Stereospecific Synthesis of (2*S*,4*S*,6*S*)-2-Amino-4,6-Dihydroxypimelic Acid†

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The Lewis acid catalyzed stereoselective carbonyl−ene-reaction between (2*S*,5*S*)-1-benzoyl-2-*tert*-butyl-3-methyl-5-(2-propenyl)imidazolidin-4-one **(2)** and anhydrous butyl glyoxylate was investigated with the aim to obtain highly functionalized amino acids. This reaction is assumed to proceed in a nonsynchronous fashion, giving rise to competing reactions within the time interval between the C−C bond formation and the proton migration step. Thus, a hypothesized dipolar intermediate could undergo two reaction pathways: besides conventional ene product **3**, two further products **4** and **5** are obtained via nucleophilic attack involving two different neighboring carbamoyl groups. Acidic hydrolysis of both products afforded title compound **1**. The absolute configuration of the two newly formed chiral centers was assigned by NMR measurements of lactone **4** and its rigid derivative **7**. By varying the temperature (−20° to 25 °C) and the type of Lewis acid ($SnCl_4$, $FeCl_3$) the reaction can be directed to give either of the possible reaction products. A plausible reaction mechanism is proposed.

Introduction

For the development of potent and effective immunomodulating compounds, considerable attention has been focused on the synthesis of lipopeptides related to FK-565.[1−4] Most of these compounds containing the unaltered α,α′-*meso*-diaminopimelyl residue are associated with undesirable side effects which preclude their therapeutic use.[5] Therefore, we were especially interested in a stereospecific synthesis of the α-amino-γ,ϵ-dihydroxypimelic acid 1. Herein we describe the synthesis of amino acid **1**, bringing into focus the nucleophilicity of carbamoyl groups which interfere with the regular course of hetero ene reactions. It is known that with peptidic substrates this type of reaction occurs only stereoselectively.[2,3] However, by using Seebach's imidazolidinone **2**[6] as substrate, this type of reaction now proceeds in a stereospecific fashion.

Results

Synthesis of Amino Acid 1 (Schemes 1 and 2). A $SnCl_4$-catalyzed carbonyl−ene-reaction of 5-(2-propenyl)-imidazolidinone **2**[6,7] and butyl glyoxylate[8] furnished a mixture of lactone **4**, ene product **3**, and rearranged ene product **5**. The reaction proceeds stereospecifically without any detectable amounts of diastereoisomers. The ratio of products **3**, **4**, and **5** depends on reaction conditions such as type of Lewis acid, temperature, and time (Table 1): at −20 °C mainly lactone **4** along with small amounts of **3** and **5** were isolated after workup. Warming up the reaction mixture from −20 °C to 25 °C with subsequent hydrolysis furnishes **5** as the main product along with **3** and minor amounts of **4**. Catalyzing the reaction with $FeCl_3$ at 25 °C effects **3** almost exclusively.

Acidic hydrolysis of **4** as well as **5**, followed by ion exchange chromatography, yielded *2S,4S,6S*-configured amino acid **1**. The use of 3% NH_4OH (instead of 0.3%) during the ion exchange procedure led to formation of minor amounts of lactam **6**. Lactone **4** was hydrolyzed under mild basic conditions to give the *N*-benzoyl-protected amino acid **8** without any detectable epimerization.

Assignment of Configuration (Figure 1 and Scheme 2). According to the proposed mechanism, compounds **3**, **4**, and **5** should be formed via the same configuration-determining transition state. Due to the exo-arrangement of imidazolidinone **2** and butyl glyoxylate, all reaction products should have identical *S*-configuration at the newly formed asymmetric centers (γ- and ϵ-carbons). This assumption could be verified by spectroscopic investigations of **4** and its rigid derivative **7**: a nuclear Overhauser effect of 3.2% between the α- and the γ-protons, as well as comparable coupling patterns of the β-protons of **4** with those of analogous compounds,[9] indicates *cis* configuration of the lactone substituents. Therefore, we assigned an *S* configuration to the γ-carbon based on the known *S* configuration of the α-carbon. Reacting **4** with dimethoxypropane resulted in a transesterification of the lactone moiety with concomitant ring closure between γ- and ϵ-hydroxy groups to give the 1,3-dioxane derivative **7**. According to coupling patterns, 1,3-diaxial relationship of the γ- and ϵ-protons in **7** could be established, clearly indicating *S* configuration for the ϵ-carbon. Therefore, the *2S,4S,6S*-configuration assigned to **4** applies as well to amino acid **1**. Acidic hydrolysis of **5** followed by ion exchange chromatography afforded two compounds identical with **1** and **6**, indicating an *S*-configuration for the γ- as well as for the ϵ-carbon of **5**.

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† This paper is dedicated to Professor D. Seebach on the occasion of his 60th birthday.

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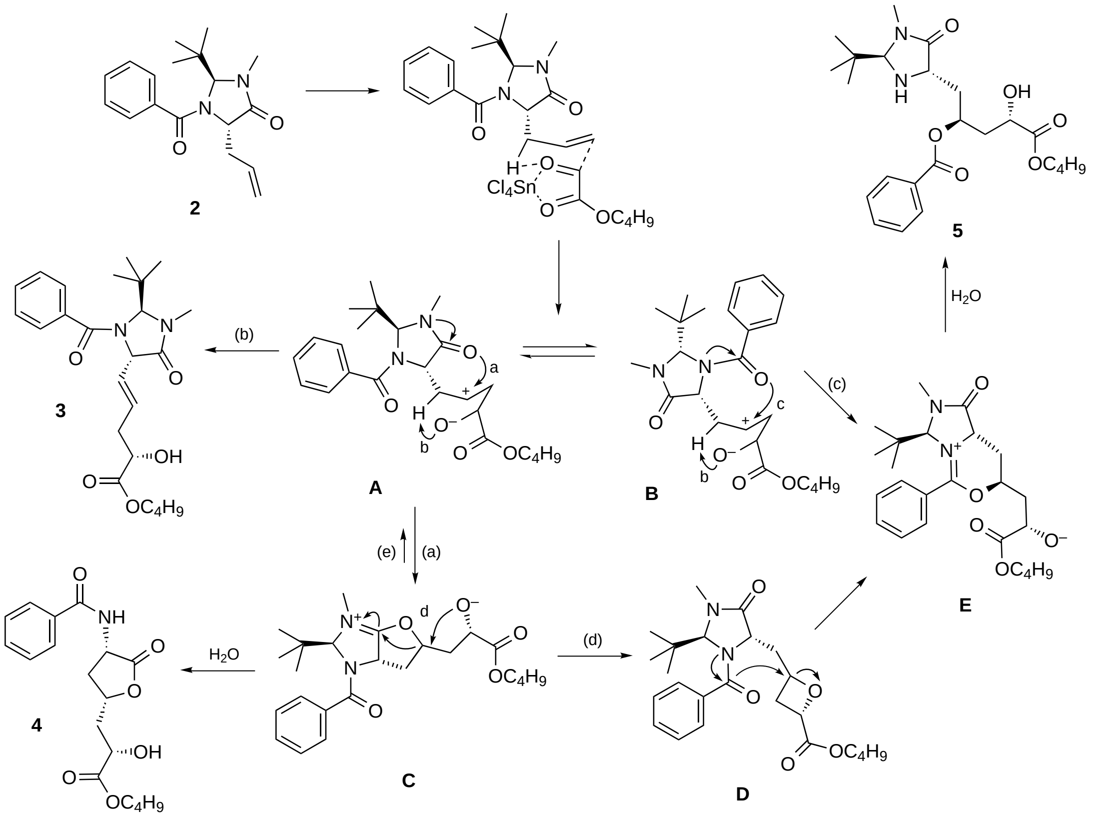
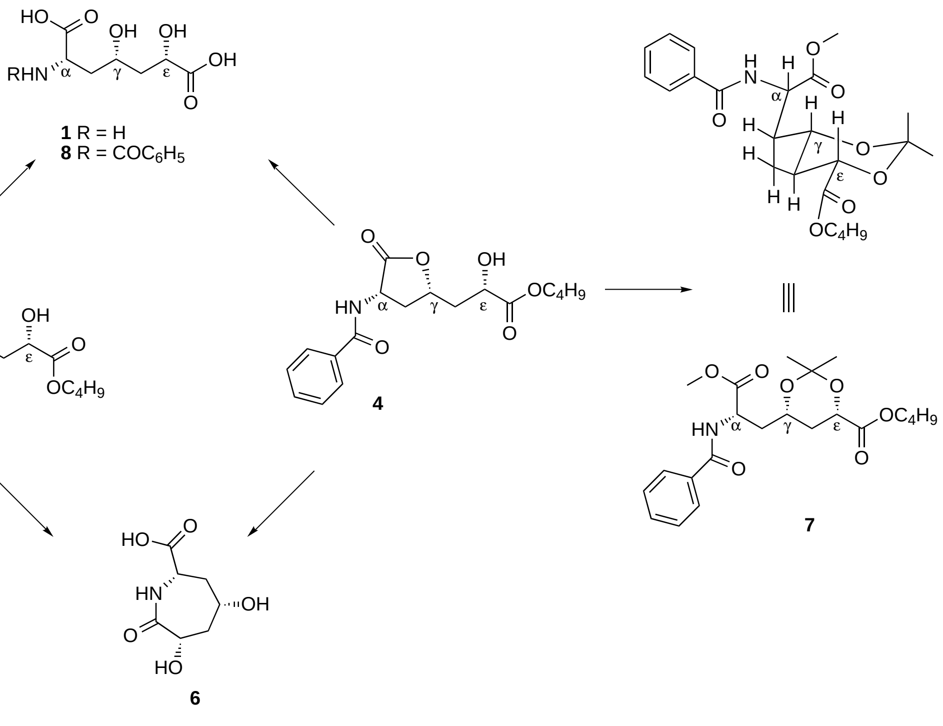
Scheme 1



Scheme 2



Mechanistic Studies (Figure 1 and Scheme 1). The mechanism of Lewis acid catalyzed ene reactions[10] has been the subject of controversy and is usually discussed in terms of a continuum from a concerted pericyclic pathway to a stepwise, cationic process involving either a π-complex or a zwitterionic intermediate.[11-13] In our case, the formation of lactone **4** and rearranged ene product **5** strongly argues in favor of a zwitterionic intermediate. Based on control experiments, a reasonable mechanism for the $SnCl_4$-mediated reaction can be proposed. In the postulated chairlike transition state[12,14]

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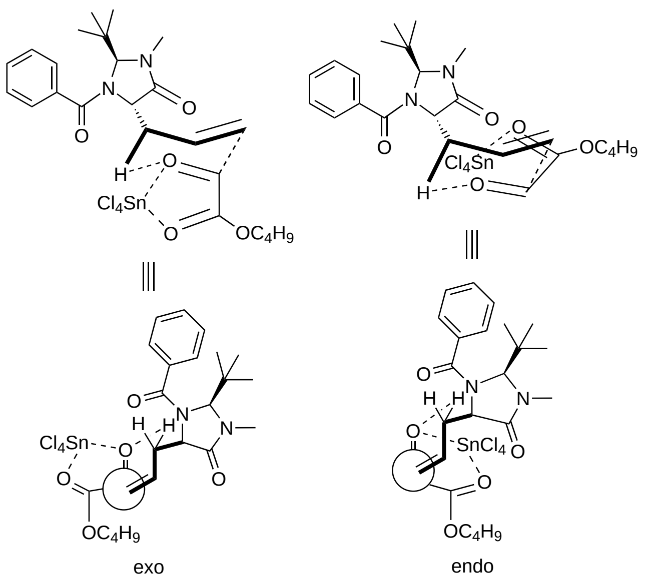

Figure 1.

a C−C bond is formed by a re−si interaction of the allylic double bond and the glyoxylate carbonyl resulting in an equilibrium of two bipolar intermediates **A** and **B**. For the second step, three different pathways (a−c) can be formulated: (a,c) the nucleophilic attack of the imidazolidinone- or benzoyl-carbonyl at the positive center of **A** or **B**, leading to the iminolactone **C** or to the oxazine **E** and (b) the transfer of the allylic proton to oxygen leading to the ene product **3**.

The stable products **3**−**5** are not transformable into each other under the conditions leading to their formation. Thus, **A** and **B** are common intermediates for these products, indicating that the nucleophilic attack has to occur prior to proton transfer. **4** is the main reaction product at −20 °C together with small amounts of **3**. Upon warming to 25 °C, the postulated intermediate **C** rearranges almost completely and irreversibly to **5**, assuming **E** as a possible intermediate. In addition, small amounts of **3** again are formed (Table 1). As the initial formation of **3** is favored over **E**, another pathway from **C** to **E** besides the obvious ($\mathbf{C} \rightarrow \mathbf{A} \rightarrow \mathbf{B} \rightarrow \mathbf{E}$) has to be considered. Immediate rearrangement of **C** to **E** is not possible due to steric reasons; the most reasonable intermediate is a highly reactive oxetane **D** generated via pathway d. Thus, **C** and **E** can be assumed as the kinetically and the thermodynamically controlled reaction products, respectively.

The almost exclusive formation of ene product **3** in the $FeCl_3$-mediated reaction indicates a strong Lewis acid dependency of the three pathways (a−c).

Discussion. These findings support the assumption that the course of Lewis acid catalyzed carbonyl−ene-reactions is characterized by very unsymmetrical transition states[11,12,14] with C−C bond formation being almost complete while C−H bond formation is just beginning. Nucleophilic domains within the substrate (carbamoyl oxygens) can interfere with the proton transfer step which gives the above reaction pattern. This particular property of Lewis acid catalyzed carbonyl−ene-reactions could be potentially useful for stereocontrolled functionalizations. In our case it was used to establish a stereospecific, high yield synthesis of title compound **1**.

Table 1. Product Distribution of the Ene Reaction under Different Reaction Conditions

		products, % yield			
no.	reaction conditions[a]	**C(4)**[b]	**3**	**E(5)**[b]	**R**[b]
1	$SnCl_4$/25 °C/10 min	47	28	5	20
2	$SnCl_4$/25 °C/3 h	5	35	40	20
3	$SnCl_4$/−20 °C/3 h	75	14	2	9
4	$SnCl_4$/−20 °C/1 h → 25 °C/3 h	6	20	58	16
5	$FeCl_3$/25 °C/3 h	3	78	2	17

[a] All experiments were conducted with a ratio of substrate/glyoxylic ester/Lewis acid as 1/3/4 in CH_2Cl_2. [b] The corresponding amounts of **C** and **E** present in a reaction mixture were determined by HPLC analysis of **4** and **5** after acidic hydrolysis of drawn samples. **R** represents the sum of undefined side and decomposition products.

Experimental Section

The general experimental procedures and the analytical instruments employed have been described in detail.[2] The abbreviations CY (cyclohexane), TFA (trifluoro acetic acid), EE (ethyl acetate), DIO (dioxane), and PTSA (*p*-toluenesulfonic acid) were used.

Measurement of the Reaction Progress. A solution of 510 mg (4 mmol) of freshly distilled butyl glyoxylate,[8] 0.35 mL (4 mmol) of $SnCl_4$, and 300 mg (1 mmol) of (2*S*,5*S*)-1-benzoyl-2-*tert*-butyl-3-methyl-5-(2-propenyl)imidazolidin-4-one[7] in 30 mL of CH_2Cl_2 was kept at 25 °C (−20 °C) and periodically drawn samples were analyzed by HPLC.

(2*S*,4*S*,6*S*)-2-Amino-4,6-dihydroxyheptanedioic Acid (1). (2*S*,4*S*,6*S*)-4,6-Dihydroxy-7-oxoazepane-2-carboxylic Acid (6). Method A. To a stirred solution of 360 mg (1.15 mmol) of **8** in a mixture of 10 mL of liquid NH_3 and 5 mL of ether was added in portions sufficient sodium to establish a permanent blue coloration. The blue solution was stirred for 10 min, and the color was then discharged by addition of the minimum amount of solid NH_4Cl. After evaporation of the NH_3 under a stream of argon the solid residue was purified by ion exchange chromatography (Dowex 50 X W8, 0.5% NH_4OH). Yield 176 mg (74%) of **1**. **Method B.** A suspension of 400 mg (0.9 mmol) **5** in 9 mL of 6 N HCl was heated in a sealed tube at 120 °C for 3 h. After cooling, the reaction mixture was diluted with water and extracted with EE. Ion exchange chromatography on Dowex 50 X W8 (0.5% NH_4OH) afforded 150 mg (81%) of **1**. Starting from lactone **4**, amino acid **1** can also be obtained in comparable yield (86%). **Method C.** By using 3% NH_4OH for the ion exchange chromatography, lactam **6** could be isolated up to an yield of 15% besides amino acid **1**: $[\alpha]^{20}_D$ −5.2° ($c = 0.5$, H_2O); ^{1}H-NMR (D_2O) ABXY-System: ($\nu_A = 1.93$, $\nu_B = 1.84$, $\nu_X = 4.13$, $\nu_Y = 4.02$, $J_{AB} = 14.3$, $J_{AY} = 5.8$, $J_{AX} = 4.5$, $J_{BX} = 8.2$, $J_{BY} = 7.2$ Hz), ABXY-System: ($\nu_A = 1.82$, $\nu_B = 1.71$, $\nu_X = 3.44$, $\nu_Y = 4.02$, $J_{AB} = 14.3$, $J_{AX} = 4.2$, $J_{AY} = 9.8$, $J_{BX} = 9.2$, $J_{BY} = 3.0$ Hz); MS-FAB *m/e* 207 (MH^+, 10), 191 (36), 137 (44), 97 (100). Anal. Calcd for $C_7H_{13}NO_6$: C, 40.58; H, 6.32; N, 6.76. Found: C, 40.32; H, 6.16; N, 6.70. **6**: ^{1}H-NMR (D_2O) ABXY-System: ($\nu_A = 2.45$, $\nu_B = 1.47$, $\nu_X = 3.92$, $\nu_Y = 4.13$, $J_{AB} = 13.3$, $J_{AY} = 4.3$, $J_{AX} = 10.5$, $J_{BY} = 11.3$ Hz), ABXY-System: ($\nu_A = 2.19$, $\nu_B = 1.69$, $\nu_X = 4.35$, $\nu_Y = 4.13$, $J_{AB} = 12.8$, $J_{AX} = 11.7$, $J_{AY} = 11.3$, $J_{BX} = 2.2$, $J_{BY} = 4.0$ Hz); ^{13}C-NMR (D_2O) 71.6, 68.2, 54.3, 43.2, 42.9. Anal. Calcd for $C_7H_{11}NO_5$ C, 44.45; H, 5.86; N, 7.40. Found: C, 44.57; H, 5.62; N, 7.48.

5-(3-Benzoyl-2(*S*)-*tert*-butyl-1-methyl-5-oxoimidazolidin-4(*S*)-yl)-2(*S*)-hydroxypent-4-enoic Acid Butyl Ester (3), 3-(4(*S*)-(Benzoylamino)-5-oxo-tetrahydrofuran-2(*S*)-yl)-2(*S*)-hydroxypropionic Acid Butyl Ester (4), Benzoic Acid 3-(Butoxycarbonyl)-1-((2(*R*)-*tert*-butyl-1-methyl-5-oxoimidazolidin-4(*S*)-yl)methyl)-3(*S*)-hydroxypropyl Ester (5). To a −20 °C solution of 650 mg (5 mmol) of freshly distilled butyl glyoxylate[8] and 0.78 mL (6.6 mmol) of $SnCl_4$ in 20 mL of CH_2Cl_2 was added dropwise via syringe a solution of 500 mg (1.7 mmol) of **2**.[7] The mixture was stirred for additional 3 h and subsequently poured into a cooled solution of 1 N HCl. After repeated extraction with CH_2Cl_2, the combined extracts were washed with brine and evaporated to dryness to give 650 mg of a mixture of **3**−**5**. Chromatography on silica gel (CY/DIO (2:1)) afforded 487 mg (75%) of **4**, 106 mg (14%) of **3**, and 14 mg (2%) of **5**. Reaction conditions determine the ratio of products **3**−**5** (Table 1). **3**: $[\alpha]^{20}_{D}$ +106° (*c* = 1.7, CH_3OH); ^1H-NMR ($CDCl_3$) 7.39−7.57 (m, 5H), 5.70 (s, 1H), 5.30 (m, 1H), 4.91 (m, 1H), 4.65 (d, 1H, J = 8.8 Hz), 4.14 (t, 2H, J = 6.7 Hz), 3.68 (dd, 1H, J = 3.5, 5.9 Hz), 3.08 (s, 3H), 2.08 (m, 2H), 1.61 (m, 2H), 1.36 (m, 2H), 1.09 (s, 9H), 0.94 (t, 3H); MS-FAB *m/e* 431 (MH^+, 58), 373 (100), 105 (43). Anal. Calcd for $C_{24}H_{34}N_2O_5$: C, 66.95; H, 7.96; N, 6.51. Found: C, 70.10; H, 7.90; N, 6.30. **4**: $[\alpha]^{20}_{D}$ +17.4° (*c* = 0.9, CH_3OH); ^1H-NMR ($CDCl_3$) 7.40−7.80 (m, 5H), 6.63 (d, 1H, J = 5.6 Hz), 4.24 (t, 2H), ABXY-System: ($\nu_A = 3.1$, $\nu_B = 2.02$, $\nu_X = 4.76$, $\nu_Y = 4.79$, $J_{AB} = 12.5$, $J_{AY} = 5.3$, $J_{AX} = 8.5$, $J_{BX} = 10.8$, $J_{BY} = 10.7$ Hz), ABXY-System: ($\nu_A = 2.27$, $\nu_B = 2.23$, $\nu_X = 4.35$, $\nu_Y = 4.79$, $J_{AB} = 14.5$, $J_{AX} = 6.4$, $J_{AY} = 6.4$, $J_{BX} = 5.3$, $J_{BY} = 5.3$ Hz), 1.69 (m, 2H), 1.41 (m, 2H), 0.97 (t, 3H, J = 7.3 Hz); MS-FAB *m/e* 350 (MH^+, 56), 105 (100). Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 61.95; H, 6.78; N, 3.92. **5**: ^1H-NMR ($CDCl_3$) 7.40−8.0 (m, 5H), ABXY-System: ($\nu_A = 2.31$, $\nu_B = 2.18$, $\nu_X = 4.30$, $\nu_Y = 5.62$, $J_{AB} = 14.5$, $J_{AY} = 4.3$, $J_{AX} = 5.5$, $J_{BX} = 5.7$, $J_{BY} = 8.7$ Hz), 4.05 (d, 1H, J = 2.3 Hz), 3.98 (m, 2H), ABXY-System: ($\nu_A = 2.27$, $\nu_B = 1.65$, $\nu_X = 3.60$, $\nu_Y = 5.62$, $J_{AB} = 14.0$, $J_{AY} = 11.2$, $J_{AX} = 2.2$, $J_{BX} = 2.2$, $J_{BY} = 10.4$ Hz), 1.56 (m, 2H), 1.31 (m, 2H), 0.93 (s, 9H), 0.91 (t, 3H); MS-FAB *m/e* 449 (MH^+, 100), 391 (24), 327 (30), 155 (26). Anal. Calcd for $C_{24}H_{36}N_2O_6$: C, 64.26; H, 8.09; N, 6.25. Found: C, 64.32; H, 7.90; N, 6.30.

6(*S*)-(2(*S*)-(Benzoylamino)-2(*S*)-(methoxycarbonyl)-ethyl)-2,2-dimethyl[1,3]dioxane-4(*S*)-carboxylic Acid Methyl Ester (7). A solution of 120 mg (0.43 mmol) of **4** and 65 mg (0.34 mmol) of PTSA in 6 mL of dimethoxypropane was heated under reflux for 5 h. After evaporation of the solvent the reaction mixture was dissolved in EE and extracted with $NaHCO_3$. Chromatography on silica gel (CY/EE (3:2)) afforded 40 mg (30%) of **7**. ^1H-NMR ($CDCl_3$) 7.42−7.80 (m, 5H), 7.50 (b, H), 3.78 (s, 6H), ABXY-System: ($\nu_A = 2.13$, $\nu_B = 2.03$, $\nu_X = 4.96$, $\nu_Y = 4.13$, $J_{AB} = 14.6$, $J_{AY} = 2.5$, $J_{AX} = 5.9$, $J_{BX} = 3.9$, $J_{BY} = 10.0$ Hz), ABXY-System: ($\nu_A = 1.86$, $\nu_B = 1.62$, $\nu_X = 4.53$, $\nu_Y = 4.13$, $J_{AB} = 13.1$, $J_{AX} = 2.8$, $J_{AY} = 2.6$, $J_{BX} = 12.1$, $J_{BY} = 11.8$ Hz), 1.57−1.49 (m, 6H); MS-FAB *m/e* 380 (MH^+, 8), 364 (18), 322 (100). Anal. Calcd for $C_{18}H_{25}NO_7$: C, 60.15; H, 6.34; N, 3.69. Found: C, 59.92; H, 6.42; N, 3.47.

(2*S*,4*S*,6*S*)-2-(Benzoylamino)-4,6-dihydroxyheptanedioic Acid (8). A solution of 300 mg (0.86 mmol) of **4** and 810 mg (2.6 mmol) of $Ba(OH)_2$ in 10 mL of CH_3OH was stirred at ambient temperature for 1.5 h. After adjustment of the reaction mixture to pH 2.8 with DOWEX 50 X W8-H^+, the resin was filtered off and the solution lyophilized to afford 230 mg (86%) of **8**. $[\alpha]^{20}_{D}$ −7.3° (*c* = 0.6, H_2O); ^1H-NMR ($CDCl_3$) 7.53 −7.85 (m, 5H), 4.60 (dd,1H, J = 4.1, 9.4 Hz), 4.12 (dd, 1H, J = 4.8, 8.6 Hz), 4.0 (m, 1H), 2.0−2.11 (m, 2H), 1.85−1.99 (m, 2H); MS-FAB *m/e* 311 (M^+, 100), 293 (82). Anal. Calcd for $C_{14}H_{17}NO_7$: C, 54.02; H, 5.50; N, 4.50. Found: C, 54.18; H, 5.33; N, 4.67.

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