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The Invention of Radical Reactions. Part XXXVI.[1] Synthetic Studies Related to 3-Deoxy-D-*manno*-2-octulosonic acid (KDO)

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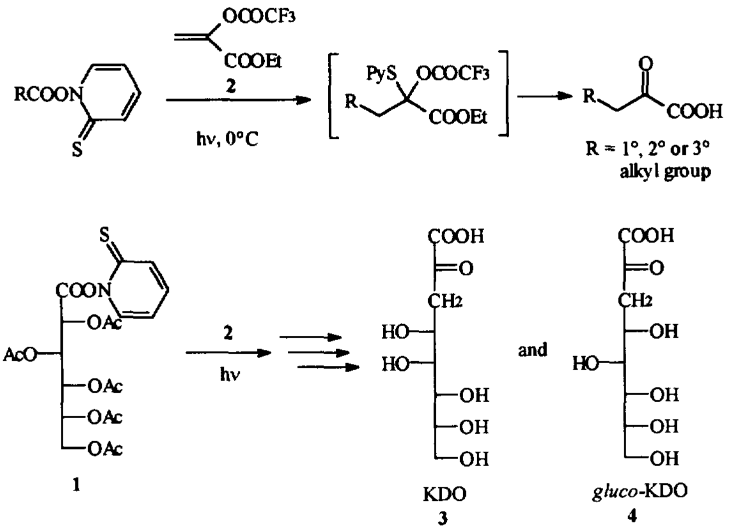
Abstract: An application of the Barton ester based radical reactions in carbohydrate chemistry is described. The chain-elongation reaction with ethyl α-trifluoroacetoxy acrylate **2**, followed by treatment with phenylhydrazine provided 3-deoxy-α-hydrazono-octulosonates **8a,b**, derivatives of KDO and its *gluco*-isomer in good yield.

Carbon-carbon bond formation and functionalization using radical reactions is an important tool in carbohydrate chemistry.[2] We have shown that acyl derivatives of thiohydroxamic acid (Barton esters) are excellent sources of disciplined radicals.[3] We have reported that this method is applicable to the synthesis of α-keto acids,[4] which are of importance in the biosynthesis of amino acids, carbohydrates and nucleic acids.[5] As part of this research, we applied the method to the synthesis of the higher monosaccharide 3-deoxy-D-*manno*-2-octulosonic acid (KDO) **3** and its *gluco*-isomer **4** (Scheme 1).

KDO,[6] known as an integral component in the outer membrane of Gram-negative bacteria, has been intensely studied in synthetic[7] and biological fields.[5, 8] Although many syntheses have been reported, the classical method (the Cornforth method[9]) has been considered to be the most practical. We assumed that the addition of an arabinosyl radical, which is furnished by the photoreaction of the Barton ester **1**, to olefin **2**, followed by the hydrolysis of intermediate (A) would afford KDO pentaacetate. Giese *et al.*[10] reported a radical addition reaction of arabinosyl radical, which was generated by using the cobalt oxime complex method. The reaction gave the corresponding α,β-unsaturated ketone as a result of an undesired β-elimination. Indeed, this result shows that the keto group has to be transformed to avoid the undesired β-elimination.



Scheme 1

Syntheses of KDO-phenylhydrazone (15a) and its *gluco*-isomer (15b)

The ester **1** was synthesized from the easily prepared pentaacetyl gluconic acid **5**[11] and N-hydroxy-2-thiopyridone **6** by using the dicyclohexylcarbodiimide (DCC) coupling method at 0°C. As expected, the photoreaction of **1** with olefin **2**,[4] followed by hydrolysis of intermediate (**A**) gave α,β-unsaturated ketone **7** as shown by Giese[10] (Scheme 2). We considered that the transformation of the masked ketone function into a hydrazone moiety would provide protection for α-keto esters. Treatment of intermediate (**A**) with phenylhydrazine or tosylhydrazine afforded the corresponding hydrazones **8a,b** (*E*-) or **9a,b** (*Z*-) as a mixture of *manno*- and *gluco*- (5:3) isomers, respectively. These results show that our strategy of protective stabilization of the α-ketoester successfully contributed to the isolation of KDO derivatives.

The geometries of the hydrazones **8a,b** and **9a,b** were determined by comparing the ^{1}H- and ^{13}C-NMR data with those of the corresponding *E*- and *Z*-isomers of the phenylhydrazone derived from ethyl pyruvate.[12] The intramolecular H-bond of N-H to the adjacent carbonyl group in the *Z*-hydrazones makes it appear at lower magnetic field in ^{1}H-NMR spectra than that of *E*-isomers. The configuration at position 4 in hydrazones **8a,b** and **9a,b** was determined by X-ray diffraction analysis of *Z*-phenylhydrazono-KDO-lactone **15a** as described

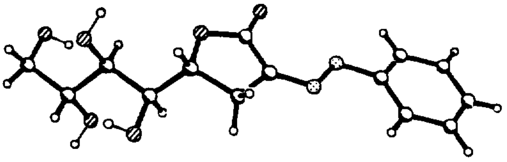
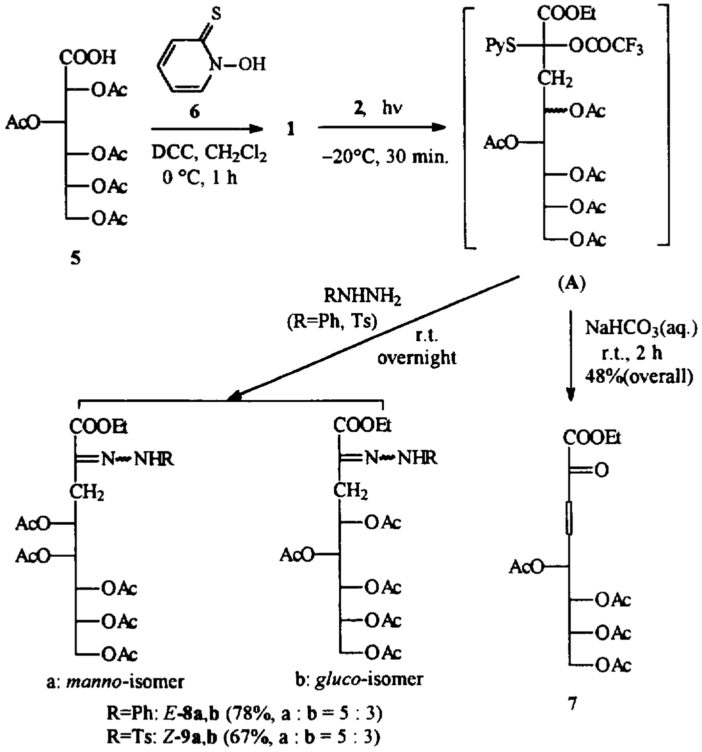
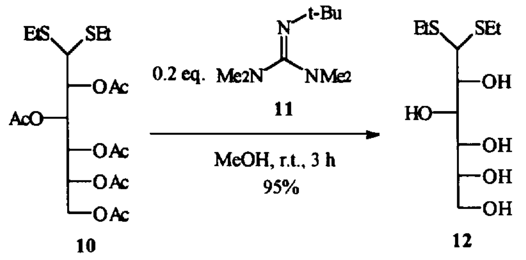


Fig. 1. X-ray crystal structure of 15a



Scheme 2

above (Figure 1). The mixture of *E*-phenylhydrazones **8a,b** was quite hard to separate on silica gel chromatography. We found that treatment of *E*-phenylhydrazones **8a,b** in acetic acid at 80°C smoothly isomerized them to the corresponding *Z*-phenylhydrazones **13a,b**. A mixture of **8a,b** and **13a,b** was successfully separated by silica gel column chromatography to give pure diastereoisomers **13a** and **13b**, and a part of the starting material **8a,b** was recovered (Scheme 4).



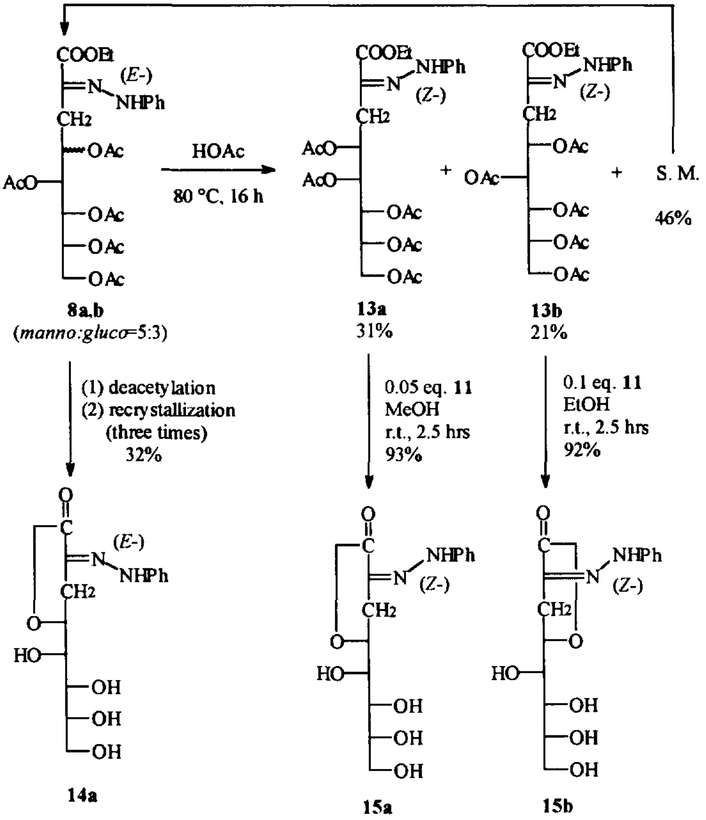
Scheme 3

After the separation, we examined the deprotection of the acetate groups under mild conditions. As a preliminary experiment, alcoholysis of pentaacetyl glucose diethylthio acetal **10**[13] was attempted in the presence of catalytic amount of 2-*t*-butyl-1,1,3,3-tetramethyl guanidine **11**[14] (Scheme 3). Glucose diethylthio acetal **12** was smoothly obtained in high yield without any use of ion-exchange resin for the purification.[15]

Phenylhydrazone acetates **8a,b**, **13a**, and **13b** were also converted to the corresponding hydrazone lactones **14a,b**, **15a**, and **15b** respectively in high yields (Scheme 4). The *E*-phenylhydrazono-KDO-lactone **14a** was purified by recrystallization. On the other hand, hydrolysis of tosylhydrazone **9a,b** under the same condition provided a complex mixture due to the usual decomposition of tosylhydrazones to the corresponding diazo compounds under basic condition, as known in the Bamford-Stevens reaction.[16] Transformation of the unprotected ketones corresponding to **15a** and **15b** to KDO[7p,v, 9b] and *gluco*-KDO[7u, 9b] is documented in the literature.

At first sight the conversion of a phenylhydrazone to a ketone seems a trivial reaction. Since hydrolytic methods would not be suitable (probabilities of β-elimination) we decided to examine oxidative procedures.[17] For environmental reasons we avoided lead tetraacetate[18] and instead studied hypervalent organoiodine reagents.[19, 20] The results that we have already reported,[19] using [bis(trifluoroacetoxy)]iodobenzene (BTIB) in CH_3CN/H_2O (5/1) at 0°C or [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's reagent[21]) in $CDCl_3$ at room temperature, show that model compounds that are derivatives of benzoylformic acid or of pyruvic acid are converted efficiently into the corresponding ketones.

However, in the sugar lactone series of compounds **14a**, **15a**, and **15b** complication arose due to the unexpected stability of the intermediate hydroxy-azo species of general formula R'R"C(-OH)(-N=NPh).[19, 22] Further studies are in hand and will be reported in due course.



Scheme 4

Conclusions

This work shows that the skeleton of KDO can be efficiently synthesized using radical chemistry. The facile synthesis of 7 in crystalline form would permit a synthesis of KDO according to the procedure of Kochetkov *et al.*[23]

EXPERIMENTAL SECTION

General methods and starting materials

Melting points were determined with a Kofler hot-stage melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 881 infrared spectrophotometer. Specific rotations were determined on a Jasco DIP-360 digital polarimeter. ^{1}H- and ^{13}C-NMR spectra were determined with TMS internal reference on Varian Gemini 200 or Varian XL 200E spectrometers. 500 MHz ^{1}H-NMR and 125 MHz ^{13}C-NMR spectra were recorded on a Varian UNITY NMR spectrometer. Chemical shifts are reported (δ) relative to TMS. TLC analysis was performed on thin layer analytical plates 60F$_{254}$ (Merck). Column chromatography was carried out on silica gel 60 (0.040-0.063 mm). Microanalyses were performed by Atlantic Microlab, Inc. N-hydroxy-2-thiopyridone **6** was isolated from its sodium salt (Omadine®), which was a kind gift of the Olin Corporation, Cheshire, CT. Starting compounds **2**,[4] **10**,[13] and **11**[14] were synthesized according to the literature method. Other reference compounds and starting materials were purchased from Aldrich Chemical Co. Inc., Milwaukee, Wisconsin, or Fluka Chemika-BioChemika, Buchs, Switzerland. Solvents were used either as purchased or dried and purified by standard methodology under dry nitrogen. Extracts were dried over anhydrous magnesium sulfate.

General procedure for the synthesis of hydrazones (8a,b) and (9a,b)

A mixture of N-hydroxy-2-thiopyridone (254 mg, 2 mmol) and DCC (422.3 mg, 2.05 mmol) in dichloromethane was placed in a round bottom flask that was covered with aluminum foil. Pentaacetyl gluconic acid **5**[11] (812 mg, 2 mmol) was added to the solution at 0°C under argon with stirring. After 1 hour, the solution was cooled to -78°C and transferred dropwise into the olefin **2**[4] (1.70 g, 8 mmol) which was placed in a round bottom flask under argon at -20°C and irradiated with a Q-Beam® Lamp.[24] After the transfer, the photoreaction was continued for further 30 minutes at -20°C. A mixture of pyridine (10 ml) and phenylhydrazine hydrochloride or free tosylhydrazine was added at 0°C and the solution was stirred at room temperature overnight. Then the solution was evaporated to remove the excess pyridine. The residue was then diluted with dichloromethane and the solution was washed with 5% aqueous hydrochloric acid, water, and brine, dried and evaporated. The residue was purified by silica gel chromatography (hexanes-Et$_2$O 3:1 to 1:3) to give a 5:3 mixture of the corresponding KDO-hydrazone derivative and its *gluco*-isomer as a pale yellow amorphous solid.

8a,b (78% yield): Anal. calcd. for C$_{26}$H$_{34}$N$_2$O$_{12}$: C(55.12); H(6.05); N(4.94). Found: C(55.33); H(6.10); N(4.72). IR (CHCl$_3$): 1744 cm^{-1}. ^{1}H-NMR (200 MHz, CDCl$_3$) (δ, ppm): 1.80~2.20 (18H, m), 2.60~2.90 (1H, m), 3.10~3.40 (1H, m), 4.00~4.40 (4H, m), 5.00~5.70 (4H, m), 6.90~7.00 (1H, m), 7.26~7.29 (4H, m), 9.20 (3/8H, s), 9.38 (5/8H, s). ^{13}C-NMR (50 MHz, CDCl$_3$) (δ, ppm): 14.0, 14.2, 31.5, 61.1, 61.2, 61.5, 67.2, 67.9, 68.7, 69.1, 69.6, 69.8, 113.8, 114.0, 122.0, 128.4, 129.0, 129.2, 143.2, 143.3, 164.8, 169.5, 169.7, 167.0, 170.5, 170.6, 171.6.

9a,b (67% yield): Anal. calcd. for C$_{27}$H$_{36}$N$_2$O$_{14}$S: C(50.30); H(5.63); N(4.30). Found: C(50.52); H(5.72); N(4.42). IR (CHCl$_3$): 3221, 1752, 1596, 1362 cm^{-1}. ^{1}H-NMR (200 MHz, CDCl$_3$) (δ, ppm): 1.35 (15/8H, t, J = 7 Hz), 1.37 (9/8H, t, J = 7 Hz), 1.73, 1.77, 2.06, 2.07. 2.08, 2.09, and 2.10 (15H, each s), 2.43 (3H, s), 2.40-

2.60 (1H, m), 2.65-2.80 (1H, m), 4.00-4.40 (4H, m), 5.00-5.20 (2H, m), 5.26-5.34 (1H, m), 5.40-5.50 (1H, m), 7.33 (2H, brdd, J = 7 and 1.5 Hz), 7.84 (2H, brdd, J = 7 and 1.5 Hz), 11.55 (3/8H, s), 11.96 (5/8H, s). ^{13}C-NMR (50 MHz, $CDCl_3$) (δ, ppm): 13.8, 20.2, 21.5, 35.4, 35.9, 61.4, 61.8, 62.0, 62.2, 67.4, 67.5, 68.7, 68.8, 70.2, 70.5, 127.9, 129.6, 129.7, 134.0, 135.5, 144.2, 161.3, 161.4, 169.5, 169.8, 169.9, 170.4, 170.5, 170.6.

α,β-Unsaturated ketone (7)[10, 25]

According to the preceding procedure, the Barton-ester **1** was synthesized *in situ* from pentaacetyl-D-gluconic acid **5** (406 mg, 1 mmol). Olefin **2** was added dropwise to the solution at 0°C under argon and photolyzed with a Q-Beam® Lamp for 30 minutes with stirring. The solution was filtered and the filtrate was poured into an aqueous saturated sodium bicarbonate solution. The mixture was then stirred for 2 hours at room temperature, diluted with dichloromethane, washed with water, dried, and evaporated. The residue was purified by silica gel chromatography (Et_2O-hexanes, 2:1) to give the *α,β*-unsaturated ketone **7** as colorless crystals (199 mg, 48%), (In the literature,[10, 25] no data were given except the ^{1}H-NMR data.) m.p. 67-68°C (Et_2O-hexanes). $[\alpha]_D^{23}$ +26.1° (c = 0.65, $CHCl_3$). Anal. calcd. for $C_{18}H_{24}O_{11}$: C(51.92); H(5.81). Found: C(51.75); H(5.79). IR ($CHCl_3$): 1748, 1632, 1196, 1126 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) (δ, ppm): 1.38 (3H, t, J = 7 Hz), 2.06 (6H, s), 2.08 (3H, s), 2.17 (3H, s), 4.17 (1H, dd, J = 12.5 and 4.5 Hz), 4.28 (1H, dd, J = 12.5 and 4.5 Hz), 4.36 (2H, d, J = 7 Hz), 5.23 (1H, ddd, J = 8.6, 4.5, and 2.5Hz), 5.46 (1H, dd, J = 8.1 and 2.5 Hz), 5.80 (1H, m), 6.79 (1H, dd, J = 16.0 and 1.7Hz), 7.00 (1H, dd, J = 16.0 and 4.4 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$) (δ, ppm): 14.0, 20.4, 20.5, 20.6, 20.7, 61.6, 62.7, 68.1, 69.3, 70.0, 125.6, 145.4, 169.3, 169.5, 169.7, 170.5, 182.1.

Isomerization of *E*-phenylhydrazones (8a,b) to the *Z*-isomers (13a,b)

A solution of *E*-phenylhydrazones **8a,b** (10 g, 17.6 mmol) in 30 ml glacial acetic acid was stirred at 80°C under argon for 16 hours. The solution was then evaporated and the residue was purified by silica gel chromatography (hexanes-Et_2O, 2:1) to give **13a** (3.1 g, 31%), **13b** (2.1 g, 21%), and the starting **8a,b** (4.6 g, 46%).

13a: $[\alpha]_D^{21}$ +23.92° (c = 6.02, $CHCl_3$). Anal. calcd. for $C_{26}H_{34}N_2O_{12}$: C(55.12); H(6.05); N(4.94). Found: C(55.39); H(6.09); N(4.84). IR ($CHCl_3$): 3260, 1742, 1676 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) (δ, ppm): 1.40 (3H, t, J = 7.1 Hz), 1.93, 2.05, 2.08, 2.11, 2.13 (each 3H, s), 2.64 (1H, dd, J = 14.7 and 8.20 Hz), 2.89 (1H, dd, J = 14.7 and 3.7 Hz), 4.00~4.50 (4H, m), 5.13 (1H, ddd, J = 8.2, 5.1, and 3.7 Hz), 5.25~5.45 (2H, m) 5.60 (1H, dd, J = 9 and 2.3 Hz), 6.98 (1H, brt, J = 7.1 Hz), 7.15~7.35 (4H, m), 12.10 (1H, s). ^{13}C-NMR (50 MHz, $CDCl_3$) (δ, ppm): 14.1, 20.6, 20.7, 20.8, 20.9, 35.1, 60.7, 61.9, 67.6, 68.0, 68.4, 70.3, 113.7, 122.1, 123.6, 129.2, 143.1, 163.1, 169.6, 169.9, 170.0, 170.1, 170.6.

13b: $[\alpha]_D^{23}$ +33.42° (c = 11.1, $CHCl_3$). Anal. calcd. for $C_{26}H_{34}N_2O_{12}$: C(55.12); H(6.05); N(4.94). Found: C (54.92); H(6.06); N(4.73). IR ($CHCl_3$): 3257, 1742, 1676 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) (δ, ppm): 1.38 (3H, t, J = 7.1 Hz), 1.97 (6H, s), 2.08, 2.10, 2.16 (each 3H, s), 2.69 (1H, dd, J =14.7 and 7.4 Hz), 3.01 (1H, dd, J = 14.7 and 3.6 Hz), 4.10~4.40 (4H, m), 5.09 (1H, ddd, J = 8.3, 5.2, and 3.3 Hz), 5.35~5.50 (2H, m), 5.63 (1H, dd, J = 7.3 and 3.7 Hz), 6.97 (1H, brt, J = 7.1 Hz), 7.15~7.40 (4H, m), 12.23 (1H, brs). ^{13}C-NMR (50 MHz, $CDCl_3$) (δ, ppm): 14.1, 20.4, 20.6, 20.7, 33.8, 60.8, 61.4, 68.5, 68.7, 69.9, 70.3, 113.7, 122.1, 123.1, 129.1, 143.0, 163.2, 169.5, 169.8, 170.2, 170.4.

General procedure for the alcoholysis of carbohydrate acetates 8a,b, 13a, 13b, and 10 catalyzed by 2-*t*-butyl-1,1,3,3-tetramethyl guanidine (11)

To a solution of given carbohydrate derivative in a minimum amount of methanol or ethanol, a catalytic amount of **11** was added under argon at room temperature. The mixture was stirred until the starting material had disappeared on TLC. The resulting precipitate was then collected and recrystallized.

D-Glucose diethylthio acetal (12): The title compound was obtained from the corresponding pentaacetate **10**[13] (500 mg, 1.01 mmol) as colorless crystals (275 mg, 95%), m.p. 127-128°C. (lit.[13] 127°C)

14a: Deacetylation of **8a,b** (2.64 g, 4.55 mmol) by methanol furnished a 5:3 mixture of the KDO and *gluco*-KDO lactones **14a,b** (1.12g, 77%). After recrystallization of the mixture from methoxyethanol three times, the *E*-hydrazone KDO lactone **14a** was obtained as colorless crystals (460 mg, 32%), m.p. 254-255°C (methoxyethanol). $[\alpha]_D^{26}$ -27.0° (c = 0.9, DMSO). Anal. calcd. for $C_{14}H_{18}N_2O_6$: C(54.19); H(5.86); N(9.03). Found: C(54.12); H(5.84); N(8.99). IR (KBr): 3377, 3285, 1733, 1577 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) (δ, ppm): 2.80-3.20 (2H, m), 3.35-3.56 (3H, m), 3.60 (1H, m), 3.78 (1H, t, J = 6.2 Hz), 4.40 (1H, t, J = 5.2 Hz), 4.50-4.60 (2H, m), 4.75 (1H, q, J = 6.0 Hz), 4.99 (1H, d, J = 7.0 Hz), 6.91 (1H, m), 7.20-7.35 (4H, m), 10.19 (1H, s). ^{13}C-NMR (50 MHz, DMSO-d_6) (δ, ppm): 27.5, 63.5, 70.4, 70.7, 71.1, 76.4, 113.6, 121.2, 129.2, 131.7, 144.2, 166.9.

15a: The title compound was obtained from the methanolysis of **13a** (809 mg, 1.43 mmol) as yellow crystals (413 mg, 93%), m.p. 182-183°C (methoxyethanol). $[\alpha]_D^{24}$ -53.50° (c = 1.14, DMSO). Anal. calcd. for $C_{14}H_{18}N_2O_6$: C(54.19); H(5.86); N(9.03). Found: C(53.96); H(5.89); N(8.95). IR (nujol): 3200, 1711, 1577 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) (δ, ppm): 3.07 (1H, dd, J = 17.8 and 8.2 Hz), 3.24 (1H, dd, J = 17.8 and 5.3 Hz), 3.50-3.80 (4H, m), 3.97 (1H, t, J = 5.6 Hz), 4.21, (1H, brt, J = 5.6 Hz), 4.39-4.46 (2H, m), 4.80-4.95 (2H, m), 6.93 (1H, brt, J = 7.2 Hz), 7.1-7.30 (4H, m), 11.56 (1H, brs). ^{13}C-NMR (50 MHz, DMSO-d_6) (δ, ppm): 27.7, 62.4, 69.2, 69.6, 70.0, 77.7, 111.8, 120.4, 125.7, 127.9, 141.7, 163.9. (X-ray crystal data are also available).

15b: The title compound was synthesized from ethanolysis of **13b** (300 mg, 0.53 mmol) as yellow crystals (151 mg, 92%), m.p. 179-180°C (methoxyethanol). $[\alpha]_D^{26}$ +32.6° (c = 0.95, DMSO). Anal. calcd. for $C_{14}H_{18}N_2O_6$: C (54.19); H (5.85); N (9.02). Found: C(54.11); H(5.89); N(8.97). IR (KBr): 3313, 1712, 1578 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) (δ, ppm): 2.82 (1H, dd, J = 17.5 and 6 Hz), 3.07 (1H, dd, J = 17.5 and 8.5 Hz), 3.20-3.77 (4H, m), 4.38 (1H, brt, J = 5.2 Hz), 4.55 (2H, m), 4.87 (1H, brq, J = 6.1 Hz), 5.20 (1H, d, J = 6.1 Hz), 6.90 (1H, brt, J = 7.2 Hz), 7.10-7.37 (4H, m), 11.47 (1H, s). ^{13}C-NMR (50 MHz, DMSO-d_6) (δ, ppm): 29.4, 63.1, 70.1, 71.3, 71.9, 80.0, 113.0, 121.4, 127.6, 129.2, 143.1, 165.0.

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