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New Building Block for Polyhydroxylated Piperidine: Total Synthesis of 1,6-Dideoxynojirimycin

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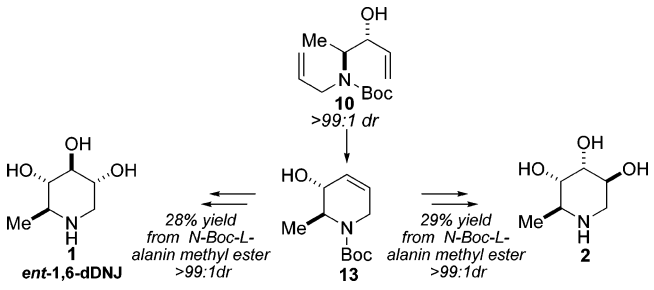

(3*R*,4*S*)-3-Hydroxy-4-*N*-allyl-*N*-Boc-amino-1-pentene **10**, an important precursor for the synthesis of polyhydroxylated piperidines, has been achieved as a single diastereomer without racemization via vinyl Grignard addition to *N*-Boc-*N*-allyl aminoaldehyde **9**, which was derived from an enantiopure natural amino acid. Having forged a tetrahydropyridine ring scaffold **13** from **10** in 85% yield via RCM using Grubbs II catalyst, we were able to effect its stereodivergent dihydroxylation, via a common epoxide intermediate to yield a range of interesting hydroxylated piperidines, including *ent*-1,6-dideoxynojirimycin (*ent*-1,6-dDNJ) **1** (28% overall yield) and 5-amino-1,5,6-trideoxyaltrose **2** (29% over all yield) in excellent dr. To the best of our knowledge, our synthesis of *ent*-1,6-dDNJ **1** is the most expeditious to date.

Herein we document our continued efforts to develop efficient stereoselective routes to polyhydroxylated heterocycles.[1] Our focus in this instance is directed at piperidine derivatives. Research into these systems has blossomed in recent years because of their unique chemical architecture which mirrors the transition states of the enzymatic glycolysis reaction.[2] Certain iminosugars have already been evaluated or accredited as therapies for a wide range of maladies.[3] Among these species, the alkaloid natural product 1,6-dideoxynojirimycin (1,6-dDNJ) and its analogues have proven to be of huge therapeutic potential.[4] Numerous strategies to synthesize 1,6-dDNJ and other iminosugars, from both carbohydrate and non-carbohydrate sources, have been developed (Figure 1).[5]

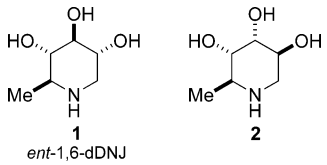

FIGURE 1. Target structures.

However, these routes generally lack directness and require an array of protection/deprotection steps, and the overall stereoselectivity often also can be low.[6] One particularly attractive methodology for the synthesis of iminosugars relies upon Grubbs metathesis[7] of a chiral nonracemic allylic alcohol to fashion the ring skeleton. To date, this approach has been significantly underutilized within the literature, however, some important examples have been communicated.[8] This approach proceeds via tetrahydropyridine **13**, a multifaceted and highly versatile chiral synthon (Figure 2).

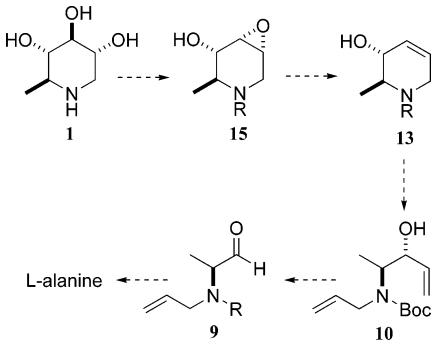

FIGURE 2. Retrosynthetic plan for the synthesis of *ent*-1,6-dDNJ **1**.

The synthesis of this crucial enantiopure intermediate was achieved by a Grubbs metathesis reaction of an enantiopure dienyl alcohol. We chose principally to showcase the versatility

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SCHEME 1. Synthesis of Crucial Vinyl Carbinol Intermediate 10

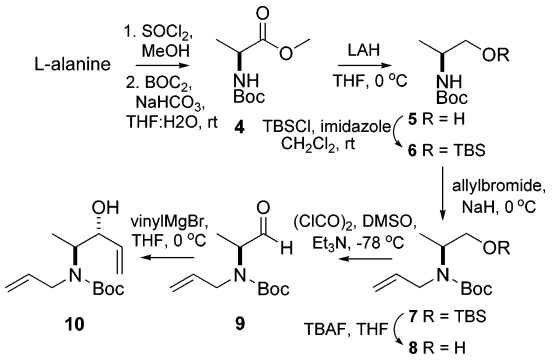
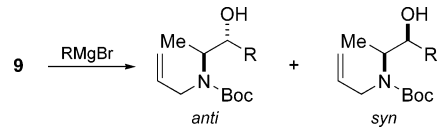


TABLE 1. Generality of Nucleophilic Addition to Amino Aldehyde



		product distribution[b]		
entry	R[a]	anti (%)	syn (%)	yield[c] (%)
1	methyl	98	>2	92
2	vinyl	>99	1	96
3	ethynyl	>99	1	96
4	phenyl	>99	1	93

[a] All reactions were carried out in THF at 0 °C. [b] Ratio calculated from ^{1}H NMR spectrum of crude mixture. [c] Isolated yield.

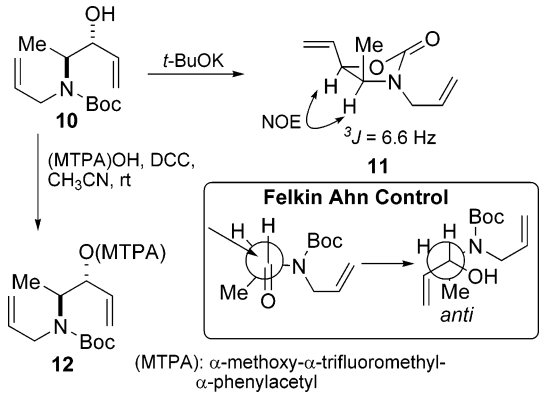
of **13** via the expeditious total synthesis of *ent*-1,6-dDNJ **1** and its diastereomer **2**.

Synthesis of the pivotal anti-allylic alcohol intermediate **10** commenced with enantiopure *N*-Boc-L-alanine methyl ester **4**, which was converted to the corresponding *O*-TBS-protected alcohol **6** (Scheme 1). Subsequent treatment with allyl bromide/NaH afforded *N*-allyl **7**, which was selectively *O*-deprotected then oxidized under Swern conditions to generate amino aldehyde **9**. This product was readily transformed to allylic alcohol **10** via nucleophilic addition of vinyl Grignard in 98% yield with >99:1 anti/syn dr.[9]

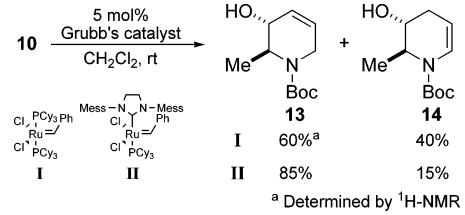
As addition to aldehyde **9** occurred with unprecedented levels of stereoselectivity,[9] we investigated the reaction scope with respect to different carbanionic nucleophiles. Excellent anti selectivity was observed across the range of nucleophiles studied (Table 1). Importantly, although similar approaches have been documented, such high selectivity across a range of substrates has to the best of our knowledge not been observed.[10]

The diastereoselectivity was demonstrated by conversion of **10** to oxazolidin-2-one **11** by base-catalyzed intramolecular cyclization (Scheme 2).[11] Analysis of the C(4)H and C(5)H ^3J coupling constants within **11** as well as NOESY data revealed that there was a cis relationship between these two groups. The stereochemical outcome is consistent with the reaction occurring under polar Felkin−Ahn control.[12] The nucleophilic addition process was shown to occur without epimerization (>95% ee)

SCHEME 2. Synthesis of Oxazolidin-2-one 11: Proof of Stereoselectivity



SCHEME 3. Metathesis Reaction



of the α-center by conversion of **10** to the corresponding Moscher's ester **12** and comparison to a racemic counterpart.

Treatment of **7** under standard RCM conditions using Grubbs I catalyst afforded the desired chiral nonracemic lynchpin, tetrahydropyridine **13** (Scheme 3). However, this product was obtained as a readily chromatographically separable 60:40 mixture with enamide **14**. Additives were unable to ameliorate this ratio.[13] Such side reactions have been widely documented in the Grubbs protocol, leading to significant reductions in product yield.[14] However, when Grubbs II catalyst was employed, an 85:15 mixture of products was observed. Purification delivered **13** in 85% yield. In **13**, due to Paulsen strain minimization, the methyl and hydroxyl appendages are both pseudoaxial.[15]

Our first effort to derivatize **13** involved Pd catalyzed hydrogenation of the olefin. This proceeded smoothly to afford piperidine **3** in 92% yield after *N*-Boc deprotection (Scheme 4). Proton-directed epoxidation of **13** was next attempted.[16] Treatment of **13** with *m*-CPBA afforded the desired oxirane syn to the alcohol motif **15** as a single diastereomer. Axial hydroxyl functions in cyclohex-2-enol systems usually proffer low diastereoselectivities in *m*-CPBA epoxidations.[17]

However, in this case the axial methyl substituent probably serves to shield the anti face. Treatment of **15** with KOH proceeded via trans diaxial ring opening (Furst Plattner control)[18] to unveil a triol motif with all adjacent groups anti, as a single regioisomer.

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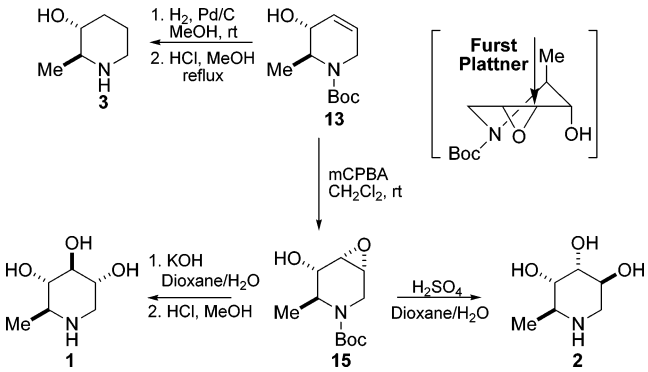
SCHEME 4. Manipulation of Tetrahydropyridine Intermediate



The crude product consisted of approximately a 90:10 mixture of *N*-Boc **1** and *ent*-1,6-dDNJ **1**. Boc deprotection followed by Dowex chromatography generated *ent*-1,6-dDNJ 1 as a single product, $[\alpha]^{20}_D$ −13.3 (*c* 0.67, H_2O) in 83% yield.[19] As anticipated, the $[\alpha]_D$ value was similar in magnitude and opposite in sign to the literature value quoted for 1,6-dideoxynojirymicin $[\alpha]^{20}_D$ +12.7 (*c* 0.8, H_2O). The alternative addition regioisomer **2** was accessed as a single product by reaction of epoxide **15** with H_2SO_4 followed by Dowex chromatography.[8,20] The regioselectivity in this instance can be ascribed to *N*-Boc hydrolysis, and subsequent conformational flip, occurring prior to epoxide ring opening.[21b] The stereochemistry of both target compounds was confirmed by 2D-NOESY and ^{1}H NMR coupling constant data. It is important to note that in the synthesis of **1** and **2** four contiguous stereocenters were set up in four overall steps using three stereoselective transformations, each of which occurred with absolute control.

In conclusion, we have developed an efficient route to a highly versatile tetrahydropyridine intermediate **15**, and shown its huge potential by effecting not only the most efficient fully stereocontrolled synthesis of *ent*-1,6-dDNJ to date but also equally expeditious syntheses of analogues. The synthesis of tetrahydropyridine **15** is expedient, and proceeds via an RCM reaction of enantiopure allylic alcohol **10**, which was accessed via a substrate directed carbonyl addition reaction. Continued investigations into the utility of this important synthon are underway.

Experimental Section

***tert*-Butyl Allyl((2*S*,3*R*)-3-hydroxypent-4-en-2-yl)carbamate (10).** Oxalyl chloride (3.24 mL, 37.15 mmol) was dissolved in 138.6 mL of dry CH_2Cl_2. The mixture was stirred and cooled to −78 °C, and DMSO (4.2 mL) was added. The mixture was stirred for 10 min, a solution of **8** (3.2 g, 14.86 mmol) in 10 mL of CH_2Cl_2 was added, the resulting mixture was stirred for 15 min, and Et_3N was added (8.28 mL, 59.44 mmol). After 15 min, the mixture was warmed to room temperature, and after 30 min, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The organic layer was washed with 0.5 N HCl and brine, dried over Na_2SO_4, and filtered, and the solvent was removed by rotary evaporation to give **9** as yellow oil: ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.35 (3H, d, J = 6.8 Hz), 1.45 (9H, s), 3.76 (2H, m), 4.17 (1H, m), 5.22 (2H, m), 5.83 (1H, t, J = 6.6 Hz); ^{13}C NMR (300 MHz; $CDCl_3$) δ 1.0, 12.8, 28.2, 50.38, 61.36, 118.2, 134.0, 199.6; FAB-MS obsd 214.1526, calcd 214.1443 [$(M + H)^+$, M = $C_{11}H_{19}NO_3$]. A precooled solution of vinylmagnesium bromide (4.3 mL, 32.35 mmol) in dry THF was added dropwise under N_2 to a stirred solution of **9** (2.3 g, 10.78 mmol) in dry THF at 0 °C. After the solution was stirred at that temperature for 10 min (TLC control), a saturated aqueous solution of ammonium chloride (10 mL) was added, and the reaction mixture was allowed to reach room temperature then extracted with EtOAc. The extracts were washed with brine, dried over Na_2SO_4, and evaporated. The product was purified by flash column chromatography (hexanes/EtOAc = 80:20) to afford compound **10** (2.55 g, 98%) as a colorless oil: $[\alpha]^{20}_D$ −0.3 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.22 (3H, d, J = 7 Hz), 1.43 (9H, s), 3.68 (3H, m), 3.79 (1H, m), 5.10 (3H, m), 5.30 (1H, m), 5.78 (2H, m); ^{13}C NMR (300 MHz; $CDCl_3$) δ 12.1, 15.2, 28.3, 49.8, 57.7, 76.0, 80.1, 115.7, 116.3, 115.7, 135.3, 138.5, 156.4; FAB-MS obsd 242.1764, calcd 242.1756 [$(M + H)^+$, M = $C_{13}H_{23}NO_3$].

(4*S*,5*R*)-3-Allyl-4-methyl-5-vinyloxazolidin-2-one (11). To a solution of **10** (100 mg, 0.414 mmol) in 2 mL of THF was added a solution of *t*-BuOK (70 mg, 0.621 mmol) in THF at −78 °C. After being stirred for 10 h at room temperature, the reaction mixture was quenched with satd aq NH_4Cl (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 80:20) to give compound **11** (65 mg, 94%) as a colorless oil: ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.10 (3H, d, J = 6.6 Hz), 3.57 (1H, dd, J = 7.5, 15.6 Hz), 3.92 (1H, m), 4.15 (1H, m), 4.93 (1H, t, J = 1.0 Hz), 5.24 (2H, m), 5.40 (2H, m), 5.82 (2H, m), 3.84 (2H, m); ^{13}C NMR (300 MHz; $CDCl_3$) δ 13.8, 44.5, 53.6, 78.0, 118.3, 119.9, 131.1, 132.3, 157.3; EI-MS (*m*/*z*) 167 (M^+); HRMS calcd for $C_9H_{13}NO_2$ (M^+) 167.0946, found 167.0947.

Representative Example of the Preperation of Mosher's Ester. Preparation of (3*R*,4*S*)-4-[Allyl(*tert*-butoxycarbonyl)-amino]pent-1-en-3-yl 3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate (12). DCC (90 mg, 0.43 mmol) was added to a solution of (*R*)-(+)-MTPA in acetonitrile (3 mL), which immediately resulted in the formation of a white precipitate of *N*,*N*-dicyclohexylurea. After this had stirred at room temperature for 15 min, the resulting solution of the MTPA anhydride was filtered through a pipet capped with cotton wool and added to samples of (*R*)-**10** (100 mg, 0.22 mmol). The resulting clear colorless solutions were stirred at room temperature for 18 h and then quenched with satd aqueous $NaHCO_3$ (6 mL). The reaction mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 80:20) to give compound **12** (65 mg, 85%) as an oil, with care being taken not to exercise a mechanical separation of one of the diasteromers over the other: ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.15 (3H, d, J = 9.5 Hz), 1.47 (9H, s), 3.53 (3H, s), 3.70 (2H, brs), 4.08 (1H, d, J = 6.6 Hz), 5.07 (2H, m), 5.35 (2H, m), 5.74 (3H, m), 7.41 (3H, m), 7.50 (2H, m); FAB-MS obsd 458.2156, calcd 458.2154 [$(M + H)^+$, M = $C_{23}H_{30}F_3NO_5$].

(5*S*,6*S*)-*tert*-Butyl 5,6-Dihydro-5-hydroxy-6-methyl-1(2*H*)-carbamate (13). To a solution of **10** (2.1 g, 8.70 mmol) in 218 mL of dry CH_2Cl_2 was added Grubbs catalyst (358 mg, 0.43 mmol) under N_2. The reaction mixture was stirred at room temperature overnight. After all starting material disappeared, 25 mL of water was added

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and stirred vigorously at room temperature for 1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine and dried (Na_2SO_4), and solvent was evaporated. The crude mixture was separated and purified by column chromatography on silica gel (hexane/EtOAc = 65:35) to afford **13** (1.58 g, 85%): $[\alpha]^{20}_D$ −95.1 (c 1, $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.07 (3H, d, J = 7 Hz), 1.49 (9H, s), 3.57 (1H, d, J = 19.54), 3.88 (1H, m), 5.97 (2H, m); ^{13}C NMR (300 MHz; $CDCl_3$) δ 14.9, 28.4, 39.8, 60.3, 67.5, 79.9, 124.4, 127.7, 155.6; EI-MS (*m*/*z*) 213 (M^+); HRMS calcd for $C_{11}H_{19}NO_3$ (M^+) 213.1365, found 213.1364.

(1*S*,4*S*,5*R*,6*R*)-*tert*-Butyl 5-Hydroxy-4-methyl-7-oxa-3-azabicyclo-[4.1.0]heptane-3-carbamate (15). To a stirred suspension of **13** (1.1 g, 5.15 mmol) was added *m*-CPBA (2.67 g, 60%, 15.47 mmol) at room temperature. The resulting suspension was stirred for 48 h, and satd aq $NaHCO_3$ (10 mL) was added to quench the reaction. The resulting two-phase mixture was stirred vigorously for 15 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 60:40) to give epoxide **15** (790 mg, 67%) as a pale yellow oil: $[\alpha]^{20}_D$ −28.8 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.09 (3H, d, J = 7.2 Hz), 1.46 (9H, s), 3.23 (1H, d, J = 15.4), 3.43 (2H, m), 3.71 (1H, brs), 4.32 (2H, m); ^{13}C NMR (300 MHz; $CDCl_3$) δ 15.0, 28.3, 36.8, 50.5, 51.9, 65.5, 80.3, 155.8; EI-MS (*m*/*z*) 229 (M^+); HRMS calcd for $C_{11}H_{19}NO_4$ (M^+) 229.1314, found 229.1316.

(2*S*,3*R*,4*S*,5*R*)-2-Methylpiperidine-3,4,5-triol (1). A solution of **15** (200 mg, 0.20 mmol), 1,4-dioxane (10 mL), and 0.3 M KOH (20 mL) was refluxed overnight. After evaporation, MeOH (10 mL) and 6 N HCl (15 mL) were added to the residue. The mixture was heated at 60 °C for 1 h and then evaporated to give an oil. The residue was separated by ion-exchange resin chromatography to give *ent*-1,6-dDNJ **1** (106 mg, 83%): $[\alpha]^{20}_D$ −13.3 (*c* 0.67, H_2O); ^{1}H NMR (300 MHz; D_2O) δ 1.04 (3H, d, J = 6.3 Hz), 2.32 (1H, m), 2.41 (1H, m), 2.89 (2H, m), 3.15 (1H, m), 3.37 (1H, m); ^{13}C NMR (300 MHz; D_2O) δ 16.4, 48.5, 54.9, 70.8, 76.2, 77.9; FAB-MS obsd 148.0970, calcd 148.0974 [$(M + H)^+$, M = $C_6H_{13}NO_3$].

(2*S*,3*S*,4*R*,5*S*)-2-Methylpiperidine-3,4,5-triol (2). To a solution of **15** (200 mg, 0.20 mmol) and 1,4-dioxane (10 mL) was added 0.2 N H_2SO_4 (10 mL) dropwise and the mixture stirred at room temperature for 3 h. The residue was separated by ion-exchange resin chromatography to give 5-amino-1,5,6-trideoxyaltrose **2** (109 mg, 85%): $[\alpha]^{20}_D$ −28.2 (c 0.34, H_2O); ^{1}H NMR (300 MHz; D_2O) δ 1.05 (3H, d, J = 6.5 Hz), 2.58 (1H, m), 2.98 (1H, d, J = 15.0), 3.18 (1H, dd, J = 4.4, 15.0 Hz), 3.38 (1H, m), 3.49 (1H, t, J = 4.4), 3.64 (1H, dd, J = 2.0, 9.1 Hz); ^{13}C NMR (300 MHz; D_2O) δ 16.7, 41.5, 49.3, 55.1, 56.1, 71.2; EI-MS (*m*/*z*) 147 (M^+); HRMS calcd for $C_6H_{13}NO_3$ (M^+) 147.0895, found 147.0895.

(2*S*,3*S*)-2-Methylpiperidin-3-ol (3). Compound **13** (100 mg, 0.46 mmol) was dissolved in methanol (5 mL), and 10% palladium on activated carbon as catalyst was added. Then hydrogen was bubbled into the mixture and stirring continued at room temperature for 10 h. The mixture was filtered through a Celite pad. The filtrate was evaporated, and MeOH (1.9 mL) and 6 N HCl (5.6 mL) were added to the residue. The mixture was refluxed for 1 h and then evaporated to give **3** (50 mg, 92%) as an oil. The residue was separated by ion-exchange resin chromatography to give **3** as off-white solid: mp 126−127 °C; $[\alpha]^{20}_D$ −24.4 (*c* 1, H_2O); ^{1}H NMR (300 MHz; D_2O) δ 1.03 (3H, d, J = 6.3 Hz), 1.22 (1H, m), 1.40 (1H, m), 1.61 (1H, m), 1.87 (1H, m), 2.41 (2H, m), 2.78 (1H, m), 3.10 (1H, m); ^{13}C NMR (300 MHz; D_2O) δ 17.0, 23.9, 32.9, 44.4, 56.9, 72.5; EI-MS (*m*/*z*) 115 (M^+); HRMS calcd for $C_6H_{13}NO$ (M^+) 115.0997, found 115.0964.

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Supporting Information Available: Spectral data and copies of the ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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