SYNTHESES AND ABSOLUTE CONFIGURATIONS OF OPTICALLY PURE 4-ISOPROPYL-*N*-TOSYL-1,3-OXAZOLIDINES

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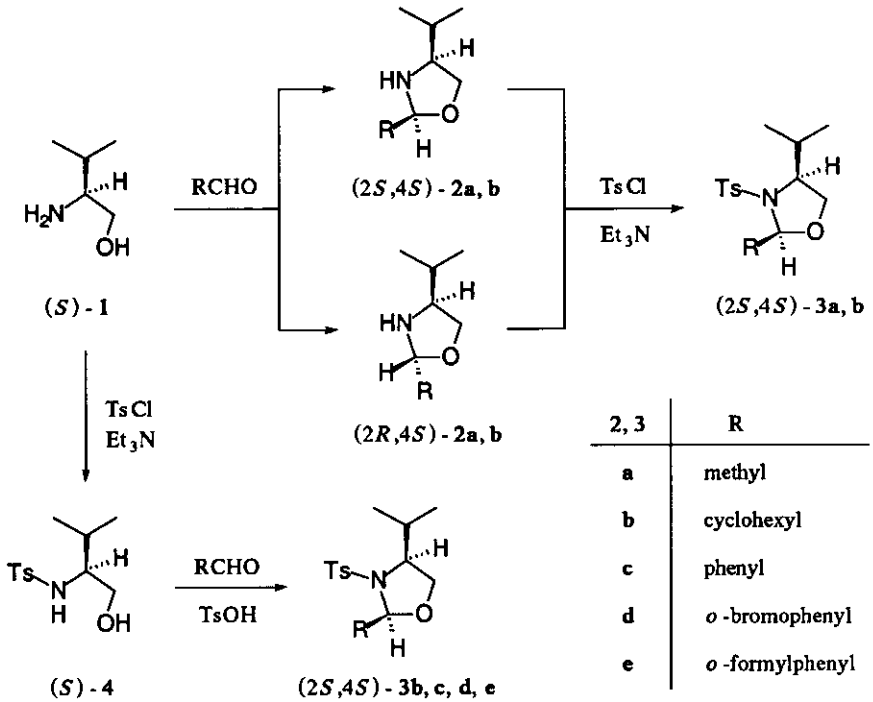
Abstract——(2*S*,4*S*)-4-Isopropyl-*N*-tosyl-1,3-oxazolidines (**3a-e**) having methyl, cyclohexyl, phenyl, *o*-bromophenyl, or *o*-formylphenyl group at the 2-position of the ring were synthesized, and these products were confirmed to consist of one isomer by ^{1}H-nmr spectral analyses in spite of a newly created asymmetric center at the 2-position. The absolute configurations of **3a-e** were determined by difference nuclear Overhauser effect studies.

The chiral 1,3-oxazolidines are easily synthesized by the condensation of (*R*)- or (*S*)-*N*-alkyl-2-hydroxyethylamines with carbaldehydes.[1,2] However, the 1,3-oxazolidine compounds lacked with group at the *N*-atom are obtained as a mixture of two isomers (the ratio is about 2:1),[1] while the *N*-methyl, *N*-ethyl, and *N*-isopropyl-1,3-oxazolidine compounds are prepared as a mixture of the major and the minor products (the ratio is about 9:1).[2-3] Pure compounds of these products could not be isolated from the mixture by

column chromatography on account of equilibration of the two isomers during column chromatography. In this paper, we wish to report a syntheses of new optically pure 4-isopropyl-*N*-tosyl-1,3-oxazolidines, and to describe elucidations of the absolute configurations of these compounds.



2, 3	R
a	methyl
b	cyclohexyl
c	phenyl
d	*o*-bromophenyl
e	*o*-formylphenyl

Condensation of (*S*)-valinol (1) with acetaldehyde gave 4-isopropyl-2-methyl-1,3-oxazolidine (2a). 2-Cyclohexyl-4-isopropyl-1,3-oxazolidine (2b) was obtained by the condensation with cyclohexylcarbaldehyde in a similar prosedure.[4] These compounds (2a and 2b) were confirmed to consist of two diastereomeric isomers and the ratio of the major to the minor components was estimated as about 2:1 by proton nuclear magnetic resonance (^{1}H-nmr) spectral analysis. The *N*-tosylation of 2a and 2b gave a colorless stable solid of 4-isopropyl-*N*-tosyl-1,3-oxazolidines (3a and 3b) in 74% and 64% yields, respectively. These products were confirmed to consist of one isomer by ^{1}H-nmr spectral analysis, and it was suggested

that the configuration of 1,3-oxazolidine ring is converted into a stable form by carbon-oxygen bond cleavage in order to introduction of the tosyl group at the *N*-atom.

Since the condensation of (*S*)-**1** with aromatic aldehydes has been known to give methylidenamine compounds,[5] (*S*)-**1** was converted into (*S*)-*N*-tosylvalinol (**4**), followed by condensations with phenyl, *o*-bromophenyl, or *o*-formylphenylcarbaldehydes to give a colorless stable solid of 4-isopropyl-*N*-tosyl-1,3-oxazolidines (**3c**, **3d**, and **3e**) in 83%, 92%, and 53% yields, respectively. The compound (**3b**) was also prepared from (*S*)-**4** and cyclohexylcarbaldehyde in 86% yield. It was confirmed that these products are not contaminated by the other diastereomeric isomer.

Recently, the X-ray crystal analysis of (2*R*,4*R*)-2-(*p*-bromophenyl)-*N*-methyl-4-phenyl-1,3-oxazolidine has been studied,[2] and the difference nuclear Overhauser effect (NOE) of two compounds [(1'*S*,2*S*,4*S*)-3-benzyl-2-[1'-(dibenzylamino)ethyl]-4-isopropyl-1,3-oxazolidine[6] and (2*R*,4*R*)-3-cyanomethyl-4-phenyl-1,3-oxazolidine[3]] has been reported. On the other hand, we have assumed that the configuration of 2-aryl-4-isopropyl-*N*-methyl-1,3-oxazolidines must be like **3c-e** by the quadrant-sector rule of the circular dichroism.[7] Now, we attempted the difference NOE spectral analyses in order to elucidate the absolute configurations of **3a-e**. The irradiation peaks and the observed difference NOE peaks are summarized in Table, and the protons of the 1,3-oxazolidine ring are shown in Figure.

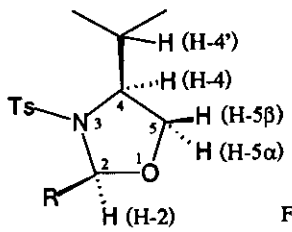


Figure Protons of 3a - e

TABLE Difference Nuclear Overhauser Effect on (2*S*,4*S*)-4-Isopropyl-*N*-tosyl-1,3-oxazolidines (**3a - e**); Irradiation and Enhanced Peaks of the Protons at 2, 4, 5α, and 5β-Position

Compound		(H-2)	(H-4)	(H-5α)	(H-5β)	(Others)
3a	Irradiation	H-2 (δ 5.01)	H-4 (δ 3.40)	H-5α (δ 3.08)	H-5β (δ 3.75)	CH_3 (δ 1.51)
	Enhanced peaks	H-5α (δ 3.08) CH_3 (δ 1.51)	H-5α (δ 3.08), H-4' (δ 1.90) CH_3 (δ 0.94), CH_3 (δ 1.02)	H-2 (δ 5.01), H-4 (δ 3.40) H-5β (δ 3.75)	H-5α (δ 3.08) H-4' (δ 1.90)	H-2 (δ 5.01), H-5β (δ 3.75) H-4' (δ 1.90) CH_3 (δ 0.94), CH_3 (δ 1.02)
3b	Irradiation	H-2 (δ 4.77)	H-4 (δ 3.33)	H-5α (δ 3.18)	H-5β (δ 3.63)	
	Enhanced peaks	H-5α (δ 3.18)	H-5α (δ 3.18)	H-2 (δ 4.77), H-4 (δ 3.33) H-5β (δ 3.63)	H-5α (δ 3.18)	
3c[1]	Irradiation	H-2 (δ 6.40)		H-5α (δ 3.29)		H-4' (δ 1.47)
	Enhanced peaks	H-5α (δ 3.29)		H-2 (δ 6.40), H-4 (δ 3.52) H-5β (δ 3.41)		H-4 (δ 3.52), H-5β (δ 3.41) CH_3 (δ 0.49), CH_3 (δ 0.99)
3d	Irradiation	H-2 (δ 6.09)	H-4 (δ 3.56)	H-5α (δ 3.26)	H-5β (δ 3.87)	H-4' (δ 2.01)
	Enhanced peaks	H-5α (δ 3.26)	H-5α (δ 3.26), H-4' (δ 2.01) CH_3 (δ 0.99), CH_3 (δ 1.22)	H-2 (δ 6.09), H-4 (δ 3.56) H-5β (δ 3.87)	H-5α (δ 3.26) H-4' (δ 2.01)	H-4 (δ 3.56), H-5β (δ 3.87) CH_3 (δ 0.99), CH_3 (δ 1.22)
3e	Irradiation	H-2 (δ 6.78)	H-4 (δ 3.53)	H-5α (δ 3.31)	H-5β (δ 3.72)	H-4' (δ 1.77)
	Enhanced peaks	H-5α (δ 3.31) CHO (δ 10.33)	H-5α (δ 3.31), H-4' (δ 1.77) CH_3 (δ 0.89), CH_3 (δ 1.16)	H-2 (δ 6.78), H-4 (δ 3.53) H-5β (δ 3.72)	H-5α (δ 3.31) H-4' (δ 1.77)	H-4 (δ 3.53), H-5β (δ 3.72) CH_3 (δ 0.89), CH_3 (δ 1.16)

1) Is obtained in C_6D_6.

The configurations of **3a-e** were assigned with the NOE difference spectroscopy results: irradiation on the resonance of H-2 enhanced H-5α; irradiation of H-4 enhanced H-5α, H-4', and CH_3 of isopropyl group; irradiation of H-5α enhanced H-2, H-4, and H-5β; and irradiation of H-5β enhanced H-5α and H-4'. These results indicate that the hydrogens of H-2, H-4, and H-5α are all below for the 1,3-oxazolidine ring, therefore the substituents at 2-position are determined to attach in a *cis* relationship to the isopropyl group at the 4-position of the ring.

EXPERIMENTAL

(*S*)-Valinol was synthesized from (*S*)-valine.[8] Tosyl chloride was purchased from Tokyo Kasei Kogyo Co. Cyclohexylcarbaldehyde, 2-bromobenzaldehyde, and phthalaldehyde were purchased from Aldrich Chemical Co. Reagent quality solvents were used without further purification. Tlc plates and silica gel (230-400 mesh) were used Kieselgel 60 F_{254} and Kieselgel 60. Melting points were taked using a Yanagimoto micromelting-point apparatus and are uncorrected. Microanalyses were obtained using a Perkin-Elmer 240B element analyser, and observed rotations at the Na-D line were obtained using a JASCO DIP-370 digital polarimeter. Mass spectra were obtained using a JEOL JMS-D300 spectrometer with CI ionization. Ir spectra were obtained using a Hitachi 215 spectrophotometer. ^{1}H-Nmr spectra were obtained using a JEOL JNM-GSX270 spectrometer.

Mixture of (2*R*,4*S*)- and (2*S*,4*S*)-4-Isopropyl-2-methyl-1,3-oxazolidine (2a)

A solution of (*S*)-valinol (1, 5.15 g, 50 mmol) in ether (15 ml) is added dropwise to a solution of acetaldehyde (4.4 g, 100 mmol) in ether (25 ml) in the presence of anhydrous Na_2SO_4 (10 g), and the reaction mixture is stirred at 0°C under a nitrogen atmosphere for 1 h. The precipitates are filtered off and the filtrate is evaporated under reduced pressure to give

2a as a colorless oil (5.8 g, 90%). This product is confirmed to consist of the two diastereomers (ratio; about 2:1) by ^{1}H-nmr spectral analysis, and these are decomposed during distillation *in vacuo*. ^{1}H-Nmr ($CDCl_3$) Major component; δ: 0.93(3H, d, *J*=6.7 Hz, $CH(C\underline{H}_3)_2$), 1.06(3H, d, *J*=6.7 Hz, $CH(C\underline{H}_3)_2$), 1.39(3H, d, *J*=5.5 Hz, $NCHC\underline{H}_3$), 1.50-1.67(1H, m, $C\underline{H}(CH_3)_2$), 1.73(1H, br, NH), 3.01(1H, q, *J*=7.6 Hz, $NC\underline{H}CH_2O$), 3.31(1H, t, *J*=7.6 Hz, $NCHC\underline{H}_2O$), 3.82(1H, t, *J*=7.6 Hz, $NCHC\underline{H}_2O$), 4.53(1H, q, *J*=5.5 Hz, $NC\underline{H}CH_3$). Minor component; δ: 0.86(3H, d, *J*=6.7 Hz, $CH(C\underline{H}_3)_2$), 1.01(3H, d, *J*=6.7 Hz, $CH(C\underline{H}_3)_2$), 1.34(3H, d, *J*=5.5 Hz, $NCHC\underline{H}_3$), 1.50-1.67(1H, m, $C\underline{H}(CH_3)_2$), 1.73(1H, br, NH), 3.02(1H, q, *J*=7.6 Hz, $NC\underline{H}CH_2O$), 3.35(1H, t, *J*=7.6 Hz, $NCHC\underline{H}_2O$), 3.98(1H, t, *J*=7.6 Hz, $NCHC\underline{H}_2O$), 4.50(1H, q, *J*=5.5 Hz, $NC\underline{H}CH_3$).

General Procedure for the Syntheses of *N*-Tosyl-1,3-oxazolidines (Method A)

Tosyl chloride (4.77 g, 25 mmol) is added to a stirred solution of the diastereomeric mixture of 4-isopropyl-1,3-oxazolidine (**2a** and **2b**, 25 mmol) and Et_3N (3.04 g, 30 mmol) in CH_2Cl_2 (40 ml) at 0°C, and stirring is continued at room temperature for 3 h. The reaction mixture is concentrated under reduced pressure. The oily residue is dissolved in ethyl acetate (40 ml) and passed through a shortcolumn of silica gel. The solvent is evaporated off under reduced pressure to give a colorless solid of **3a** and **3b**. These products are confirmed to consist of one diastereomeric isomer by ^{1}H-nmr spectral analysis.

(2*S*,4*S*)-4-Isopropyl-2-methyl-*N*-tosyl-1,3-oxazolidine (3a)

Yield, 5.24 g (74%). Colorless plates, mp 79-80°C (hexane). *Anal.* Calcd for $C_{14}H_{21}NO_3S$: C,59.34; H,7.47; N,4.94. Found: C,59.35; H,7.66; N,4.98. $[\alpha]_D^{29}$ +26.2° (*c*=1.37, $CHCl_3$). Ms *m/z*: 284(M^++1, 100%). Ir ($CHCl_3$) cm^{-1}: 1342(SO_2), 1158(SO_2). ^{1}H-Nmr ($CDCl_3$) δ : 0.94(3H, d, *J*=7.0 Hz, $CH(C\underline{H}_3)_2$), 1.02(3H, d, *J*=7.0 Hz, $CH(C\underline{H}_3)_2$), 1.51(3H, d, *J*=5.5 Hz, $NCHC\underline{H}_3$), 1.90(1H, double septet, *J*=7.9, 7.0 Hz, $C\underline{H}(CH_3)_2$), 2.44(3H, s, $C_6H_4C\underline{H}_3$), 3.08(1H, dd,

J=6.1, 9.2 Hz, NCHC$\underline{H}_2$O), 3.40(1H, ddd, J=2.4, 6.1, 7.9 Hz, NC$\underline{H}$CH$_2$O), 3.75 (1H, dd, J=2.4, 9.2 Hz, NCHC$\underline{H}_2$O), 5.01(1H, q, J=5.5 Hz, NC$\underline{H}$CH$_3$), 7.34(2H, d, J=8.2 Hz, aromatic H), 7.73(2H, d, J=8.2 Hz, aromatic H).

(2*S*,4*S*)-2-Cyclohexyl-4-isopropyl-*N*-tosyl-1,3-oxazolidine (3b)

Yield, 5.63 g (64%). Colorless prisms, mp 114,5-115.5°C (hexane). *Anal.* Calcd for $C_{19}H_{29}NO_3S$: C,64.92; H,8.32; N,3.98. Found: C,64.98; H,8.44; N,4.16. $[\alpha]_D^{29}$ -25.1° (c=1.40, $CHCl_3$). Ms m/z : 352(M^++1, 100%). Ir ($CHCl_3$) cm^{-1}: 1342(SO_2), 1158(SO_2). ^{1}H-Nmr ($CDCl_3$) δ : 0.89(3H, d, J=6.7 Hz, CH(C$\underline{H}_3$)$_2$), 0.99-1.30(5H, m, C_6H_{11}), 1.09(3H, d, J=6.7 Hz, CH(C$\underline{H}_3$)$_2$), 1.55-1.90(7H, m, C_6H_{11} and C$\underline{H}$(CH$_3$)$_2$), 2.43(3H, s, $C_6H_4C\underline{H}_3$), 3.18(1H, dd, J=6.7, 8.6 Hz, NCHC$\underline{H}_2$O), 3.33(1H, ddd, J=3.7, 6.7, 9.2 Hz, NC$\underline{H}$CH$_2$O), 3.63 (1H, dd, J=3.7, 8.6 Hz, NCHC$\underline{H}_2$O), 4.77(1H, d, J=6.7 Hz, NCHO), 7.32(2H, d, J=8.5 Hz, aromatic H), 7.72(2H, d, J=8.5 Hz, aromatic H).

(*S*)-*N*-Tosylvalinol (4)

Tosyl chloride (3.8 g, 20 mmol) is added to a stirred solution of (*S*)-1 (2.1 g, 20 mmol) and Et_3N (2.2 g, 22 mmol) in CH_2Cl_2 (25 ml) at 0°C, and stirring is continued at room temperature for 2 h. The reaction mixture is worked up as described for the preparations of **3a** and **3b** to give a colorless solid (4.1 g, 80%). Colorless needles, mp 85-86°C (hexane-CH_2Cl_2). *Anal.* Calcd for $C_{12}H_{19}NO_3S$: C,56.00; H,7.44; N,5.44. Found: C,55.99; H,7.64; N,5.47. $[\alpha]_D^{25}$ -28.5° (c=2.76, $CHCl_3$). Ms m/z: 258 (M^++1, 100%). Ir ($CHCl_3$) cm^{-1}: 3540(OH), 3400(NH), 1320(SO_2), 1150(SO_2). ^{1}H-Nmr ($CDCl_3$) δ: 0.79(3H, d, J=6.7 Hz, CH(C$\underline{H}_3$)$_2$), 0.80(3H, d, J=6.7 Hz, CH(C$\underline{H}_3$)$_2$), 1.78(1H, octet, J=6.7 Hz, C$\underline{H}$(CH$_3$)$_2$), 1.98(1H, dd, J=5.5, 6.1 Hz, OH), 2.43(3H, s, $C_6H_4C\underline{H}_3$), 3.00-3.09(1H, m, NC$\underline{H}$CH$_2$OH), 3.54(1H, ddd, J=5.5, 6.1, 11.6 Hz, NCHC$\underline{H}_2$OH), 3.60(1H, dt, J=11.6, 5.5 Hz, NCHC$\underline{H}_2$OH), 4.79(1H, d, J=8.6 Hz, NH), 7.31(2H, J=7.9 Hz, aromatic H), 7.78(2H, d, J=7.9 Hz, aromatic H).

General Procedure for the Synthesis of *N*-Tosyl-1,3-oxazolidines

(Method B)

A mixture of (*S*)-**4** (2.57 g, 10 mmol), aldehyde (cyclohexylcarbaldehyde, benzaldehyde, *o*-bromobenzaldehyde, or phthalaldehyde, 12 mmol), and *p*-toluenesulfonic acid monohydate (0.25 g, 1.3 mmol) in benzene (20 ml) is refluxed for 1 h using a Dean-Stark trap. After addition of ethyl acetate (50 ml) and water (10 ml) to the reaction mixture, the organic solution is washed with water (10 ml) and brine (10 ml), and dried (Na_2SO_4). Removal of the solvent gives coloeless solids of **3b**, **3c**, **3d**, and **3e**. These products are confirmed to consist of one diastereomeric isomer by ^{1}H-nmr spectral analysis.

(2*S*,4*S*)-2-Cyclohexyl-4-isopropyl-*N*-tosyl-1,3-oxazolidine (3b)

Yield, 3.02 g (86%). The experimental data are similar to that described above.

(2*S*,4*S*)-4-isopropyl-2-phenyl-*N*-tosyl-1,3-oxazolidine (3c)

Yield, 2.87 g (83%). Colorless prisms, mp 80.5-81.5°C (hexane-isopropanol). *Anal.* Calcd for $C_{19}H_{23}NO_3S$: C,66.06; H,6.71; N,4.05. Found: C, 65.97; H,6.74; N,4.03. $[\alpha]_D^{29}$ -66.1° (*c*=1.57, $CHCl_3$). Ms *m/z*: 346(M^++1, 100%). Ir ($CHCl_3$) cm^{-1}: 1345(SO_2), 1158(SO_2). ^{1}H-Nmr (C_6D_6) δ: 0.49(3H, d, *J*=6.7 Hz, $CH(C\underline{H}_3)_2$), 0.99(3H, d, *J*=6.7 Hz, $CH(C\underline{H}_3)_2$), 1.47(1H, double septet, *J*=8.9, 6.7 Hz, $C\underline{H}(CH_3)_2$), 1.94(3H, s, $C_6H_4C\underline{H}_3$), 3.29(1H, dd, *J*=7.0, 8.2 Hz, $NCHC\underline{H}_2O$), 3.41(1H, dd, *J*=4.9, 8.2 Hz, $NCHC\underline{H}_2O$), 3.52(1H, ddd, *J*=4.9, 7.0, 8.9 Hz, $NC\underline{H}CH_2O$), 6.40(1H, s, NCHO), 6.80-7.74(9H, m, aromatic H). ^{1}H-Nmr ($CDCl_3$) δ: 0.74(3H, d, *J*=6.7 Hz, $CH(C\underline{H}_3)_2$), 0.99(3H, d, *J*=6.7 Hz, $CH(C\underline{H}_3)_2$), 1.49(1H, octet, *J*=6.7 Hz, $C\underline{H}(CH_3)_2$), 2.45(3H, s, $C_6H_4C\underline{H}_3$), 3.50-3.71(3H, m, $NCHCH_2O$), 6.22(1H, s, NCHO), 7.27-7.80(9H, m, aromatic H).

(2*S*,4*S*)-2-(*o*-Bromophenyl)-4-isopropyl-*N*-tosyl-1,3-oxazolidine (3d)

Yield, 3.90 g (92%). Colorless plates, mp 139.5-140.5°C (hexane-CH_2Cl_2). *Anal.* Calcd for $C_{19}H_{22}NO_3BrS$: C,53.78; H,5.23; N,3.30. Found: C,53.79;

H,5.31; N,3.27. $[\alpha]_D^{29}$ -78.9° (*c*=1.59, $CHCl_3$). Ms *m/z*: 426(M^++3, 100%), 424(M^++1, 94%). Ir ($CHCl_3$) cm^{-1}: 1350(SO_2), 1160(SO_2). ^{1}H-Nmr ($CDCl_3$) δ: 0.99(3H, d, *J*=6.7 Hz, $CH(C\underline{H}_3)_2$), 1.22(3H, d, *J*=6.7 Hz, $CH(C\underline{H}_3)_2$), 2.01(1H, double septet, *J*=8.5, 6.7 Hz, $C\underline{H}(CH_3)_2$), 2.45(3H, s, $C_6H_4C\underline{H}_3$), 3.26(1H, dd, *J*=6.1, 8.5 Hz, $NCHC\underline{H}_2O$), 3.56(1H, ddd, *J*=1.8, 6.1, 8.5 Hz, $NC\underline{H}CH_2O$), 3.87 (1H, dd, *J*=1.8, 8.5 Hz, $NCHC\underline{H}_2O$), 6.09(1H, s, NCHO), 7.18-7.80(8H, m, aromatic H).

(2*S*,4*S*)-2-(*o*-Formylphenyl)-4-isopropyl-*N*-tosyl-1,3-oxazolidine (3e)

Yield, 1.98 g (53%). Colorless prisms, mp 165-166°C (benzene). *Anal.* Calcd for $C_{20}H_{23}NO_4S$: C,64.32; H,6.21; N,3.75. Found: C,64.12; H,6.26; N,3.69. $[\alpha]_D^{21}$ -96.6° (*c*=1.60, $CHCl_3$). Ms *m/z*: 374(M^++1, 94%). Ir ($CHCl_3$) cm^{-1}: 1687(C=O), 1345(SO_2), 1150(SO_2). ^{1}H-Nmr ($CDCl_3$) δ: 0.89(3H, d, *J*=6.7 Hz, $CH(C\underline{H}_3)_2$), 1.16(3H, d, *J*=6.7 Hz, $CH(C\underline{H}_3)_2$), 1.77(1H, double septet, *J*=9.2, 6.7 Hz, $C\underline{H}(CH_3)_2$), 2.47(3H, s, $C_6H_4C\underline{H}_3$), 3.31(1H, dd, *J*=6.1, 8.6 Hz, $NCHC\underline{H}_2O$), 3.53(1H, ddd, *J*=3.1, 6.1, 9.2 Hz, $NC\underline{H}CH_2O$), 3.72(1H, dd, *J*=3.1, 8.6 Hz, $NCHC\underline{H}_2O$), 6.78(1H, s, NCHO), 7.36-7.96(8H, m, aromatic H), 10.33(1H, s, CHO).

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