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An Efficient Synthesis of Valienamine via Ring-Closing Metathesis

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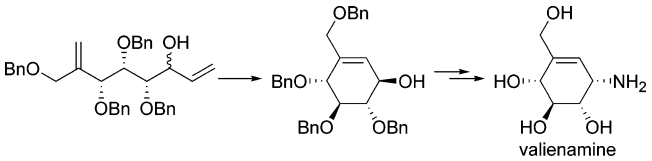

An efficient synthesis of valienamine is described. Valienamine was synthesized starting from commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucose in nine steps, using ring-closing metathesis of (4*S*,5*S*,6*S*)-4,5,6-tribenzyloxy-7-(benzyloxymethyl)octa-1,7-dien-3-ol as a key step.

Valienamine (**1**) is an α-glucosidase inhibitor[1] that was first isolated from the microbial degradation of validoxyamine A with *Pseudomonas denitrificans* in 1972.[2] Later, it was produced from the degradation of validoxylamine A with *Flavobacterium saccharophilum*[3] or from the NBS cleavage of validoxylamine A or its derivatives.[4] Valienamine has been found to be a key component for biological activities in pseudo-aminosugars and pseudo-oligosaccharides, which exhibit stronger enzyme inhibitory activities than valienamine itseif, such as validamycins, acarbose, amylostatins, adiposins, acarviosin, and trestatins.[5] Since the first isolation in 1972, a great deal of effort has been devoted to the development of various methodologies for the enantiospecific syntheses of valienamine.[6−18] The first synthesis was reported by Paulsen et al. using L-quebrachitol as the chiral starting material in 1980.[6] In most syntheses valienamine (**1**) was synthesized from D-glucose or its derivatives.[7−13] In some other methods the cyclohexene skeleton of **1** was constructed through Diels−Alder reaction.[14−16] The latest two syntheses were performed from (−)-quinic acid by the Shing group.[17,18] In this note, we report a new strategy for the efficient stereospecific synthesis of valienamine from D-glucose through ring-closing metathesis of an acyclic diene.

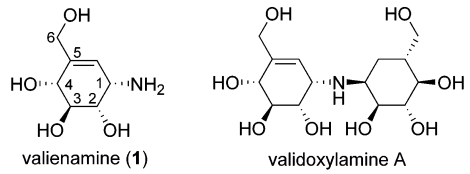

FIGURE 1. Structures of valienamine (**1**) and validoxylamine A.

Our approach to valienamine (**1**) employed commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **2** as the starting material (Scheme 1). Opening of the pyranose ring with concurrent protection of the aldehyde functionality was accomplished by using a slight modification of a previously reported procedure.[19] Thus, in our modified method, reaction of **2** with ethanethiol containing TFA afforded diethyl dithioacetal **3** in 77% yield, while that with ethanethiol containing HCl in dioxane afforded **3** in 56% yield as reported in the literature.[19] The hydroxy dithioacetal **3** was oxidized with acetic anhydride and DMSO[20] to give the corresponding ketone **4** in 94% yield (Table 1). It is notable that none of the desired ketone was produced by using Oppenauer oxidation[21] and sodium hypochlorite oxidation.[22] On the other hand, **4** was obtained in 50% yield from Pfitzner−Moffatt oxidation,[23] in 48% yield from PCC oxidation,[24] and in 80% yield from tetrapropylammonium perruthenate (TPAP) method,[25] respectively. Exposure of **4** to ylide $CH_2{=}PPh_3$, formed in situ, smoothly gave olefin **5** in 88%

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SCHEME 1

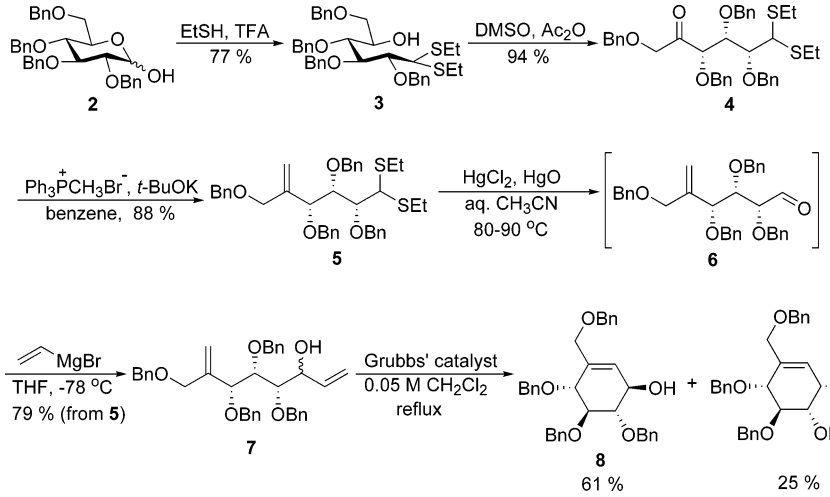


TABLE 1. Oxidation of 3 to 4 under Various Conditions

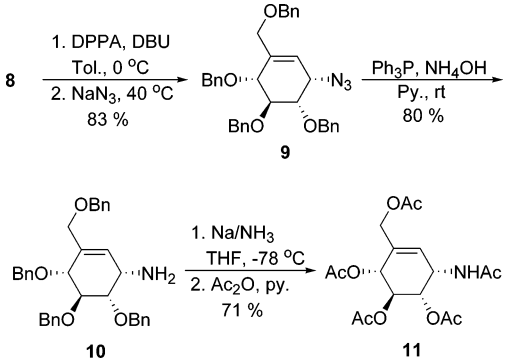
		reaction condition		
oxidizing agent	solvent	temp (°C)	time (h)	yield (%)
Al(O-*i*Pr)$_3$, acetic acid[21]	toluene	90	24	NR[a]
10−13% NaOCl, acetic acid[22]		rt	24	NR[a]
DCC, DMSO, TFA[23]	toluene	rt	overnight	50
PCC[24]	CH_2Cl_2	rt	overnight	48
TPAP, NMO[25]	CH_2Cl_2	rt	overnight	80
DMSO, Ac_2O[20]		rt	overnight	94

[a] NR = no reaction.

yield, while the reaction of **4** with Tebbe reagent provided **5** in 78% yield. Hydrolysis of the dithioacetal function in **5** was accomplished by treatment with HgO/$HgCl_2$ in CH_3CN/H_2O (10/1) solvent to give aldehyde **6**, which was not stable enough for column chromatography. After workup, therefore, the crude **6** was used for the next step without further purification. Addition of vinylmagnesium bromide to the aldehyde **6** afforded an inseparable epimeric mixture (7:3 by ^{1}H NMR) of allylic alcohol **7** in 79% yield from **5** in two steps. Ring-closing metathesis of the diastereomeric diene **7** with 5 mol % of Grubbs' second-generation catalyst[26] in refluxing CH_2Cl_2 provided the desired (1*R*)-cyclohexenol derivative **8** in 61% yield after separation by column chromatography, along with its diastereomeric (1*S*)-cyclohexenol derivative in 25% yield. The absolute configuration of **8** was assigned by comparing its ^{1}H NMR spectrum and specific rotation with the reported values.[11]

Treatment of the alcohol **8** with diphenylphosphoryl azide (DPPA) in the presence of DBU followed by addition of 1 equiv of sodium azide afforded azide **9** in 83% yield (Scheme 2).[27] Although a phthalimide compound also could be prepared by direct substitution of the alcohol

SCHEME 2



under Mistunobu reaction,[11] we had a difficulty in purification of the product from the remaining excess phthalimide and the reaction yield (74%) was lower than that of the azide substitution. Treatment of **9** with triphenylphosphine-ammonium hydroxide[28] effected reduction of the azido group to furnish allylic amine **10**[11] in 80% yield. Since the presence of the alkene moiety in **10** precluded the use of catalytic hydrogenolysis, debenzylation of **10** was carried out with sodium in liquid ammonia at −78 °C to provide valienamine (**1**).[18] Acetylation of **1** then afforded pentaacetate **11** for isolation and characterization. The spectroscopic data and physical properties of the pentaacetate **11** derived from **10** were completely identical with those reported earlier.[18]

In conclusion, we synthesized valienamine (**1**) from 2,3,4,6-tetra-*O*-benzyl-D-glucose (**2**) in nine steps in an overall 14.5% yield, using ring-closing metathesis of **7** as a key step.

Experimental Section

2,3,4,6-Tetra-*O*-benzyl-D-glucose Diethyl Dithioacetal (3). To a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**2**, 119 g, 0.22 mol) in EtSH (300 mL) was added TFA (60 mL). After being stirred overnight at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with Et_2O. The organic layer was washed with

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saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 4:1) to give the title compound **3** (108 g, 77%) as a colorless oil: R_f 0.59 (acetone/PhMe, 1:9); $[\alpha]_D$ +20.0 (*c* 0.97, $CHCl_3$) [lit.[19] $[\alpha]_D$ +19.5 (*c* 2.3, $CHCl_3$)]; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, J = 7.4 Hz, 3H), 1.19 (t, J = 7.4 Hz, 3H), 2.51−2.61 (m, 2H), 2.67 (q, J = 7.4 Hz, 2H), 3.08 (d, J = 4.8 Hz, 1H), 3.60−3.69 (m, 2H), 3.72 (dd, J = 9.3, 3.6 Hz, 1H), 3.94 (d, J = 3.7 Hz, 1H), 4.05−4.11 (m, 1H), 4.15 (dd, J = 6.6, 3.7 Hz, 1H), 4.28 (dd, J = 6.6, 3.6 Hz, 1H), 4.49−4.61 (m, 4H), 4.68 (d, J = 11.2 Hz, 1H), 4.80 (d, J = 11.3 Hz, 1H), 4.81 (d, J = 11.2 Hz, 1H), 4.90 (d, J = 11.2 Hz, 1H), 7.23−7.39 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 138.6, 138.4, 128.79, 128.76, 128.6, 128.53, 128.50, 128.4, 128.23, 128.18, 128.1, 127.8, 83.1, 80.5, 77.7, 75.7, 75.3, 73.9, 73.2, 71.9, 71.3, 54.3, 25.9, 25.7, 14.8; IR (neat) 3484, 1606, 1496, 1454 cm^{-1}.

2,3,4,6-Tetra-*O*-benzyl-D-*xylo*-hexos-5-ulose Diethyl Dithioacetal (4). A solution of **3** (7.62 g, 11.8 mmol), dimethyl sulfoxide (21 mL), and acetic anhydride (14.1 mL) was stirred overnight at room temperature. The reaction mixture was then quenched with H_2O (60 mL) and aqueous NH_4OH (30 mL). The resulting solution was extracted with Et_2O. The organic layer was separated, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 4:1) to give the title compound **4** (7.18 g, 94%) as a colorless oil: R_f 0.59 (acetone/PhMe, 1:9); $[\alpha]_D$ −9.67 (*c* 1.04, $CHCl_3$) [lit.[25b] $[\alpha]_D$ −7 (*c* 0.92, $CHCl_3$)]. The spectral data were in agreement with earlier reported values.[25b]

2,3,4,6-Tetra-*O*-benzyl-5-deoxy-5-methylene-D-*xylo*-hexose Diethyl Dithioacetal (5). A solution of methyltriphenylphosphonium bromide (5.5 g, 15.4 mmol) and potassium *tert*-butoxide (1.7 g, 15.2 mmol) in benzene (60 mL) was heated to reflux for 2 h, and then allowed to return to room temperature. After addition of **4** (1.0 g, 1.6 mmol) to the above solution at room temperature, the reaction mixture was stirred for further 2 h at room temperature, and then filtered. The filtrate was concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 5:1) to give the title compound **4** (0.88 g, 88%) as a colorless oil: R_f 0.45 (hexane/EtOAc, 8:1); $[\alpha]_D$ −7.48 (*c* 2.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, J = 7.4 Hz, 3H), 1.20 (t, J = 7.5 Hz, 3H), 2.55 (q, J = 7.5 Hz, 2H), 2.67 (q, J = 7.4 Hz, 2H), 3.72 (d, J = 4.3 Hz, 1H), 4.04 (dd, J = 6.5, 4.3 Hz, 1H), 4.10 (d, J = 4.6 Hz, 2H), 4.15 (dd, J = 8.4, 4.3 Hz, 1H), 4.23 (d, J = 4.1 Hz, 1H), 4.36 (d, J = 11.9 Hz, 1H), 4.59 (d, J = 1.9 Hz, 1H), 4.69 (d, J = 12.0 Hz, 1H), 4.75 (d, J = 4.5 Hz, 2H), 4.83 (d, J = 11.1 Hz, 1H), 5.46 (s, 1H), 5.54 (s, 1H), 7.28−7.42 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 140.4, 140.1, 139.8, 139.4, 129.9, 129.8, 129.5, 129.2, 129.1, 129.0, 128.9, 128.8, 128.6, 117.7, 84.3, 83.2, 81.0, 76.9, 76.4, 74.2, 72.1, 55.2, 26.6, 26.4, 15.9; IR (neat) 3030, 2925, 1496, 1454, 1349 cm^{-1}. Anal. Calcd for $C_{39}H_{46}O_4S_2$: C, 72.86; H, 7.21; S, 9.97. Found: C, 73.10; H, 7.25; S, 9.77.

(4*S*,5*S*,6*S*)-4,5,6-Tri-*O*-benzyl-7-(benzyloxymethyl)-octa-1,7-dien-3,4,5,6-tetrol (7). To a solution of **5** (2.44 g, 3.8 mmol) in CH_3CN (100 mL) and H_2O (10 mL) was added mercury(II) oxide (3.3 g, 15.2 mmol). After the solution was stirred for 5 min at room temperature, mercury(II) chloride (3.1 g, 11.4 mmol) was added. The reaction mixture was stirred for an additional 1 h at room temperature, quenched with saturated aqueous $NaHCO_3$ solution, and filtered through Celite. The filtrate was extracted with Et_2O. The organic layer was separated, dried over $MgSO_4$, and concentrated to give the crude aldehyde **6**, which was used for the next step without further purification. To a solution of **6** in dry THF (30 mL) at 0 °C was added vinylmagnesium bromide (8.6 mL, 8.6 mmol, 1.0 M in THF). After being stirred for 3.5 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with Et_2O. The organic layer was separated, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 4:1) to give an epimeric mixture (7:3) of the title compound **7** (1.68 g, 79%) as a colorless oil: R_f 0.40 (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 2.61 (d, J = 6.5 Hz, 0.7H), 3.31 (d, J = 6.6 Hz, 0.3H), 3.64 (dd, J = 6.0, 4.5 Hz, 0.3H), 3.71 (dd, J = 6.2, 3.0 Hz, 0.7H), 3.89 (dd, J = 6.2, 4.5 Hz, 0.7H), 3.99 (m, 0.3H), 4.05−4.15 (m, 3H), 4.30−4.45 (m, 2.3H), 4.52−4.78 (m, 6.4H), 4.91 (d, J = 10.9 Hz, 0.3H), 5.13−5.53 (m, 4H), 5.75−5.86 (m, 1H), 7.32−7.41 (m, 20H); IR (neat) 3468, 3063, 1496, 1454, 1395, 1352 cm^{-1}. Anal. Calcd for $C_{37}H_{40}O_5$: C, 78.69; H, 7.14. Found: C, 78.65; H, 7.22.

(1*R*,2*S*,3*S*,4*R*)-2,3,4-Tri-*O*-benzyl-5-(benzyloxymethyl)-5-cyclohexene-1,2,3,4-tetrol (8). A solution of **7** (11.8 g, 20.9 mmol) and 2nd generation Grubbs catalyst (0.89 g, 1.05 mmol) in CH_2Cl_2 (480 mL) was heated to reflux overnight. The reaction mixture was allowed to return to room temperature and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give the title compound **8** (6.85 g, 61%) as a white solid: R_f =0.58 (EtOAc/hexane, 1:2); mp 72−73.5 °C (lit.[11] mp 74−75 °C); $[\alpha]_D$ −68.4 (*c* 0.12, $CHCl_3$) [lit.[11] $[\alpha]_D$ −66.9 (*c* 1, $CHCl_3$)]; ^1H NMR (300 MHz, $CDCl_3$) δ 2.11 (d, J = 4.0 Hz, 1H), 3.56 (dd, J = 9.8, 7.4 Hz, 1H), 3.85 (dd, J = 9.8, 7.2 Hz, 1H), 3.91 (d, J = 12.3 Hz, 1H), 4.24 (d, J = 13.1 Hz, 1H), 4.27−4.33 (m, 2H), 4.45 (d, J = 11.9 Hz, 1H), 4.52 (d, J = 11.9 Hz, 1H), 4.69 (d, J = 5.9 Hz, 1H), 4.73 (d, J = 6.6 Hz, 1H), 4.79 (d, J = 3.1 Hz, 1H), 4.83 (d, J = 3.2 Hz, 1H), 4.93 (d, J = 11.5 Hz, 1H), 4.97 (d, J = 11.8 Hz, 1H), 5.73 (s, 1H), 7.25−7.35 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 137.83, 137.78, 137.6, 135.4, 128.0, 127.9, 127.8, 127.4, 127.3, 127.1, 127.0, 126.7, 83.3, 83.0, 79.2, 74.5, 74.4, 73.9, 71.7, 70.7, 69.4; IR (neat) 3349, 3029, 1497, 1453, 1361 cm^{-1}. Anal. Calcd for $C_{35}H_{36}O_5$: C, 78.33; H, 6.76. Found: C, 78.21; H, 6.81.

(1*S*,2*S*,3*S*,4*R*)-1-Azido-2,3,4-tri-*O*-benzyl-5-(benzyloxymethyl)-5-cyclohexene-2,3,4-triol (9). To a solution of **8** (6.7 g, 12.5 mmol) and diphenylphosphoryl azide (8.0 mL, 37.1 mmol) in toluene (50 mL) was slowly added DBU (5.5 mL, 36.8 mmol) at 0 °C. After the solution was stirred for 4 h at 0 °C, sodium azide (1.0 g, 15.4 mmol) was added. The reaction mixture was further stirred overnight at 35−40 °C, allowed to return to room temperature, quenched with aqueous 2 N HCl solution (110 mL), and diluted with EtOAc (200 mL) and H_2O (120 mL). The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 4:1) to give the title compound **9** (5.8 g, 83%) as a white solid: R_f 0.52 (EtOAc/hexane, 1:4); mp 79−80.5 °C (lit.[27b] mp 82.5−83.5 °C); $[\alpha]_D$ +49.3 (*c* 0.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.69 (dd, J = 9.7, 4.3 Hz, 1H), 3.94 (d, J = 11.6 Hz, 1H), 4.04 (dd, J = 9.6, 7.1 Hz, 1H), 4.11−4.15 (m, 3H), 4.42 (d, J = 11.8 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 4.62 (d, J = 11.2 Hz, 1H), 4.69−4.79 (m, 4H), 4.95 (d, J = 11.0 Hz, 1H), 5.79 (dd, J = 5.2, 1.3 Hz, 1H), 7.17−7.35 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 137.9, 137.8, 137.3, 129.3, 127.9, 127.83, 127.79, 127.4, 127.3, 127.24, 127.15, 127.1, 125.0, 120.0, 119.6, 119.5, 79.5, 78.7, 78.3, 74.4, 73.5, 72.4, 72.2, 69.3, 57.5; IR (neat) 3031, 2104, 1589, 1489 cm^{-1}. Anal. Calcd for $C_{35}H_{35}N_3O_4$: C, 74.84; H, 6.28; N, 7.48. Found: C, 74.82; H, 6.25; N, 7.62.

(1*S*,2*S*,3*S*,4*R*)-1-Amino-2,3,4-tri-*O*-benzyl-5-(benzyloxymethyl)-5-cyclohexene-2,3,4-triol (10). To a solution of **9** (3.8 g, 6.8 mmol) in pyridine (100 mL) were added 32% NH_4OH (20 mL) and triphenylphosphine (2.7 g, 10.3 mmol). After the solution was stirred overnight at room temperature, CH_2Cl_2 (200 mL) was added to the reaction mixture. The resulting solution was washed with saturated NaCl solution several times. The organic layer was separated, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography ($CHCl_3$/MeOH, 10:1) to give the title compound **10** (2.9 g, 80%) as a colorless oil: R_f 0.40 ($CHCl_3$/MeOH, 10:1); $[\alpha]_D$ +6.6 (*c* 0.75, $CHCl_3$) [lit.[11] $[\alpha]_D$ +6.3 (*c* 1, $CHCl_3$)]; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (br s, 2H), 3.54−3.61 (m, 2H), 3.88−3.96 (m, 2H), 4.16 (d, J = 6.6 Hz, 1H), 4.25 (d, J = 11.9 Hz, 1H), 4.43 (d, J = 11.7 Hz, 1H), 4.49 (d, J = 11.7 Hz, 1H), 4.63−4.83 (m, 5H), 4.91 (d, J = 11.0 Hz, 1H), 5.87 (d, J = 4.0 Hz, 1H), 7.24−7.36 (m, 20H) ;^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 140.0, 139.9, 139.7, 138.5, 133.6, 133.5, 129.8, 129.4, 129.2, 129.1, 80.92, 80.86, 80.6, 76.1, 76.0, 74.0, 73.9, 72.0, 49.9; IR (neat) 3376, 3309, 1605, 1496 cm^{-1}. Anal. Calcd for $C_{35}H_{37}NO_4$: C, 78.48; H, 6.96; N, 2.61. Found: C, 78.49; H, 6.88; N, 2.60.

(1*S*,2*S*,3*S*,4*R*)-1-Acetamido-5-(acetoxymethyl)-2,3,4-tri-*O*-acetyl-5-cyclohexene-2,3,4-triol (11). To a solution of **10** (0.80 g, 1.5 mmol) in dry THF (15 mL) and liquid NH_3 (30 mL) was added sodium (0.5 g, 21.7 mmol) at −78 °C. After the solution was stirred for 2 h at −78 °C, solid NH_4Cl (1.0 g) was added to the reaction mixture at −78 °C. All solvents were removed under reduced pressure to give crude valienamine (**1**). The crude **1** was dissolved in pyridine (20 mL) and acetic anhydride (10 mL) containing a catalytic amount of DMAP. The resulting solution was stirred overnight at room temperature, then was diluted with EtOAc and washed with saturated $NaHCO_3$ solution. The aqueous layer was further extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 1:4) to give the title compound **11** (0.41 g, 71%) as a white solid: R_f 0.30 (EtOAc/hexane, 4:1); mp 91.5−93 °C (lit.[18] mp 93−94 °C); $[\alpha]_D$ +21.1 (*c* 0.90, $CHCl_3$) [lit.[18] $[\alpha]_D$ +20.1 (*c* 0.8, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02−2.07 (m, 15 H), 4.39 (d, J = 13.2 Hz, 1H), 4.65 (d, J = 13.4 Hz, 1H), 5.00−5.12 (m, 2H), 5.37 (d, J = 6.4 Hz, 1H), 5.46 (dd, J = 9.4, 6.4 Hz, 1H), 5.66 (d, J = 8.5 Hz, 1H), 5.89 (d, J = 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 170.22, 170.15, 169.9, 169.8, 134.4, 126.2, 71.3, 69.1, 68.5, 62.9, 44.9, 23.3, 20.7; IR (neat) 3365, 3281, 1745, 1660 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_9$: C, 52.98; H, 6.02; N, 3.63. Found: C, 52.91; H, 6.05; N, 3.59.

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