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Asymmetric Synthesis of α-Hydroxy Acids *via* β-Lactams

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Abstract : A diastereoselective synthesis of β-Lactams **5a-e** and **6a-e** has been achieved, *via* a Staudinger reaction using imines derived from (1*S*)-(+)-camphor-10-sulfonamide, in good yields. The major diastereomers **6a-e** were isolated in pure form by crystallization. The absolute configuration of the β-lactam **6b** was established as 3*R* and 4*S* by X-ray analysis. The major diastereomers **6b** and **6c** were converted into enantiomerically pure α-hydroxy ester derivatives **7-9**.

Enantiomerically pure α-hydroxy acid derivatives are important synthons for the synthesis of various natural products and biologically active molecules.[1] Several methodologies have been developed for the synthesis of α-hydroxy acids.[2] Among these methods, the reduction of α-keto esters (attached where necessary to suitable chiral auxiliaries) to α-hydroxy esters using microbial transformation,[3] catalytic hydrogenation[4] and chiral organometallic reagents[3] are well documented.[5] The most commonly used chiral auxiliaries are either derived from amino acids or sugars.[5] Camphor has also been used as a chiral auxiliary in the asymmetric synthesis of α-hydroxy esters either by alkylation or hydroxylation of suitably substituted esters and amides.[6] Our approach to the synthesis of α-hydroxy esters is based on the diastereoselective synthesis of β-lactams and their conversion to O-protected α-hydroxy esters by hydrogenolysis of the benzylic C-N bond of the β-lactam followed by alcoholysis of the sulfonamide.

Recently we had shown that sterically demanding bicyclic as well as tricyclic chiral auxiliaries derived from (+)-3-carene and Oppolzer's sultam play a major role in controlling the diastereoselectivity of the β-lactam formation in ketene-imine cycloaddition reaction.[7] As a continuation of our research on the utilization of easily available chiral auxiliaries, we were interested in examining the effect of imines derived from camphor-10-sulfonamide in (2+2) cycloaddition reactions. Herein we wish to report our results on the diastereoselective synthesis β-lactams using camphor-10-sulfonamide as a chiral auxiliary and their conversion to O-protected α-hydroxy esters.

The enantiomerically pure camphor-10-sulfonic acid[8] **1** was converted into camphor-10-sulfonamide **2** by the reported procedure.[9] Diethyl acetals of aromatic aldehydes on condensation with camphor-10-sulfonamide yielded the corresponding imines **3a-c** in quantitative yields. The imines **3** on subsequent annulation with various acid chlorides **4a-c** in the presence of triethylamine, gave diastereomeric mixtures of *cis* β-lactams **5** and **6** (Scheme 1) in good yields.[10] The ratio of the two diastereomers was determined by ^{1}H NMR spectral data and HPLC[11] analysis (Table 1). Our attempts to separate these diastereomers by column chromatography were unsuccessful. However, in all cases, the major diastereomer **6** was isolated pure by crystallization. The minor diastereomer **5** could not be isolated pure either by column chromatography or by crystallization.

Scheme 1

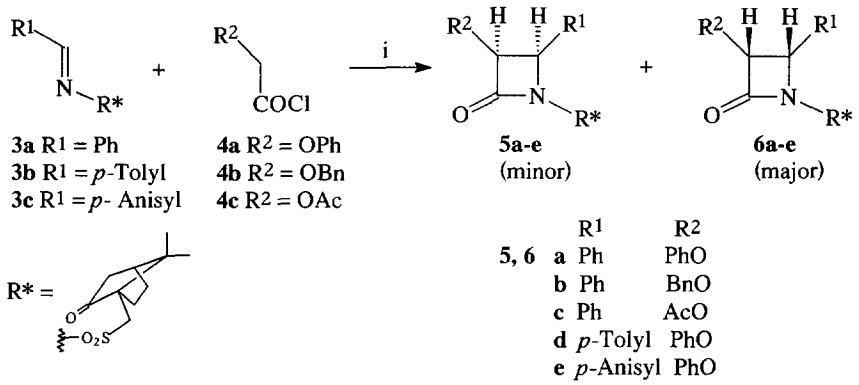


Table 1. Synthesis of β-lactams **5** and **6** from imines **3** and acid chlorides **4** *via* Staudinger reactions.

Compounds	R^1	R^2	Ratio of **6** and **5**	Yield[a] (%)	M.p.[b] (°C)
a	Ph	PhO-	73 : 27	72 (62)[c]	128 - 131
b	Ph	BnO-	58 : 42	77(56)[c]	122 - 124
c	Ph	AcO-	70 : 30	64	144 - 146
d	*p*-Tolyl	PhO-	64 : 36	69	186 - 188
e	*p*-Anisyl	PhO-	55 : 45	43	138 -140

[a] Isolated yield of diastereomeric mixtures of **6** and **5**. [b] Melting points of the major diastereomers **6** . [c] The figure in parenthesis represents the isolated yield of pure major diastereomer **6** by single crystallization.

The absolute configurations of the major diastereomer **6b** was established from single crystal X-ray analysis.[12] The configurations of the β-lactam **6b** were assigned as 3*R* and 4*S* respectively on the basis of the known absolute configuration 1′*S* of the camphor-10-sulfonyl moiety (Fig. 1).

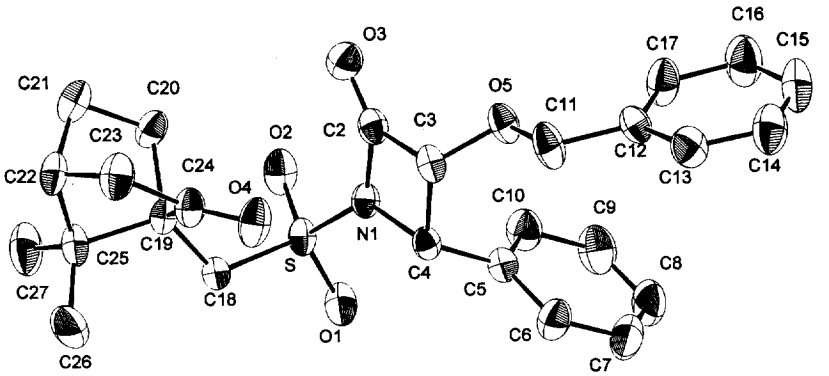
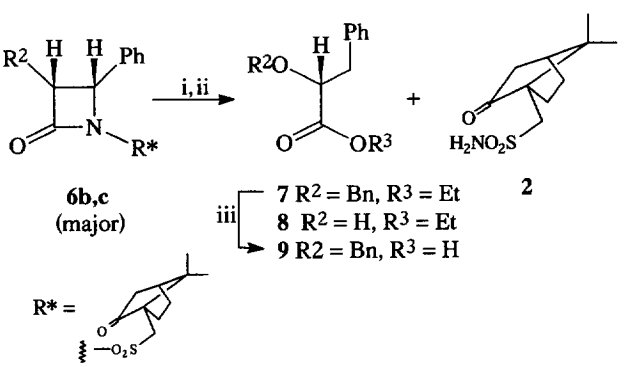


Fig. 1 ORTEP diagram of β-lactam **6b**

The cleavage of the N1 - C4 bond of the β-lactams **6b** and **6c** was carried out under hydrogenolysis conditions[13] using Pd/C in refluxing EtOH, the reaction was complete in 12 h (TLC). The reaction mixture was filtered to remove Pd/C; the filtrate, on removal of ethanol, gave the crude amides, which were used for further reaction without purification. These crude amides were refluxed with ethanolic HCl solution for 8 h (Scheme 2) to afford the crude esters **7** and **8**. Column chromatography (silica gel, 60 - 120, pet-ether/acetone) of the crude reaction product gave pure α-benzyloxy esters **7** (70%) and α-hydroxy esters **8** (65%)[14] along with the chiral auxiliary, camphor-10-sulfonamide **2**, which was recovered by further elution of the column.

Scheme 2



Reagent and conditions : i) H_2/Pd-C, EtOH, reflux, 12 h. ii) HCl/EtOH, reflux, 8 h. iii) KOH/MeOH, r.t., 8 h.

The ester **7** was hydrolyzed by methanolic KOH under reflux conditions to the corresponding acid **9** in quantitative yield. The absolute configuration of α-hydroxy ester **8** and α-benzyloxy acid **9** was confirmed as 2*R* by comparing the specific rotation with the reported values.[2c,15,16]

In conclusion, we have presented an efficient and novel synthesis of O-protected α-hydroxy esters *via* β-lactams. These β-lactams in turn have been synthesized in high enantiomeric purity using easily available camphor-10-sulfonic acid as a recyclable chiral auxiliary.

Acknowledgment : We thank Dr. S. Rajappa and Dr. A. Sarkar for valuable suggestions and one of the authors (VS) thanks CSIR for the financial support.

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.

General procedure for the preparation of imine 3a-c. A mixture of camphor-10-sulfonamide **2** (10 mmol) and diethyl acetals of aromatic aldehydes (12 mmol) was heated at 140 °C for 15 min. The ethanol formed during reaction was collected using distillation condenser. The reaction mixture on crystallization from benzene/ pet. ether gave pure imines **3a-c** in very high yield.

(1'*S*)-N-Camphor-10-sulfonyl benzaldimine 3a. M. p. : 112 -114 °C. ^{1}H NMR : δ 0.9 (s, 3H); 1.2 (s, 3H); 1.4 (m, 1H); 1.8 - 2.1 (m, 4H); 2.4 (m, 1H); 2.6 (m, 1H); 3.1 and 3.7 (d, J = 15.6 Hz, 1H); 7.5 - 7.7 (m, 3H); 8.0 (d, J = 10.4 Hz, 2H); 9.1 (s, 1H). ^{13}C NMR : 19.3, 19.5, 24.7, 26.6, 42.1, 42.3, 47.6, 49.2, 58.1, 128.9, 130.9, 131.9, 134.7, 171.2, 213.6. IR : 1730, 1610 $[\alpha]^{25}_D$: +20.6 (c 1, CH_2Cl_2). Anal. Cald for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39; S, 10.02. Found : C, 63.98; H, 6.72; N, 4.50; S, 10.35.

(1'*S*)-N-Camphor-10'-sulfonyl tolualdimine 3b. M. p. : 79 - 80°C. ^{1}H NMR : 0.95 (s, 3H); 1.15 (s, 3H); 1.45 (m, 1H); 1.7 - 2.2 (m, 4H); 2.35 (m, 1H); 2.5 (s, 3H); 2.8 (m, 1H); 3.1 and 3.7 (d, J = 15 Hz, 1H); 7.35 (d, J = 8 Hz, 2H); 7.9 (d, J = 8 Hz, 2H); 9.0 (s, 1H). IR : 1730, 1600. $[\alpha]^{25}_D$: +30.3 (c 1.3, CH_2Cl_2).

(1'*S*)-N-Camphor-10'-sulfonyl anisaldimine 3c. Isolated as an oil. ^{1}H NMR : 0.85 (s, 3H); 1.15 (s, 3H); 1.4 (m, 1H); 1.65 - 2.2 (m, 4H); 2.35 (m, 1H); 2.6 (m, 1H); 3.05 and 3.6 (d, J = 16 Hz, 1H); 3.85 (s, 3H); 7.0 and 7.9 (d, J = 8 Hz, 2H); 8.9 (s, 1H). IR : 1730, 1600. $[\alpha]^{25}_D$ = +24.9 (c 2.5, CH_2Cl_2).

Typical procedure for the preparation of β-lactams 5 and 6. A solution of the acid chloride (1.4 mmol) in dry CH_2Cl_2 was slowly added to a solution of imines (1.2 mmol) and triethylamine in CH_2Cl_2 (15 mL) at -23°C. The reaction mixture was then allowed to warm to r.t. and stirred further for 15 h. It was then washed with water (15 X 2 mL), satd. $NaHCO_3$ (10 mL), brine and dried (Na_2SO_4). The removal of organic solvent by distillation and filtration of crude product through short silica gel column gave diastereomeric mixture of β-lactams **5a-e** and **6a-e** in good yields. The major diastereomers **6a-e** were isolated in pure form by crystallization from pet-ether/acetone.

(3*R*,4*S*,1'*S*)-1-(Camphor-10-sulfonyl)-3-phenoxy-4-phenylazetidin-2-one 6a. M.p. : 128 - 131°C. ^{1}H NMR : δ 0.85 (s, 3H); 1.05 (s, 3H); 1.5 (m, 1H); 1.85 - 2.2 (m, 4H); 2.4 (m, 2H); 3.05 (d, J = 14.6 Hz, 1H); 3.55 (d, J = 14.6 Hz, 1H); 5.6 (d, J = 5.0 Hz, 1H); 5.75 (d, J = 5.0 Hz, 1H); 6.7 - 7.05 (m, 3H); 7.1 - 7.65 (m, 7H). ^{13}C NMR : 19.5, 19.7, 26.1, 27.1, 42.8, 42.9, 48.9, 52.6, 59.3, 64.8, 81.6, 115.9, 122.7, 128.4, 128.5, 129.1, 129.5, 129.8, 132.6, 163.2, 215.4. IR : 1800, 1740. $[\alpha]^{25}_D$: +76.07 (c 1.6, CH_2Cl_2). Anal. Cald for $C_{25}H_{27}NO_5S$: C, 66.20; H, 6.00; N, 3.09; S, 7.06. Found : C, 65.96; H, 6.10; N, 3.24; S, 7.43.

(3*R*,4*S*,1'*S*)-3-Benzyloxy-1-(camphor-10-sulfonyl)-4-phenylazetidin-2-one 6b. M.p. 122 - 124 °C. ^{1}H NMR : δ 0.8 (s, 3H); 1.05 (s, 3H); 1.45 (m, 1H); 1.8 - 2.2 (m, 4H); 2.35 (m, 2H); 3.05 (d, J = 15 Hz, 1H); 3.45 (d, J = 15 Hz, 1H), 4.25 (d, J = 10 Hz, 1H); 4.40 (d, J = 10 Hz, 1H); 5.20 (d, J = 5 Hz, 1H); 5.5 (d, J = 5 Hz, 1H); 6.90 - 7.50 (m, 10H). ^{13}C NMR : 19.6, 19.6, 24.8, 27.1, 42.5, 42.7, 48.7, 51.8, 58.6, 64.4, 73.0, 83.6, 128.1, 128.4, 128.5, 128.7, 129.1, 132.8, 135.9, 164.3, 215.0. IR : 1800, 1740. $[\alpha]^{25}_D$: +119.3 (c 1, CH_2Cl_2). Anal. Calcd for $C_{26}H_{29}NO_5S$: C, 66.79; H, 6.25; N, 3.00; S, 6.86. Found : C, 66.67; H, 6.34; N, 3.20; S, 7.12.

(3*R*,4*S*,1'*S*)-3-Acetoxy-1-(camphor-10-sulfonyl)-4-phenylazetidin-2-one 6c. M.p. : 144 - 146°C. ^{1}H NMR : δ 0.9 (s, 3H); 1.0 (s, 3H); 1.45 (m, 1H); 1.7 (s, 3H); 1.8 - 2.3 (m, 5H) 2.45 (m, 1H) 3.05(d, J = 14.6 Hz, 1H); 3.95(d, J = 14.6 Hz, 1H); 5.5 (d, J = 5.0 Hz, 1H); 6.2 (d, J = 5.0 Hz, 1H); 7.4 (m, 5H) . ^{13}C NMR : 19.5, 19.8, 26.2, 27.2, 42.7, 42.9, 49.1, 52.5, 59.3, 64.6, 128.1, 128.5, 129.1, 132.3, 162.6, 169.5, 216.0. IR : 1800,

1740. $[\alpha]^{25}_D$: -22.9 (c 1, CH_2Cl_2). Anal. Cald for $C_{21}H_{25}NO_6S$: C, 60.12; H, 6.01; N, 3.34; S, 7.63. Found : C, 60.25; H, 6.14; N, 3.64; S, 7.40.

(3*R*,4*S*,1'*S*)-1-(Camphor-10-sulfonyl)-3-phenoxy-4-*p*-tolylazetidin-2-one 6d. M.p. : 186 -188°C. ^{1}H NMR : δ 0.9 (s, 3H); 1.05 (s, 3H); 1.5 (m, 1H); 1.75 - 2.2 (m, 5H); 2.35 (s, 3H); 2.8 (m, 1H); 3.0 (d, *J* = 14 Hz, 1H); 3.5 (d, *J* = 14 Hz, 1H); 5.6 (d, *J* = 5 Hz, 1H); 5.7 (d, *J* = 5 Hz, 1H); 6.75 (d, *J* = 10 Hz, 2H); 6.95 (m, 2H); 7.10 - 7.45 (m, 5H). IR.: 1800, 1740. $[\alpha]^{25}_D$: +50.33 (c 0.18, $CHCl_3$). Anal. Cald for $C_{26}H_{29}NO_5S$: C, 66.79; H, 6.25; N, 3.00; S, 6.86. Found : C, 66.94; H, 6.47; N, 2.96; S, 7.11.

(3*R*,4*S*,1'*S*)-4-*p*-Anisyl-1-(camphor-10-sulfonyl)-3-phenoxyazetidin-2-one 6e. M.p. : 138 - 140°C. ^{1}H NMR : δ 0.9 (s, 3H); 1.05 (s, 3H); 1.5 (m, 1H); 1.85 - 2.25 (m, 4H); 2.4 (m, 2H); 3.0 (d, *J* = 15.0 Hz, 1H); 3.5 (d, *J* = 15.0 Hz, 1H); 3.8 (s, 3H); 5.6 (d, *J* = 5.3 Hz, 1H); 5.7(d, *J* = 5.3 Hz, 1H); 6.7 - 7.5 (m, 10). ^{13}C NMR : 19.7, 19.8, 24.9, 27.2, 42.7, 42.9, 48.9, 52.1, 55.4, 58.8, 64.5, 82.2, 114.0, 115.9, 122.8, 124.1, 129.6, 130.2, 160.4, 163.6, 215.4. IR : 3020, 1800, 1740. $[\alpha]^{25}_D$: +17.89 (c 0.6, CH_2Cl_2). Anal. Cald for $C_{26}H_{29}NO_6S$: C, 64.57; H, 6.05; N, 2.90; S, 6.62. Found : C, 64.71; H, 6.06; N, 3.10; S, 6.89.

Procedure for the preparation of esters 7 and 8. To a solution of β-lactam **6b** or **6c** (1 mmol) in ethanol (20 mL), Pd/C (20 mg) was added and it was refluxed under H_2 atmosphere (1 atm) for 12 h. The reaction mixture was cooled, filtered to remove Pd/C and ethanol was removed under reduced pressure. To the residue, satd. EtOH with HCl (15 mL) was added and refluxed for 8 h. The solvent was distilled off under reduced pressure and the residue was purified by column chromatography (silica gel, 60 - 120, pet.-ether/acetone) to give α-benzyloxy ester **7** (0.190 g , 70%) or α- hydroxy ester **8** (0.055 g , 65%).

(2*R*)-Ethyl 2-benzyloxy-3-phenylpropionate 7. Isolated as an oil. ^{1}H NMR : δ 1.3 (t, *J* = 7.5 Hz, 3H); 3.15 (m, 2H); 4.2 (m, 3H); 4.4 (d, *J* = 12.5 Hz, 1H); 4.7 (d, *J* = 12.5 Hz, 1H); 7.3 (m, 10H). ^{13}C NMR : 14.1, 39.2, 60.8, 72.3, 79.2, 126.1, 127.7, 128.1, 128.3, 129.4, 136.9, 137.2, 172.8. IR : 2990, 1730. $[\alpha]^{25}_D$: +5.18 (c 1.2, CH_2Cl_2). Anal. Cald for $C_{18}H_{20}O_3$: C, 76.02; H, 7.09. Found : C, 76.17; H, 7.30.

(2*R*)-Ethyl 2-hydroxy-3-phenylpropionate 8. Isolated as an oil. ^{1}H NMR : δ 1.3 (t, *J* = 7.3 Hz, 3H); 3.0 (dd, *J* = 5.5 and 14 Hz, 1H); 2.75 (bs, 1H); 3.15 (dd, *J* = 4.8 and 14 Hz, 1H); 4.25 (q, *J* = 7.0 Hz, 2H); 4.45 (m, 1H); 7.25 (m, 5H). ^{13}C NMR : 13.9, 40.4, 61.5, 71.0, 126.6, 128.1, 129.3, 136.2, 173.9. IR : 2980 and 1730. $[\alpha]^{25}_D$: +21.89 (c 0.57, C_6H_6). Anal. Cald for $C_{11}H_{14}O_3$: C, 68.01; H, 7.27. Found : C, 68.36; H, 7.30.

(2*R*)-2-Benzyloxy-3-phenylpropionic acid 9. To a solution of ester **7** (0.190 g, 0.7 mmol) in methanol (10 mL), a solution of KOH (1.0 g) in methanol (10 mL) was added slowly at room temperature and stirred for 8 h. The solvent was removed under reduced pressure and the residue was diluted with water and extracted with EtOAc. The aqueous layer was acidified with 20% aq. HCl and extracted with ethyl acetate (10 X 3 mL). The ethyl acetate extract was washed with brine (10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to get crude product which on purification by column chromatography afforded 0.160 g (93%) of pure acid **9** as an oil. ^{1}H NMR : δ 3.15 (m, 2H); 4.2 (m, 1H); 4.4 (d, *J* = 12.9 Hz, 1H); 4.7 (d, *J* = 12.9 Hz, 1H); 7.15 - 7.45 (m, 10H); 9.0 (broad s, 1H). ^{13}C NMR : 38.8, 72.7, 78.5, 126.7, 127.7, 127.8, 128.3, 129.4, 136.5, 136.6, 176.1. IR : 3500 - 3000, 2924, 1720. $[\alpha]^{25}_D$: +79.10 (c 2.37, EtOH). Anal. Cald for $C_{16}H_{16}O_3$: C, 74.97; H, 6.30. Found : C, 74.83; H, 6.52.

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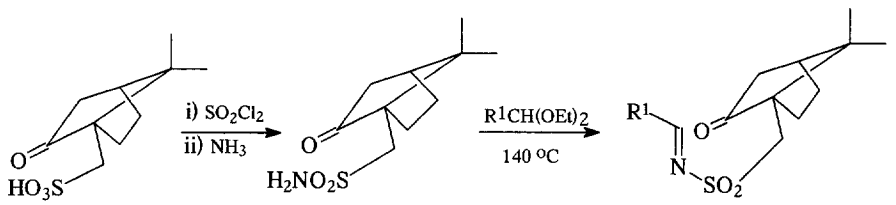

1 **2** **3a-c**

10. In all the cases ^1H NMR (200 MHz) spectral analyses of the crude reaction mixture showed formation of only *cis* diastereomers.

11. HPLC : Perkin-Elmer 410-pump. H.P. 1050 MWD at 270 nm connected to H-P 3396 Ser-II integrater. Col. MN-C-18, 8 mm, 4 mm X 100 mm length. Solvent system (v/v): CH_3CN:H_2O (68:32), flow rate 1 mL/min.

12. X-ray determination of **6b** : Data were measured on a PC-controlled Enraf-Nonius CAD-4 single crystal X-ray diffractometer using graphite monochromator Mo-Kα (λ = 0.7107°A) radition. Crystal belongs to triclinic space group P1 with a = 6.751(1), b = 9.270(2), c = 9.926(2) °A; α = 86.97(1), β = 82.04(2), γ = 89.01(1)°; V = 614.3(2)°A; Z = 1, dcalc = 1.264 Mg m^{-3}, μ = 0.168 mm^{-1}, out of 1989 reflections measured, 1955 were treated observed with [I ≥ 2.0 σ (I)]. The structure was solved by the direct methods using MULTAN - 80 (NRCVAX - program).[17a] Least square refinement of scale factor positional and anisotropic thermal parameters for non hydrogen atoms converged to R = 0.0440, Rw = 0.130. Hydrogen atoms were geometrically fixed during the refinement and confirmed by a difference Fourier transform. Refinements were carried out by using SHELXL - 93 program.[17b]

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14. During the hydrogenolysis followed by hydrolysis of a β-lactams **6c**, the acetoxy group also under went hydrolysis to give α-hydroxy esters **8**.

15. **10** : {$[\alpha]^D_{25}$ = +21.9 (c 0.57, C_6H_6); lit.[16] $[\alpha]^D_{25}$ = +21.4 (c 0.43, C_6H_6)}.

    11 : {$[\alpha]^D_{25}$ = +79.10 (c 2.37, EtOH); lit.[2c] value for its antipode $[\alpha]^D_{25}$ = -81.0 (c 2.24, EtOH)}.

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