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Tetrahedron: *Asymmetry* 19 (2008) 379–383

Resolution of racemic 12-hydroxyl-1,15-pentadecanlactam using D-glucose derivative as a chiral auxiliary

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Received 11 December 2007; accepted 5 January 2008

Abstract—Racemic 12-hydroxyl-1,15-pentadecanlactam **2** was resolved using glucose as a chiral auxiliary for the first time. Both the (*R*)- and (*S*)-isomers were obtained in high enantiomeric excesses (>99% by HPLC). The absolute configuration of (+)-**2b** and (−)-**2a** was determined by Horeau's method and a modified Mosher's method.

1. Introduction

Carbohydrates are readily available inexpensive natural products with many functional groups and chiral carbons in one molecule. A number of carbohydrate templates have been used as chiral auxiliaries.[1] The steric, stereoelectronic, and coordinating properties of carbohydrate templates can be used in various asymmetric reactions such as Diels–Alder reactions,[2] [2 + 2] cycloadditions,[3] 1,3-dipolar cycloadditions,[4] cyclopropanations[5] and Michael additions.[6] They have also proved to have the possibility of versatile stereoselective applications in the synthesis of enantiomerically pure α-amino acid[7] by Strecker[8] and Ugi[9] reactions. Despite the intrinsic elegance of highly selective asymmetric synthesis, the fact that both enantiomers are usually desired for biological assays has sustained interest in resolution methods. There have been a few reports of carbohydrates as chiral auxiliaries in classic enantiomer resolutions. For example, Köll's[10] D-Xylofuranosyl oxazolidinone was described as an efficient chiral auxiliary for the resolution of carboxylic and sulfonic acids. Banki[11] showed that β-lactams may be resolved via Ferrier rearrangement with tri-*O*-acetyl-D-glucal. Itoh et al.[12] had used aD-glucose template to kinetically resolve auxiliary chiral biaryl compounds. Moreover, Lubineau[13] and Yoshida[14] had obtained enantiomerically pure alcohols using carbohydrates as chiral auxiliaries.

Macrocyclic lactams comprise a small family of compounds that have shown a wide variety of biological activities.[15] Among them, some macrocyclic lactam glycosides showed good antibacterial activity.[16] Stimulated by these findings, we focus on the synthesis of compounds with the structure of macrocyclic lactams and glycosides. Interestingly, we find, in this course, that the D-glucose-derived trichloroacetimidate **3** has the ability to function as a chiral auxiliary since it may be easily removed after the separation of the anomers formed, leaving a new enantiomerically pure substance, which provides a novel and convenient method for the resolution of racemic macrocyclic lactams. Herein, we would like to report the resolution of 12-hydroxyl-1,15-pentadecanlactam **2**.

2. Results and discussion

The key step of this method is to attach the sugar to a macrocyclic lactam molecule (aglycon). The well-known Koenigs–Knorr method,[17] introduced in 1901, is the oldest and most classical method.[18] However, inherent disadvantages of the Koenigs–Knorr method (the use of heavy metal salts, especially in large-scale reactions) could not be overcome. Therefore, many attempts have been made to search for new methods, which do not require the use

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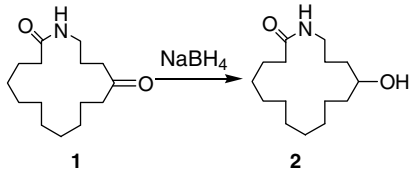
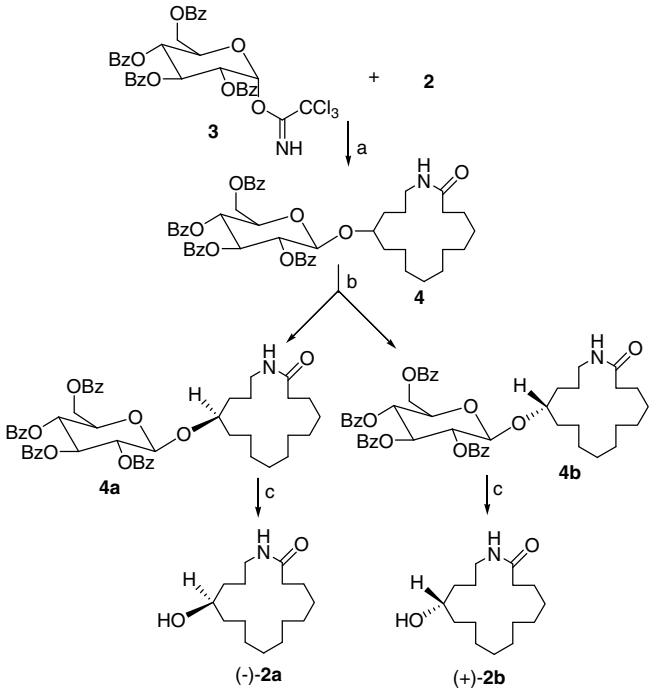
doi:10.1016/j.tetasy.2008.01.007

of heavy metal salts.[19] Among them, Schmidt's trichloroacetimidate method[20] has proved to be the most successful method in the synthesis of O-glycosides. The glycosylation reaction was smoothly promoted by a catalytic quantity of $BF_3{\cdot}Et_2O$,[21] TMSOTf[22] and Cl_3CCHO[23] under mild conditions. Other catalysts such as PPTS,[24] $ZnBr_2$[25] and DDBOTf[26] were also reported for the glycosylation. Recently this has become the most widely used method due to its good yield and high diastereoselectivity.

We choose 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate **3**[27] as the donor. This benzoyl-protected glucosyl imidate, which was readily prepared from the corresponding 1-OH sugar,[28] was quite stable; no decomposition was detected under anhydrous conditions for several months. 12-Hydroxyl-1,15-pentadecanlactam **2**, which was obtained by the reduction of 12-oxo-1,15-pentadecanlactam **1**[29] with $NaBH_4$ (Scheme 1), was selected as the acceptor. To our surprise, we failed to obtain the coupling product under normal Schmidt condition, probably due to the lower reactivity of the hydroxyl group of **2**. Fortunately, when an 'inverse Schmidt's procedure'[30] was adopted, the glycosylation proceeded smoothly under a mild condition. Thus the acceptor **2** and the catalyst TMSOTf were first mixed in dry CH_2Cl_2, and then stirred for 15 min (Scheme 2). Glycoside **4** was obtained in good yield (yield 88%) and high diastereoselectivity. Only the β-isomer was obtained on the basis of the ^1H NMR spectra ($J_{1,2} = 7.9$ Hz). Glycoside **4** appeared as a mixture of diastereomers (β,*R*/β,*S*). Indeed one of the isomers **4b** ($R_f = 0.6$, petroleum ether/ethyl acetate, 1:2) can be easily obtained when recrystallized twice from EtOAc (yield 92%). Another isomer **4a** ($R_f = 0.5$, petroleum ether/ethyl acetate, 1:2) was then obtained by silica gel chromatography (yield 72%). Removal of the benzoyl group of **4a** and **4b** with NH_3 in MeOH and then hydrolysis[31] under acid condition gave enantiomerically pure (−)-**2a** and (+)-**2b** (the total yield was 57% and 48%, respectively). The deprotection of the OBz group of **4a** and **4b** with NH_3 was necessary because the sugar template cannot be removed directly.

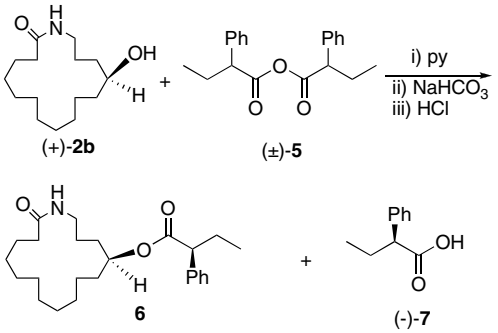


Scheme 1.



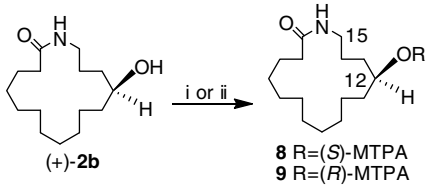
Scheme 2. Reagents and conditions: (a) TMSOTf, CH_2Cl_2; (b) recrystallization and chromatography; (c) (i) methanol/NH_3(g); (ii) 1 M HCl.

The absolute configuration of (−)-**2a** and (+)-**2b** was detected by Horeau's method[32,33] (Scheme 3). Thus, the secondary alcohol (+)-**2b** was reacted with an excess of racemic 2-phenylbutyric acid anhydride **5** in pyridine. After 20 h at room temperature, the excess anhydride was hydrolyzed and the remaining 2-phenylbutyric acid **7** separated from the Horeau ester **6**. The optical rotation of acid **7** had a negative signal, indicating that (+)-2-phenylbutyric acid had reacted preferentially. This is indicative of an (*S*)-configuration of (+)-**2b**. So the absolute configuration of (−)-**2a** was assigned as (*R*).



Scheme 3.

The absolute configuration of (−)-**2a** and (+)-**2b** can be further confirmed by modified Mosher's method.[34] Thus compound **2b** was treated with commercially available (*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA) and (*R*)-MTPA to afford the corresponding MTPA esters **8** and **9** (Scheme 4).



Scheme 4. Reagents and conditions: (i) (*S*)-MTPA, DCC, DMAP; (ii) (*R*)-MTPA, DCC, DMAP.

The ^{1}H NMR signal of **8** at δ 5.67 disappeared upon shaking with D_2O and two multiplets at δ 3.23–3.33 and δ 3.34–3.43 simultaneously collapsed to two 'ddd's. Therefore, the triplet at δ 5.67 can be assigned to the proton at the nitrogen atom and two multiplets at δ 3.23–3.33 and δ 3.34–3.43 to the two protons at C15, respectively. Further consideration indicated that the oxygen atom at C12 is more close to C15–H_a and far away from C15–H_b, therefore the multiplet at δ 3.23–3.33 could be assigned to C15–H_b and the multiplet at δ 3.34–3.43 to C15–H_a. The same result can be obtained by homonuclear decoupling at δ 5.67. The separate signals for the protons at C13 and C14 cannot be observed due to the overlap of the signals. Analogously, in the ^{1}H NMR spectrum of **9** the triplet at δ 5.56 can be assigned to the proton at the nitrogen atom, and two multiplets at δ 3.14–3.25 and δ 3.26–3.37 can be assigned to two protons at C15, respectively, in the same way. The ^{1}H NMR data of **8** and **9** are listed in Table 1.

From Table 1 we can see that ^{1}H NMR signals of the (*R*)-MTPA ester appeared upfield relative to those of the (*S*)-MTPA ester and the absolute values of $\Delta\delta$ ($\delta_S - \delta_R$) are proportional to the distance from the MTPA moiety, which indicated that the protons at the nitrogen atom and C15 are on the right side of the MTPA plane (Fig. 1), namely (+)-**2b** is the (*S*)-configuration. Of course (−)-**2a** must be the (*R*)-configuration. Although we did not obtain the $\Delta\delta$ values for the protons at C13 and C14, the results obtained are in accordance with that of the Horeau's method.

The enantiomer excess of **2a** and **2b** as their (*R*)-MTPA esters as determined by HPLC was >99% (Fig. 2).

Thus, racemic 12-hydroxyl-1,15-pentadecanlactam **2** was resolved using an inexpensive and easily accessible glucose derivative as chiral auxiliary. More importantly, both of the (*R*)- and (*S*)-isomers can be obtained in good yield and high enantiomeric excess. The chiral template is a glucose derivative which can easily be attached to the OH group of macrocyclic lactam and removed after hydrolysis. This new methodology might be very useful in the resolution of secondary alcohol compounds. Further study of the scope and limitations of this method will reveal its full potential.

3. Experimental

Melting points were determined with a Yanagimoto MFG.CO micro melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR were recorded at Bruker DPX300 NMR spectrometer. Chemical shifts were expressed in δ value (ppm) using tetramethylsilane (TMS) as an internal standard. High resolution mass spectra were obtained with Bruker Apex II. FT-ICR MS spectrometer. High performance liquid chromatography (HPLC) was performed on a JASCO 2000 HPLC system (JASCO Corporation, Japan) equipped with PU-2089 plus quaternary pump, UV-2075 plus ultraviolet (UV) detector, CD-2095 plus circular dichroism detector and 20 μL sample loop. Elemental analysis was performed by the Institute of Chemistry, Chinese Academy of Sciences. Commercially available (+)- and (−)-MTPA (Matrix Scientific, No. 007167, 99%; No. 007168, 99%, respectively) were used without purification. Other reagents and solvents were purchased from common commercial sources and some were purified with standard methods.

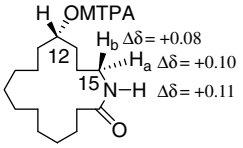


Figure 1. $\Delta\delta$ values [$\Delta\delta$ (in ppm) = $\delta_S - \delta_R$] obtained for (*S*)- and (*R*)-MTPA ester of **2b**.

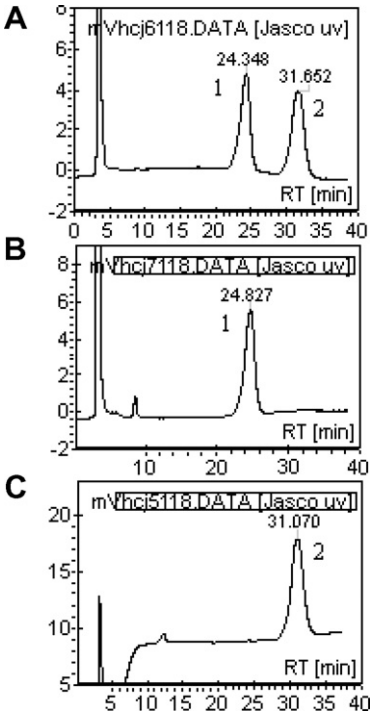


Figure 2. Chromatographic separation of (*R*)-MTPA esters of **2a** and **2b** (2 and 1). Column: KROMASIL 5 SIL 100R (250 × 4.6 mm 5 μm). Mobile phase: 90:10 (hexane/isopropanol). A: (*R*)-MTPA esters of **2a** and **2b**. B: (*R*)-MTPA ester of **2b**. C: (*R*)-MTPA ester of **2a.**

Table 1. ^{1}H NMR data of (*S*)- and (*R*)-MTPA esters of **2b** (in part)

	8 (*S*)-MTPA	**9** (*R*)-MTPA	$\Delta\delta$ ($\delta_S - \delta_R$)
C15–H_a[a]	3.39 (ddd, J = 4.4, 6.5, 14.0 Hz)	3.31 (ddd, J = 4.4, 6.7, 14.0 Hz)	0.08
C15–H_b[a]	3.29 (ddd, J = 4.2, 8.1, 14.0 Hz)	3.19 (ddd, J = 4.1, 7.6, 14.0 Hz)	0.10
NH	5.67 (t, J = 5.7 Hz)	5.56 (t, J = 5.8 Hz)	0.11

[a] After homonuclear decoupling.

3.1. 12-Hydroxyl-1,15-pentadecanlactam 2

To a stirred solution of 12-oxo-1,15-pentadecanlactam (**1**) (2.53 g, 0.01 mol) in methanol (20 mL) was added $NaBH_4$ (0.38 g, 0.01 mol). The mixture was stirred for 1 h at room temperature and then acidified with 1 N HCl. It was then extracted with CH_2Cl_2, dried over anhydrous sodium sulfate, filtrated and evaporated to give 2.28 g white solid (yield 89%). Mp 133–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31–1.71(m, 22H), 1.89 (s, 1H, OH), 2.18 (t, $J = 6.4$ Hz, 2H), 3.28–3.34 (m, 1H), 3.39–3.48 (m, 1H), 3.70–3.71 (m , 1H), 5.83 (s, 1H, NH); ^{13}C NMR δ 22.47, 25.18, 25.54, 25.60, 26.14, 26.20, 26.90, 27.45, 27.83, 32.97, 36.24, 36.81, 38.89, 70.81, 173.29; Anal. Calcd for $C_{15}H_{29}NO_2$: C 70.54, H 11.45, N 5.48. Found: C 70.06, H 11.21, N 5.72.

3.2. 12-(2′,3′,4′,6′-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,15-pentadecanlactam (4)

To a stirred solution of 12-hyroxyl-1,15-pentadecanlactam (**2**) (0.26 g, 0.001 mol) in dry CH_2Cl_2 (10 mL) at 0 °C was added catalytic amount of TMSOTf. The mixture was stirred for 15 min and trichloroacetimidate **3** (0.74 g, 0.001 mol) was added dropwise within 30 min. The above mixture was stirred for another 30 min and saturated aq $NaHCO_3$ solution was added. It was then extracted with CH_2Cl_2, dried over anhydrous sodium sulfate, filtrated and evaporated to give yellow oil, which was further purified by column chromatography (silica gel/petroleum ether (v)/ethyl acetate (v) = 2:5) to give 0.73 g of a white solid (mixture of **4a** and **4b**) (yield 88%).

Five grams of glucoside mixture of **4a** and **4b** was recrystallized twice from ethyl acetate to give 2.3 g one isomer **4b** (yield 92%). The mother liquor was purified by column chromatography (silica gel/petroleum ether (v)/ethyl acetate (v) = 1:2) and then recrystallized from ethyl acetate to give 1.8 g another isomer **4a** (yield 72%) and a mixture of **4a** and **4b**. Compound **4a**: mp 188–190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93–1.71 (m, 22H), 2.05–2.26 (m, 2H), 2.96–3.02 (m, 1H), 3.52–3.58 (m, 1H), 3.76–3.80 (m, 1H), 4.10–4.16 (m, 1H), 4.49 (dd, $J = 5.4$, 12.0 Hz, 1H), 4.66 (dd, $J = 3.2$, 12.0 Hz, 1H), 4.87 (d, $J = 7.9$ Hz, 1H), 5.49 (dd, $J = 5.4$, 9.8 Hz, 1H), 5.59–5.68 (m, 2H), 5.91 (t, $J = 9.7$ Hz, 1H), 7.28–7.58 (m, 12H), 7.82–8.04 (m, 8H); ^{13}C NMR δ 21.28, 24.57, 25.37, 25.59, 25.79, 26.27, 26.63, 27.35, 27.70, 30.49, 31.79, 36.81, 38.38, 62.98, 69.93, 72.02, 72.05, 72.85, 79.45, 99.80, 128.23, 128.30, 128.36, 128.74, 128.79, 129.19, 129.55, 129.63, 129.69, 129.76, 133.12, 133.16, 133.22, 133.38, 165.10, 165.19, 165.74, 165.99, 173.10; HRMS: calcd for $C_{49}H_{56}NO_{11}^+$, 834.3848; found, 834.3841. Compound **4b**: mp 222–223 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21–1.61 (m, 22H), 1.95–2.05 (m, 1H), 2.11–2.20 (m, 1H), 2.60–2.66(m, 1H), 3.16–3.22 (m, 1H), 3.62–3.65 (m, 1H), 4.13–4.19 (m, 1H), 4.49 (dd, $J = 6.2$, 12.0 Hz, 1H), 4.61(dd, $J = 3.1$, 12.0 Hz, 1H), 4.87 (d, $J = 7.9$Hz, 1H), 5.15–5.19 (m, 1H), 5.52 (dd, $J = 7.9$, 9.8 Hz, 1H), 5.61 (t, $J = 9.8$ Hz, 1H), 5.90 (t, $J = 9.7$ Hz, 1H), 7.28–7.57 (m, 12H), 7.82–8.03(m, 8H); ^{13}C NMR δ 22.39, 24.98, 25.10, 25.59, 26.15, 26.18, 26.97, 27.56, 27.84, 30.33, 33.64, 36.81, 38.27, 63.40, 69.98, 72.17, 72.90, 81.71, 101.67, 128.27, 128.31, 128.40, 128.43, 128.76, 128.82, 129.30, 129.60, 129.64, 129.67, 129.73, 129.82, 133.09, 133.19, 133.32, 133.42, 164.95, 165.26, 165.78, 166.04, 173.00; HRMS: calcd for $C_{49}H_{56}NO_{11}^+$, 834.3848; found, 834.3838.

3.3. (*R*)- and (*S*)-12-hydroxyl-1,15-pentadecanlactam [(+)-2b and (−)-2a]

The macrocyclic lactam glucoside **4a** (1.80 g, 2.16 mmol) was dissolved in MeOH (20 mL) saturated with dry NH_3 and stirred at room temperature for 72 h. The methanol was removed in vacuo and washed with ethyl acetate and acetone to give white solid ,which was dissolved in 1 N HCl (30 mL). The above solution was stirred for 24 h at 60 °C. After cooling to room temperature the mixture was extracted with CH_2Cl_2 and dried over anhydrous sodium sulfate, filtered and evaporated to give 0.39 g white solid **2a** (yield 71%). Mp 133–134 °C. $[\alpha]_D^{20} = -10.5$ (*c* 0.46, $CHCl_3$). The ^{1}H NMR was in accordance with **2**.

The other isomer **2b** was obtained with a similar procedure (yield 76%). Mp 133–134 °C. $[\alpha]_D^{20} = +10.0$ (*c* 0.46, $CHCl_3$). The ^{1}H NMR was in accordance with **2**.

3.4. Determination of absolute configuration of (+)-2b

3.4.1. Horeau's method. A solution of (+)-**2b** (20 mg, 0.078 mmol) and racemic 2-phenylbutyric acid anhydride (57.9 μL, 0.20 mmol) in dry pyridine (2 mL) was stirred for 20 h at room temperature. Then 3 mL of 10% aq $NaHCO_3$ was added and stirring was continued for additional 1 h. After adding 10 mL H_2O, the reaction mixture was extracted with 5 × 8 mL of ether. The combined ether phase was dried over Na_2SO_4, and the solvent was evaporated in vacuo to give the diastereomeric mixture of ester of (+)-**2b** with (+)- and (−)-2-phenylbutyric acid. The aq phase was acidified with 10 mL of 2 M HCl and extracted with 4 × 8 mL benzene. The benzene phase was washed with water to neutral, dried over Na_2SO_4 and the solvent was evaporated. The remaining 2-phenylbutyric acid, dissolved in a minimum amount of benzene, showed a specific optical rotation ($\alpha_D = -0.132$) indicating an (*S*)-configuration for (+)-**2b**.

3.4.2. Modified Mosher's method. To a stirred solution of **2b** (0.0255 g, 0.10 mmol) and (*S*)-MTPA or (*R*)-MTPA (0.0272 g, 0.12 mmol) in dry CH_2Cl_2 (10 mL) were added DCC (0.0206 g, 0.10 mmol) and DMAP (a catalytic amount). The above mixture was stirred for 24 h and the precipitated urea was then filtered off. The filtrate was washed twice with 0.5 N HCl and with saturated $NaHCO_3$ solution, and then dried over Na_2SO_4. The solvent was removed to give a white solid **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07–1.73 (m, 22H), 2.16–2.20 (m, 2H), 3.23–3.33 (m, 1H), 3.34–3.43 (m, 1H), 3.54 (s, 1H), 5.07–5.15 (m, 1H), 5.67 (t, $J = 5.7$Hz, 1H), 7.37–7.44 (m, 3H), 7.51–7.54 (m, 2H). Compound **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07–1.73 (m, 22H), 2.14–2.19 (m, 2H), 3.14–3.25 (m, 1H), 3.26–3.37 (m, 1H), 3.56 (s, 1H), 5.06–5.14 (m, 1H), 5.56 (t, $J = 5.8$ Hz), 7.36–7.44 (m, 3H), 7.52–7.55 (m, 2H).

Acknowledgement

We acknowledge financial support of this investigation by the National Basic Research Programme of China (2003CB114407).

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