal. Calcd for $C_9H_{15}NO_6$: C, 46.35; H, 6.48; N, 6.01. Found: C, 46.58; H, 6.59; N, 5.79.

Methyl 5-Acetamido-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside (4). (a) A solution of 2 (45 mg) in methanol (5 ml) was hydrogenated in the presence of Raney nickel T-4[14] in the initial

hydrogen pressure of 2.7 kg/cm^2. After 1 h, the catalyst was filtered off, and acetic anhydride (0.2 ml) was added to the filtrate. The solution was concentrated, and the residue was chromatographed using 2:1 ethyl acetate-toluene as the eluant to give 39 mg (82%) of 4: R_f 0.59 on TLC (10:1 chloroform-methanol); mp 86-87°C; $[\alpha]_D^{28}$ -91.6° (*c* 0.6, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.27, 1.42 (2s, 6H, CMe_2), 1.93 (s, 3H, NAc), 3.30 (s, 3H, OMe), 4.81 (s, 1H, H-1).

Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 54.14; H, 7.67; N, 5.77.

(b) A suspension of 1 (430 mg) and sodium azide (178 mg) in N,N-dimethylformamide (10 ml) was heated under reflux for 20 min. After the solution was cooled, water was added to the solution and the mixture was extracted with chloroform (2 x 35 ml). The combined chloroform layer was washed with water, dried over Na_2SO_4 and concentrated. The residue was hydrogenated and subsequently acetylated analogously as described in (a), to give 286 mg (77%) of 4 which was identical with the sample obtained in the method (a).

Methyl 5-Acetamido-5-deoxy-2,3-O-isopropylidene-α-L-lyxofuranoside (5). Compound 3 (20 mg) was worked up analogously as described in the preparation of 4, to give 19 mg (90%) of 5: R_f 0.65 on TLC (10:1 chloroform-methanol); mp 89-90°C; $[\alpha]_D^{22}$ -72.1° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.30, 1.43 (2s, 6H, CMe_2), 1.93 (s, 3H, NAc), 3.23 (s, 3H, OMe), 4.42 (d, 1H, $J_{2,3}$=6 Hz, H-2), 4.57 (dd, 1H, $J_{2,3}$=6 Hz, $J_{3,4}$=4 Hz, H-3), 4.77 (s, 1H, H-1).

Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 54.01; H, 7.65; N, 5.75.

Methyl 2-(Benzyloxycarbonyl)amino-2,7-dideoxy-3,4:9,10-di-O-isopropylidene-7-nitro-β-L-glycero-L-altro-D-galacto-undecodialdo-[methyl (11R)-furanosid-(8,11)]-pyranoside-(1,5) (8). To a solution of methyl 2-(benzyloxycarbonyl)amino-2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside[6] (6, 200 mg) in a mixture of dimethylsulfoxide (1 ml), toluene (0.4 ml), pyridine (30 μl) and phosphoric acid (15 μl), dicyclohexylcarbodiimide (130 mg) was added. After 2.5 h at room temperature, a solution of oxalic acid (200 mg) in methanol (0.2 ml) was added to the reaction mixture under ice cool-

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ing. After 1 h, toluene (10 ml) was added to the mixture and the insoluble matter was removed by filtration. To the filtrate, ethyl acetate (30 ml) was added, and the solution was washed with water, dried over Na_2SO_4 and concentrated. The residue was dissolved in a mixture of ethyl acetate (2.5 ml) and toluene (12.5 ml). The solution was filtered and the filtrate was concentrated to give a crude product of methyl 2-(benzyloxycarbonyl)amino-2-deoxy-3,4-O-isopropylidene-α-D-galactodialdopyranoside-(1,5) (7).

To a stirred solution of crude 7 in toluene (3 ml), a mixture of 2 (102 mg), potassium fluoride (50 mg) and tetrabutylammonium chloride (100 mg) was added. After 1 h, water (10 ml) and ethyl acetate (30 ml) were added to the reaction mixture. The organic layer was separated, dried over Na_2SO_4 and concentrated. The residue was chromatographed using 1:6 ethyl acetate-toluene as the eluant to give 161 mg (61% from 2) of 8. Recrystallization from cyclohexane-toluene afforded 130 mg of 8: R_f 0.32 on TLC (1:3 ethyl acetate-toluene); mp 163-164°C; $[\alpha]_D^{26}$ +69.4° (*c* 1.1, chloroform); IR (KBr) 1370, 1540 (NO_2), 1710 (C=O), 3380 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31, 1.35, 1.50, 1.56 (4s, 12H, $2CMe_2$), 3.36 (s, 3H, OMe), 3.39 (s, 3H, OMe), 7.33 (s, 5H, C_6H_5).

Anal. Calcd for $C_{27}H_{38}N_2O_{13}$: C, 54.18; H, 6.40; N, 4.68. Found: C, 53.94; H, 6.29; N, 4.58.

X-Ray Crystal Structure Analysis of 8. The crystals of 8 are monoclinic, space group $P2_1$, $Z=2(C_{27}H_{38}N_2O_{13}$, $M_r=598.7)$, with a= 11.197(1), b=13.117(1), c=10.399(1) Å, β=91.58(2)°, V=1526.8(2) Å^3, D_x=1.30 Mgm^{-3}, λ(Cu Kα)=1.54178 Å, μ(Cu Kα)=0.893 mm^{-1}. A spherical crystal 0.6 mm in diameter was used for the data collection. The data were collected on a Philips automated four-circle diffractometer with graphite monochromated Cu Kα radiation (λ=1.54178 Å). The intensities of 3377 reflections with $2\theta \leq 156°$ were measured by employing the ω-2θ scan mode with a scanning rate of $4°(2\theta)$ min^{-1}. Among them 3322 reflections were regarded as observed ($I > 2\sigma(I)$). Periodic checks of the intensity values of three standard reflections showed no significant X-ray damage or crystal decay. Corrections for absorption or extinction were not applied.

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TABLE 1.

Positional Parameters($x10^4$) and Equivalent Isotropic Thermal Parameters(x10) with e.s.d.'s in Parentheses. For monoclinic cells,

$$B_{eq} = 4/3(a^2\beta_{11} + b^2\beta_{22} + c^2\beta_{33} + 2ab(\cos\beta)\beta_{13})$$

	X	Y	Z	B_{eq}(A)x10
O 1	5860 (3)	293 (3)	9178 (3)	36 (1)
O 2	6769 (3)	-1330 (3)	5062 (3)	40 (1)
O 3	8133 (3)	-1856 (3)	6569 (3)	43 (1)
O 4	6203 (3)	1003 (3)	5186 (3)	43 (1)
O 5	4253 (3)	1442 (3)	5503 (3)	40 (1)
O 6	3990 (3)	511 (3)	8120 (3)	30 (1)
O 7	3172 (3)	3147 (3)	7456 (3)	35 (1)
O 8	2222 (3)	3427 (3)	10134 (3)	48 (1)
O 9	3454 (3)	2214 (3)	10561 (3)	66 (1)
O10	451 (3)	1822 (3)	7325 (3)	40 (1)
O11	-776 (3)	3137 (4)	9473 (4)	59 (1)
O12	-1940 (3)	1910 (4)	8566 (4)	65 (1)
O13	413 (4)	163 (4)	8119 (5)	75 (2)
N 1	6790 (3)	-716 (3)	7133 (3)	34 (1)
N 2	2639 (3)	2613 (4)	9930 (3)	42 (1)
C 1	5049 (4)	-79 (4)	8238 (4)	32 (1)
C 2	5714 (4)	-94 (3)	6982 (4)	29 (1)
C 3	5994 (4)	992 (4)	6548 (4)	32 (1)
C 4	4931 (4)	1707 (4)	6644 (4)	32 (1)
C 5	4210 (4)	1577 (3)	7843 (4)	28 (1)
C 6	2995 (4)	2092 (4)	7667 (4)	29 (1)
C 7	2162 (4)	1982 (4)	8800 (4)	31 (1)
C 8	893 (4)	2377 (4)	8439 (4)	35 (1)
C 9	-29 (5)	2251 (5)	9447 (5)	45 (1)
C10	-858 (5)	1384 (5)	8938 (6)	54 (2)
C11	-278 (5)	1004 (5)	7766 (5)	51 (2)
C12	5509 (6)	125 (6)	10480 (4)	55 (2)
C13	7189 (4)	-1281 (4)	6172 (4)	33 (1)
C14	8617 (5)	-2514 (4)	5607 (5)	53 (2)
C15	9443 (4)	-3260 (4)	6248 (5)	42 (1)
C16	10582 (5)	-3382 (5)	5829 (6)	56 (2)
C17	11335 (5)	-4125 (6)	6395 (7)	63 (2)
C18	10962 (6)	-4698 (5)	7368 (8)	69 (2)
C19	9823 (6)	-4588 (6)	7828 (7)	68 (2)
C20	9069 (5)	-3866 (5)	7262 (6)	56 (2)
C21	5076 (5)	1224 (5)	4512 (4)	49 (2)
C22	5298 (7)	2158 (7)	3671 (6)	80 (3)
C23	4628 (7)	280 (7)	3778 (6)	73 (2)
C24	-2009 (5)	2854 (6)	9294 (6)	63 (2)
C25	-2655 (6)	3633 (8)	8503 (9)	95 (3)
C26	-2557 (7)	2637 (10)	10631 (8)	97 (3)
C27	914 (8)	-357 (8)	6970 (10)	104 (4)

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The structure was solved by the direct method with the program MULTAN 78[11] using 420 reflections with $|E|>1.26$. When the set with the highest combined figure of merit and lowest residual value was used to synthesize an E map, 17 geometrically acceptable positions out of 42 nonhydrogen atoms were obtained. The Karle recycling of this structural fragment gave the additional 19 atoms. The remaining atoms could be located by successive Fourier synthesis. Block-diagonal least-squares refinement with anisotropic nonhydrogen atoms reduced R to 0.080. At this stage, all the hydrogen atoms were found by the difference Fourier synthesis. Five strong reflections were excluded, because they seemed to suffer from secondary extinctions. Refinement using anisotropic and isotropic temperature factors for the nonhydrogen and hydrogen atoms, respectively, gave the final R value 0.053 and R_w=0.049 for 3317 reflections. The function minimized was $R_w=[\Sigma\omega(|F_o|-|F_c|)^2/\Sigma\omega|F_o|^2]^{1/2}$, where the weight was 1.0 for all the reflections. At the final stage of the refinement all the parameter shifts were less than one seventh of the corresponding standard deviations, and the difference Fourier synthesis had no region of electron density higher than 0.22 e A^{o-3}. Atomic scattering factors were taken from International Tables for X-ray crystallography.[12] The final positional parameters are given in Table 1.

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