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An Efficient use of Oppolzer Sultam for Diastereospecific Synthesis of *cis*-β-Lactams

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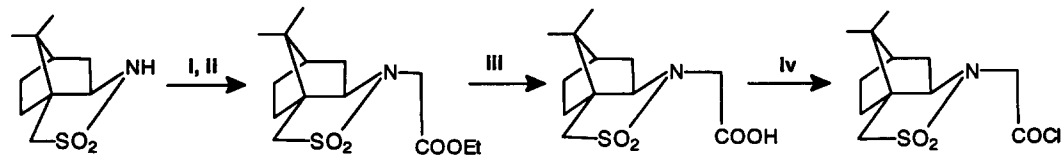
Abstract: Diastereospecific Synthesis of *cis*-β-Lactams (**6a-g**) has been achieved in ketene-imine cycloaddition reaction (Staudinger reaction) by using homochiral ketene precursors **3** and **4** derived from Oppolzer sultam, in very good yields. Copyright © 1996 Elsevier Science Ltd

Oppolzer sultam has been extensively used as a chiral auxiliary and consistently excellent diastereoselectivities have been achieved for a wide range of organic reactions.[1] Recently a few reports have appeared wherein a camphor-derived chiral auxiliary has been used in β-lactam synthesis *via* an enolate-imine cycloaddition reaction.[2] The efficacy of this chirality directing group has been attributed mainly to its rigid, bicyclic framework which allows well-defined conformations and consequent effective stereoface-discrimination for diastereotopic transition states. While there are hundreds of reports on β-lactam synthesis using chiral aldehydes and chiral amines, only a few examples are known, in which a chiral ketene precursor has been successfully used to achieve high diastereoselectivity.[3]

In the course of our investigation of steric factors controlling the relative stereochemistry of β-lactams obtained from the Staudinger reaction, we became interested in examining the effectiveness of ketenes derived from Oppolzer sultam with reference to diastereoselection. We have recently shown that a sterically demanding bicyclic system derived from (+)-3-carene can actually control diastereoselectivity of this ketene-imine cycloaddition.[4] Oppolzer sultam has a structure related to the bicyclic framework of (+)-3-carene used in our previous study. The sultam-derived ketene precursor was expected to provide a high degree of diastereoselectivity, since the auxiliary has now three rings in place of two, and hence is conformationally more rigid. We herein report an efficient use of the sultam-derived ketene precursor for the diastereospecific synthesis of β-lactams *via* a cycloaddition reaction.

The Oppolzer sultam **1** was prepared from (1*S*)-(+)-camphor-10-sulphonic acid[5] by the reported procedure.[6] Alkylation of **1** with ethyl bromoacetate in presence of NaH and a catalytic amount of tetrabutylammonium iodide in dry THF gave the N-alkylated sultam **2** in 90% yield (Scheme 1). The ester **2** on base-catalyzed hydrolysis with methanolic KOH offered acid **3** in 68% yield. The acid **3** when heated with thionyl chloride under reflux, gave acid chloride **4** in quantitative yield.

Scheme 1

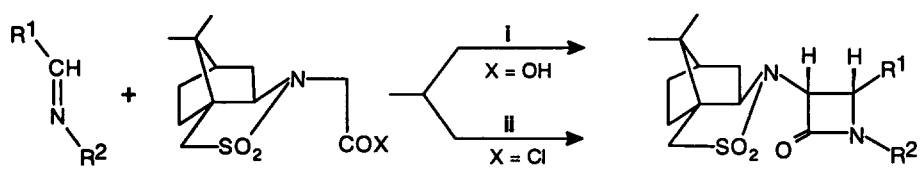


1 **2** **3** **4**

Reagents and conditions: i) NaH/dry THF, reflux, 1 h; ii) NBu_4I/$BrCH_2COOEt$, r.t., 3 h. iii) CH_3OH/KOH, r.t., 16 h. iv) $SOCl_2$, reflux, 5 h.

The imines **5** on treatment with acid chloride **4** in the presence of excess triethylamine at -23°C (Method A) underwent annulation reaction to give *cis*-β-lactams (**6a-g**) in 60-91% yields (see Scheme 2, Table 1). In all the cases the formation of only one *cis* diastereomer was observed.[7] Some of the β-lactams (**6a-d**) were also prepared by reacting the corresponding acid **3** with imines **5** in the presence of an acid activator, phenoxy dichlorophosphate, and excess triethylamine (Method B, Scheme 2). In this case also only one *cis* diastereomer could be isolated. However, this method gave a lower yield of the product compared to the acid chloride method except for compound **6a** (see Table 1).

Scheme 2



5 **3** X = OH, **4** X = Cl **6a-g**

Reagents and conditions: i) $PhOP(O)Cl_2$ /Et_3N /dry CH_2Cl_2, -23 °C to r.t., 15 h. ii) Et_3N /dry CH_2Cl_2, -23 °C to r.t., 15 h.

Table 1. Synthesis of β-lactams (**6a-g**) *via* cycloaddition reaction of imines **5** with ketenes derived from acid **3** or acid chloride **4**.

Entry No.	Compd No.	R^1	R^2	Yield[a] (%) Method A	Yield[a] (%) Method B	M.p. (°C)	$[\alpha]^{25}_D$
1	**6a**	Styryl	PMP	70	82	208-210	+60.89
2	**6b**	Ph	PMP	88	61	242-243	+39.20
3	**6c**	PMP	PMP	91	83	215-216	+60.63
4	**6d**	Ph	Bn	60	47	221-222	+62.00
5	**6e**	Styryl	Bn	82	-	174-175	+55.20
6	**6f**	Styryl	(S)-PhEt	82	-	213-215	+22.10
7	**6g**	Styryl	(*R*)-PhEt	75	-	199-201	+68.90

[a] Isolated yields of pure products after column chromatographic purification.
PMP = *p*-methoxyphenyl; Ph = Phenyl; Bn = Benzyl; PhEt = α-phenylethyl.

The absolute configuration of the β-lactam **6d** (crystallized from acetone/pet. ether) has been established from single crystal X-ray diffraction analysis.[8] The configuration at C3′ and C4′ of the β-lactam **6d** were assigned as 3*R*′, 4*S*′ on the basis of the known absolute configuration 2*R*, 3*S*, 6*R* of the 2,10-camphorsultam moiety (Fig. 1). Attempts to remove the chiral auxiliary by acid or base hydrolysis as well as by reductive technique were unsuccessful.

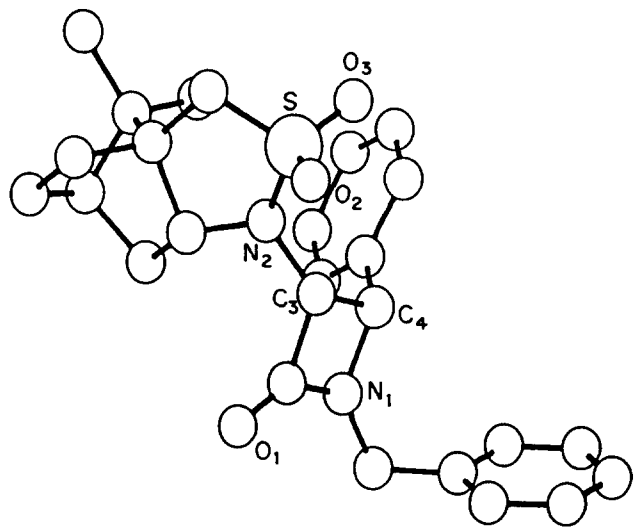


Fig. 1. Pluto diagram of **6d**

In summary, we have demonstrated that the tricyclic structure of Oppolzer sultam provides an effective steric bias to obtain a single diastereoisomer of *cis* β-lactams by Staudinger reaction. The utility of this method for practical synthesis of optically pure, diversely functionalised β-lactams is currently being explored.

Experimental Section

^{1}H NMR Spectra were recorded in $CDCl_3$ solution on a Brucker AC 200 spectrometer at 200 MHz and chemical shifts are reported in ppm downfield from tetramethylsilane. ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker AC 200 and Bruker MSL 300 instruments and chemical shifts are reported in ppm relative to the center line of $CDCl_3$ (77.0 ppm). Infrared spectra were recorded on a Perkin-Elmer Infracord Spectrophotometer Model 599-B using sodium chloride optics. Melting points were determined on a Thermonik Campbell melting point apparatus and were uncorrected. The microanalysis were performed on a Carlo-Erba, CHNS-O EA 1108 Elemental analyzer. Optical rotations were recorded on a JASCO-181 digital polarimeter under standard conditions. Methylene chloride was distilled over P_2O_5 under argon. Silica gel (SD's, 60 - 120 mesh) was used for column Chromatography.

Preparation of N-alkylated (2*R*, 3*S*, 6*R*)-2,10-camphorsultam (2). To a solution of *d*-2,10-camphorsultam (Oppolzer sultam) (**1**, 0.537, 2.5 mmol) in dry THF (20 mL), a suspension to NaH (0.065, 2.8 mmol) in 5 mL of THF was added at 0 °C and it was then refluxed for 1.5 h. The reaction mixture was cooled to 0 °C and tetrabutylammonium iodide (0.018 g, 0.05 mmol) and ethyl bromoacetate (0.467 g, 2.8 mmol) were added successively and refluxed for 4 h. It was then cooled to room temperature, quenched with water (5 mL) and extracted with ether (2 X 25 mL). The ether extract was dried (Na_2SO_4) and concentrated to give crude product, which was column chromatographed (silica gel, pet. ether/acetone) to give 0.680 g (90.5%) of N-alkylated product **2**. White solid, m. p. 75 - 77 °C; $[\alpha]^{23}_D$: -35.4 (c, 1, CH_2Cl_2).

Preparation of acid 3. To a solution of N-alkylated sultam **2** (0.600 g, 3 mmol) in methanol (20 mL), KOH (2.0 g) was added slowly and stirred overnight. The methanol was then removed under reduced pressure, water (15 mL) was added to the residue and acidified with 20% dil. HCl. The acidic solution was extracted with ethyl acetate (2 X 30 mL), washed with brine (10 mL) and dried (Na_2SO_4). It was then filtered and filtrate on removal of solvent gave 0.375 g (68.9%) of acid **3** as a white crystalline solid, m.p. 205 - 207 °C; $[\alpha]_{25D}$: -40.6 (c, 1, CH_2Cl_2); IR : 3200 - 3500 (br), 2900, 1730, 1440 cm^{-1}; Anal. Calcd for $C_{12}H_{19}NO_4S$: C, 52.73; H, 7.01; N, 5.12; S, 11.73. Found: C, 52.39; H, 6.84; N, 5.43; S, 11.39.

Preparation of acid chloride 4. A mixture of acid **4** (0.410 g, 1.5 mmol) and thionyl chloride (0.212 g, 1.8 mmol) was refluxed until the evolution of HCl ceases (about 4 h). The excess of thionyl chloride was removed under vacuum at 50 °C. m.p. 85 - 87°C; $[\alpha]^{25}_D$: -25.8 (c, 1, CH_2Cl_2); IR : 3020, 2960, 1800, 1410 cm^{-1}.

General procedure for the preparation of β-lactams (6a-g).

Method A. A solution of acid chloride **4** (0.291 g, 1 mmol) in dry CH_2Cl_2 (15 mL), was added to a stirred solution of imines **5a-g** (1.2 mmol) in dry CH_2Cl_2 (10 mL) in presence of excess of triethylamine (6.0 mmol) at -23 °C. The resulting solution was allowed to warm up to rt and stirred for 15 h. The reaction mixture was then successively washed with water (30 mL), satd. bicarbonate solution (30 mL) and brine (30 mL) and dried (Na_2SO_4). The CH_2Cl_2 solution was concentrated to give the crude product, which was column chromatographed (silica gel, 60-120, pet. ether/acetone) to furnish pure β-lactams (**6a-g**). All compounds (**6a-g**) were crystallized from pet. ether/acetone.

Method B. To a stirred solution of acid **3** (0.400 g, 1.5 mmol), imine **5a-d** (1.8 mmol), triethylamine (6.0 mmol) in dry CH_2Cl_2 (15 mL), a solution of phenyl dichlorophosphate (0.378 g, 1.8 mmol) in dry CH_2Cl_2 (20 mL) was added at -23 °C. The reaction mixture was then allowed to warm-up to rt and stirred further for 15 h. The usual work-up as described in method A gave pure β-lactams (**6a-d**).

(2*R*,3*S*,6*R*,3′*R*,4′*S*)-N-[1′-(*p*-Anisyl)-4′-styrylazetidin-2′-one-3′-yl]-2,10-camphorsultam (6a). M.p. 208 - 210 °C. $[\alpha]^{25}_{D}$: +60.89 (c, 1, CH_2Cl_2). ^{1}H NMR : δ 0.85 (s, 3H, CH_3); 0.95 (s, 3H, CH_3); 1.35 - 1.55 (m, 2H, CH_2); 1.75 - 2.1 (m, 5H, CH_2 and CH); 3.2 (q, 2H, *J* = 4.0 Hz, CH_2); 3.7 (m, 1H, CH); 3.8 (s, 3H, OCH_3); 4.85 (dd, 1H, *J* = 4.8 Hz and 7.0 Hz, C4H); 5.05 (d, 1H, *J* = 5.0 Hz, C3H); 6.35 (dd, 1H, *J* = 10.0 and 20.0 Hz, CH); 6.6 (d, 1H, *J* = 20.0 Hz, CH); 6.8 (d, 2H, *J* = 10.0 Hz, Ar); 7.25 - 7.50 (m, 7H, Ar). ^{13}C NMR : 20.0, 20.4, 26.4, 32.7, 38.3, 45.0, 47.6, 49.0, 50.4, 55.5, 58.5, 60.8, 66.2, 114.4, 118.5, 124.0, 126.7, 128.1, 128.5, 131.2, 133.9, 136.0, 156.5, 160.0. IR : 1750 cm^{-1}. Anal. Calcd for $C_{28}H_{32}N_2O_4S$: C, 68.27; H, 6.55; N, 5.69; S, 6.51. Found C, 68.63; H, 6.65; N, 5.69; S, 5.90.

(2*R*,3*S*,6*R*,3′*R*,4′*S*)-N-[1′-(*p*-Anisyl)-4′-phenylazetidin-2′-one-3′-yl]-2,10-camphorsultam (6b). M.p. 242 - 243 °C. $[\alpha]^{25}_{D}$: +39.20 (c, 1, CH_2Cl_2). ^{1}H NMR : δ 0.1 (s, 3H, CH_3); 0.75 (s, 3H, CH_3); 1.25 - 1.45 (m, 2H, CH_2); 1.75 (m, 5H, CH_2 and CH_1); 3.0 (dd, 2H, *J* = 14.0 and 20.0 Hz, CH_2); 3.7 (t, 1H, CH); 3.8 (s, 3H, CH_3); 5.3 (broad s, 2H, C3H and C4H); 6.85 (d, 2H, *J* = 10.0 Hz, Ar); 7.25 - 7.45 (m, 7H, Ar). ^{13}C NMR : 19.1, 20.7, 26.8, 32.6, 37.6, 45.0, 47.4, 48.5, 50.0, 55.5, 60.2, 61.4, 65.6, 114.5, 118.7, 127.8, 128.3, 128.7, 130.9, 133.8, 156.6, 160.6. IR : 1750 cm^{-1}. Anal. Calcd for $C_{26}H_{30}N_2O_4S$: C, 66.93; H, 6.48; N, 6.00; S, 6.87. Found C, 66.69; H, 6.23; N, 5.89; S, 6.70.

(2*R*,3*S*,6*R*,3′*R*,4′*S*)-N-[1′-(*p*-Anisyl)-4′-*p*-anisylazetidin-2′-one-3′-yl]-2,10-camphorsultam (6c). M.p. 215 - 216 °C. $[\alpha]^{25}_{D}$: +60.63 (c, 1, CH_2Cl_2). ^{1}H NMR : δ 0.2 (s, 3H, CH_3); 0.75 (s, 3H, CH_3); 1.25 - 1.50 (m, 2H, CH_2); 1.65 - 1.80 (m, 5H, CH_2 and CH_1); 3.0 (dd, 2H, *J* = 12.0 and 20.0 Hz, CH_2); 3.65 (t, 1H, CH); 3.8 (s, 6H, CH_3); 5.25 (q, 2H *J* = 5.0 Hz, C3H and C4H); 6.85 (dd, 4H, *J* = 5.0 and 10.0 Hz, Ar); 7.3 (dd, 4H, *J* = 10.0 and 20.0 Hz, Ar). ^{13}C NMR : 19.0, 20.0, 26.7, 32.5, 37.5, 45.0, 47.3, 48.4, 49.9, 55.3, 55.4, 59.7, 61.2, 65.5, 114.1, 114.4, 118.6, 125.6, 128.9, 130.9, 156.7, 160.6. IR : 1750 cm^{-1}. Anal. Calcd for $C_{27}H_{32}N_2O_5S$: C, 65.30; H, 6.49; N, 5.64; S, 6.46. Found C, 65.61; H, 6.89; N, 5.33; S, 6.70.

(2*R*,3*S*,6*R*,3′*R*,4′*S*)-N-[1′-(Benzyl)-4′-phenylazetidin-2′-one-3′-yl]-2,10-camphorsultam (6d). M.p. 221 - 222 °C. $[\alpha]^{25}_{D}$: +62.00 (c, 1, CH_2Cl_2). ^{1}H NMR : δ 0.20 (s, 3H, CH_3); 0.75 (s, 3H, CH_3); 1.30 (m, 2H, CH_2); 1.7 (m, 5H, CH_2 and CH); 2.95 (dd, 2H, *J* = 14.0 and 35.0 Hz, CH_2); 3.55 (m, 1H, CH); 4.05 and 5.00 (dd, 2H, *J* = 16.0 and 192.0 Hz); 4.7 (d, 1H, *J* = 5.4 Hz, C4H); 5.05 (d, 1H, *J* = 5.4 Hz, C3H); 7.10 - 7.45 (m, 10H, Ar). ^{13}C NMR : 19.2, 20.5, 26.7, 32.6, 37.6, 45.0, 45.5, 47.4, 48.5, 50.0, 59.6, 62.6, 65.8, 127.7, 128.1, 128.2, 128.5, 129.0, 134.5, 134.8, 164.1. IR : 1760 cm^{-1}. Anal. Calcd for $C_{26}H_{30}N_2O_3S$: C, 69.31; H, 6.71; N, 6.22; S, 7.12. Found C, 68.97; H, 6.46; N, 6.12; S, 7.25.

(2*R*,3*S*,6*R*,3′*R*,4′*S*)-N-[1′-Benzyl-4′-(2″-styryl)azetidin-2′-one-3′-yl]-2,10-camphorsultam (6e). M.p. 174 - 175 °C. $[\alpha]^{25}_{D}$: +55.20 (c, 1, CH_2Cl_2). ^{1}H NMR : δ 0.85 (s, 3H, CH_3); 1.1 (s, 3H, CH_3); 1.3 - 1.6 (m, 2H, CH_2); 1.7 (m, 1H, CH); 1.8 - 1.9 (m, 5H, $2CH_2$ and CH1); 3.15 (q, 2H, *J* = 5.0 Hz, CH_2); 3.6 (m, 1H, CH); 4.2 and 4.75 (dd, 2H, *J* = 14.0 and 95.0 Hz, CH_2); 4.25 (d, 1H, *J* = 5.0 Hz, C4H); 4.9 (d, 1H, *J* = 5.0 Hz, C3H); 6.15 (dd, 1H, *J* = 5.0 and 15.0 Hz, CH); 6.5 (d, 1H, *J* = 15.0 Hz, CH); 7.15 - 7.50 (m, 10H, Ar). ^{13}C NMR : 20.1, 20.58, 26.8, 32.8, 38.4, 45.1, 45.7, 47.8, 49.1, 50.3, 58.3, 61.9, 66.5, 124.6, 126.7, 128.1, 128.2, 128.6, 128.7, 129.0, 134.1, 135.2, 136.3, 163.0. IR : 1750 cm^{-1}. Anal. Calcd for $C_{28}H_{32}N_2O_3S$: C, 70.56; H, 6.77; N, 5.88; S, 6.73. Found C, 70.51; H, 6.71; N, 5.79; S, 6.20.

(2*R*,3*S*,6*R*,3′*R*,4′*S*,1″*S*)-N-[1′-(1″-phenyl)ethyl-4′-(2″-styryl)azetidin-2′-one-3′-yl]-2,10-Camphorsultam (6f). M.p. 213 - 215°C. $[\alpha]^{25}_{D}$: +22.10 (c, 1, CH_2Cl_2). ^{1}H NMR : δ 0.9 (s, 3H, CH_3); 1.1 (s, 3H, CH_3); 1.4 (m, 2H, CH_2); 1.65 (d, 3H, *J* = 7.0 Hz, CH_3); 1.85 (m, 3H, CH_2 and CH); 2.0 (d, 2H, *J* = 7.0 Hz, CH_2); 3.1 (q, 2H, *J* = 15.0 Hz, CH_2); 3.65 (t, 1H, CH); 4.2 (dd, 1H, *J* = 4.8 and 5.7 Hz, C4H); 4.75 (d, 1H, *J* = 5.0 Hz, C3H); 4.95 (q, 1H, *J* = 7.0 Hz, CH); 6.10 (dd, 1H, *J* = 7.0 and 15.0 Hz, CH); 6.45 (d, 1H, *J* = 17.0 Hz, CH); 7.25 - 7.45 (m,

10H, Ar). ^{13}C NMR : 119.5, 20.1, 20.6, 26.8, 32.8, 38.4, 45.2, 47.8, 49.0, 50.4, 53.2, 58.9, 61.1, 66.4, 125.8, 126.7, 127.3, 128.1, 128.6, 128.9, 134.6, 136.4, 139.9, 163.1. IR : 1750 cm^{-1}. Anal. Calcd for $C_{29}H_{34}N_2O_3S$: C, 70.99; H, 6.98; N, 5.71; S, 6.53. Found C, 70.64; H, 6.71; N, 5.57; S, 6.29.

(2*R*,3*S*,6*R*,3'*R*,4'*S*,1''*R*)-N-[1'-(1''-Phenyl)ethyl-4'-(2''-styryl)azetidin-2'-one-3'-yl]-2,10-camphorsultam (6g). M.p. 199 - 201 °C. $[\alpha]^{25}_D$: +68.90 (c, 1, CH_2Cl_2). ^{1}H NMR : δ 0.85 (s, 3H, CH_3); 1.0 (s, 3H, CH_3); 1.4 (m, 2H, CH_2); 1.8 (d, 3H, *J* = 7.0 Hz, CH_3); 1.85 (m, 3H, CH_2 and CH); 1.95 (d, 2H, *J* = 7.0 Hz, CH_2); 3.1 (q, 2H, *J* = 15.0 Hz, CH_2); 3.65 (t, 1H, CH); 4.3 (m, 1H, C4H); 4.7 (q, 1H, *J* = 7.0 Hz, CH); 4.85 (d, 1H, *J* = 4.8 Hz, C3H); 6.0 (dd, 1H, *J* = 7.0 and 15.0 Hz, CH); 6.35 (d, 1H, *J* = 17.0 Hz, CH); 7.15 - 7.50 (m, 10H, Ar). ^{13}C NMR : 18.8, 20.1, 20.5, 26.8, 32.8, 38.4, 45.1, 47.7, 49.0, 50.4, 53.8, 58.1, 61.0, 66.4, 124.9, 126.7, 127.0, 127.9, 128.5, 128.9, 134.3, 136.3, 141.0, 163.1. IR : 1750 cm^{-1}. Anal. Calcd for $C_{29}H_{34}N_2O_3S$: C, 70.99; H, 6.98; N, 5.71; S, 6.53. Found C, 70.80; H, 6.50; N, 5.70; S, 6.80.

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7. In all the cases ^{1}H (200 MHz) & ^{13}C NMR spectral analyses of the crude reaction mixture showed formation of only one *cis*-diastereomer. The formation of one *cis*-diastereomer was also confirmed by HPLC analysis of the crude reaction product.

8. X-ray determination of **6d** : Data were measured on a PC-controlled Enraf-Nonius CAD-4 single crystal X-ray diffractometer with Mo-Kα (λ = 0.7107 Å) radiation at 293 K. Crystals belong to orthorhambic, space group $P2_12_12_1$ with a = 8.552 (2), b = 15.515 (4), c = 17.680 (4) Å; V = 2345.9 (10) Å3, Z = 4, dcalc = 1.276 Mgm^{-3}, μ = 0.16 mm^{-1}, data collection of 1978 unique reflections ($2d_{max}$ = 47°), 1602 observed [I > 3.0 ρ(I)]. The structure was solved by direct methods using MULTAN-80 Least squares refinement of scale factor, positional and anisotropic thermal parameters for non hydrogen atoms (289 parameters) converged to R = 0.041 and R_w = 0.048. Hydrogen atoms geometrically fixed and confirmed by difference furrier were held fixed during refinement. Structure solution and refinement were carried out using NRCVAX programs.[9]

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