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Polyhydroxylated Indolines and Oxindoles from *C*-Glycosides via Sequential Henry Reaction, Michael Addition, and Reductive Amination/Amidation

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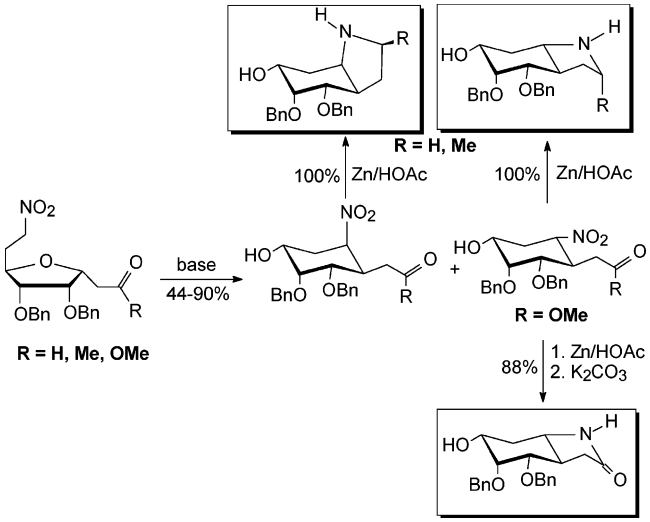

6-Nitro-2′-carbonyl-*C*-glycofuranosides synthesized via Henry reaction from 1-*C*-allyl 5-aldo-*C*-glycoside underwent an intramolecular Michael addition to afford nitrocyclohexanol derivatives in good to excellent yield. Reduction of the nitro group followed by intramolecular amination with ketone and aldehyde and amidation with ester produced indoline and oxindole derivatives, respectively, in excellent yield.

Azasugars inhibit glycosidases by mimicking the oxocarbenium ion transition state generated from cleavage of the glycosidic bond in enzymatic catalysis.[1] Because the initial step of glycoside hydrolysis is likely the protonation of the glycosidic oxygen,[2] compounds that mimic an exocyclic oxonium ion could also be potential glycosidase inhibitors. In fact, it is known that the pseudoglucosylamines (aminocyclohexenol and aminocyclohexanol) in acarbose[3] and voglibose[4] actively inhibit α-glycosidase (α-amylase) activity. Several other glycosidase inhibitors such as allosamidin (Chitinase),[5] trehalostatin (α,α-trehalase),[6] and mannostatin (α-D-mannosidase)[7] all contain aminocyclopentanol. Accordingly, various aminocyclopentanols[8] as well as glycoimidazoles and glycotriazoles (fused heterobicycles) were designed and synthesized as inhibitors.[9] In addition, some plant alkaloids with polyhydroxylated indoline, oxindole, and quinoline skeletons[10] are also able to inhibit glycosidases,[11] likely due to the presence of the aminocyclopentanol/aminocyclohexanol subunit. Thus, we reasoned that polyhydroxylated indolines and quinolines might be potential glycosidase inhibitors.

Recently, we have reported the syntheses of aza-*C*-glycosides,[12] thio-*C*-glycosides,[13] and hydroxylated quinolizidines[14] from 2′-carbonyl-*C*-glycosides by an intramolecular hetero-Michael reaction, in which an α,β-conjugated carbonyl inter-

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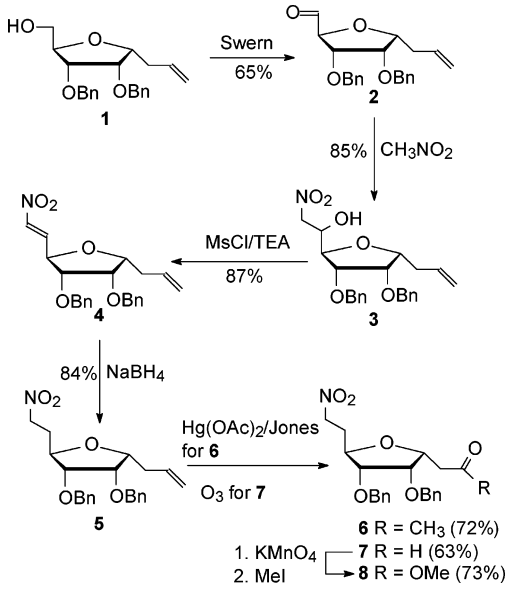
SCHEME 1. Synthesis of 1-(2′-Oxoalkyl)-*C*-glycosides



mediate was generated by β-elimination.[15] Here, we exploit similar chemistry for the synthesis of aminocyclohexanols from 1-*C*-(2′-carbonyl)-6-nitro-*C*-glycosides. This strategy requires an intramolecular Michael addition between the nitronate anion and the α,β-conjugated carbonyl intermediate generated under basic conditions. In addition, the presence of both nitro and carbonyl groups in the resultant nitrocyclohexanols allows us to explore the reductive amination and amidation to obtain polyhydroxylated indoline and oxindole derivatives.[16]

The key functional group manipulations involved the introduction of 6-nitro and 1-*C*-2′-oxoalkyl groups. The nitroaldol (Henry) reaction provides C−C bond formation[17] and is commonly used to extend the carbon chain and to prepare aminosugars in carbohydrate chemistry.[18] Thus, the primary alcohol **1**[13] was converted to the 5-aldehyde **2** (Scheme 1) by Swern oxidation[19] and by a modified procedure using cyanuric chloride activated DMSO.[20] Both procedures were effective, but the former appears more reliable. Henry reaction between the aldehyde and nitromethane in 1% NaOMe−methanol produced a diastereomeric mixture of nitroalcohol **3** in a ratio of ca. 2:1. Although high stereoselectivity may be achieved using various catalysts,[21] no attempt was made to improve the stereoselectivity. Instead, nitroalcohol **3** was converted to nitroalkene **4** via β-elimination (MsCl/TEA).[22] Further reduction of the double bond of **4** with $NaBH_4$ afforded nitroalkane **5**. Because these reactions proceeded efficiently, we were also able to obtain **5** from **1**, without chromatographic purification of the intermediates, in 50−60%.

To introduce a latent Michael acceptor at the anomeric center, the allyl group of **5** was converted to 2′-ketone **6** using $Hg(OAc)_2$/Jones reagent[23] and the 2′-aldehyde **7** by ozonolysis using dimethyl sulfide as the reducing reagent[24] (see Scheme 1). 2′-Ester **8** was obtained by oxidation of aldehyde **7** using $KMnO_4$ to a carboxylic acid followed by treatment with iodomethane in the presence of $NaHCO_3$.[13]

Treatment of **6** with base (4% NaOMe or 1% K_2CO_3 in MeOH) at room temperature produced nitrocyclohexanols, **9** and **10**, via β-elimination followed by an intramolecular Michael addition. As expected, the thermodynamically more stable **9**, with 1,6-trans configuration, was obtained as the major product (60−70%), and 1,6-cis **10** was obtained as the minor product (20−30%). We were unable to completely convert **10** to **9** even with prolonged reaction time (overnight) because of equilibrium between **9** and **10**, as evidenced by the fact that both purified **9** and **10** were able to partially convert to the other under the same basic conditions. On the other hand, the base treatment of 2′-aldehyde **7** under the same conditions led to many byproducts and the desired nitrocyclohexanol **13** was isolated in low yield (20−45%), likely due to undesirable intra- and intermolecular Henry reactions associated with the high reactivity of the aldehyde. We reasoned that the reaction could likely be improved with a less basic and more dilute solution at lower temperature. Consequently, compound **7** was treated with 1.25% NaOMe at 0 °C for 1 h, which resulted in a clean reaction to give products **13** and **14** in a ratio of 1:1, in excellent yield (see Scheme 2).[25] The diastereoselectivity is more likely a result of the epimerization at C6 after Michael addition. Apparently, such epimerization (from **14** to **13**) was greatly suppressed under mild conditions resulting in the isolation of equal amounts of **13** and **14** before they reach a thermodynamic equilibrium.

The attempt to convert **9** to a hydroxylated indoline in a single step by catalytic hydrogenation was not successful due to the incomplete removal of the *O*-benzyl groups. Repetitive catalytic hydrogenation led to low recovery yield, and catalytic reduction of the nitro group in other systems has also been problematic. As an alternative, zinc dust under acidic conditions was successfully used.[26] Accordingly, we reduced the nitro groups of **9**, **10**, **13**, and **14** to the respective amines using Zn−HOAc, which spontaneously underwent intramolecular reductive ami-

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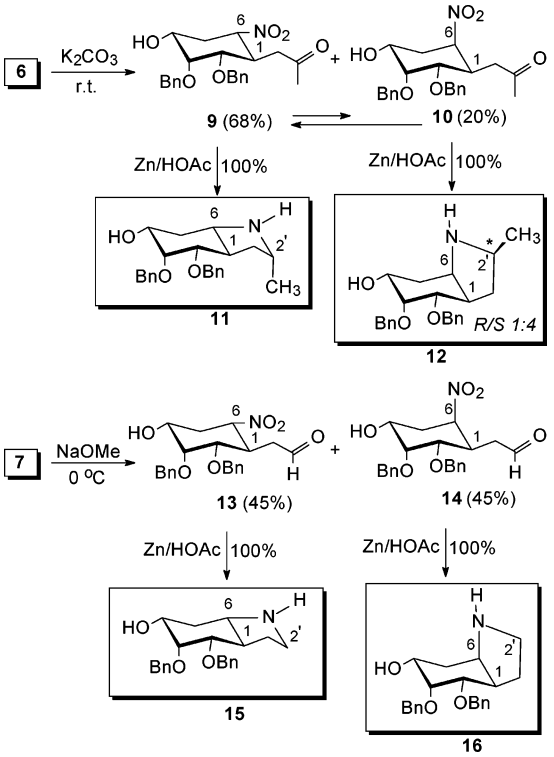
(25) We also treated substrate **6** under the same conditions, but the reaction was extremely slow.

SCHEME 2. Synthesis of Indolines

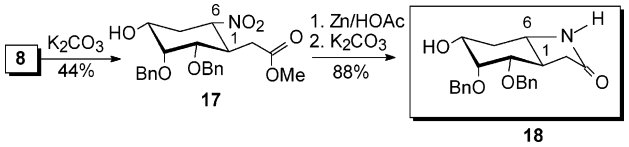


nation with the 2′-ketone and 2′-aldehyde to give indolines **11**, **12**, **15**, and **16** in quantitative yield. The products obtained as ammonium acetates after filtration and removal of acetic acid were fairly pure. Free amines were obtained by dissolving the ammonium salt in organic solvent followed by washing with $NaHCO_3$. As a result, a marked upfield shift of H-2′ and H-6 signals was observed in ^{1}H NMR spectra.

Apparently, the reduction of the imine intermediate derived from **9** was totally stereoselective producing a single diastereomer **11**. The conversion of **10** to indoline **12** was somewhat less selective providing a mixture of two diastereomers in a ratio of 4:1 (*S*/*R* or endo/exo) as indicated by NMR analysis. The difference in stereoselectivity between **11** and **12** likely resulted from the fact that the imine intermediate from **9** with a 1,6-trans configuration is quite rigid and that from **10** with a 1,6-cis configuration is relatively flexible.

Similarly, we applied the same reaction to 2′-ester **8**. The reaction under basic conditions was much slower than its counterparts (**6** and **7**). Before complete consumption of starting material, significant polar byproducts were observed at the original spot on TLC, likely due to the hydrolysis of methyl ester of starting material and/or product. Therefore, after treatment of **8** with 1% K_2CO_3 in methanol for 2 days, the 1,6-trans product **17** was isolated in 44% yield. We did not obtain the other diastereomer, but we did observe a very minor product on TLC very close to the starting material. Reduction of the nitro group of **17** was again achieved using Zn/HOAc overnight, which produced an amine intermediate with an intact methyl ester as indicated by ^{1}H NMR analysis. After filtration and

SCHEME 3. Synthesis of Oxindole



removal of solvent, the intermediate was treated with K_2CO_3 in MeOH to afford oxindole **18** as a single product, which was isolated by chromatography in 88% yield (Scheme 3).

The 1,6-trans bicyclic compounds (**11**, **15**, and **18**) and 1,6-cis indolines (**12** and **16**) provided a distinctive ^{1}H NMR pattern (see Supporting Information). NMR analysis indicated that the cyclohexane ring (carbosugar) of 1,6-trans bicycles was in a $^4C_1$ conformation as indicated by ^{1}H−^{1}H coupling constants (e.g., $J_{1,2} = 10.8$ Hz, $J_{2,3} = 2.0$ Hz, $J_{3,4} < 1.0$ Hz in **11**), NOEs observed among axial protons (H-2, H-4, and H-6) (see Figure 1), and significant downfield H_{5ax} (2.0−2.1 ppm) resonance in

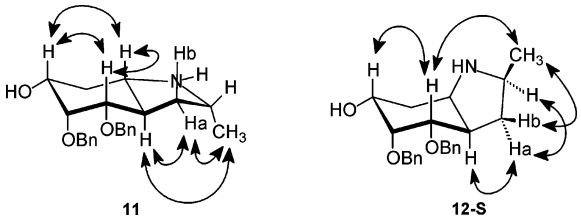


FIGURE 1. Important NOEs observed in **11** and **12-S**.

comparison to that of H_{5eq} (1.5−1.6 ppm). However, the $^4C_1$ conformation of cyclohexane in **12** and **16** was slightly twisted around C_5−C_6 as suggested by the fact that two H-5 protons were observed with similar chemical shifts (1.8−1.9 ppm). In addition, the newly created chiral C-2′ of **11** was assigned *R*-configuration (endo) on the basis of the observation of strong NOEs between H-1 and H-1′a and between H-1′a and 2′-Me as well as the weak NOE between H-1 and 2′-Me (Figure 1). Similarly, we also determined the stereochemistry of the major diastereomer **12-S** obtained from **10** (see Figure 1), which has an *S*-configuration (endo) at C-2′.

In summary, we described an effective method for the synthesis of hydroxylated indolines and oxindoles from 2′-carbonyl-*C*-glycosides via Henry reaction, intramolecular Michael addition, and reductive amination/amidation. In addition to the mild reaction conditions and the use of common reagents, this synthetic strategy is very concise and atom-economical. The method provides an entry to diverse polyhydroxylated indoline and oxindole structures.

Experimental Section

(1*S*,2*S*,3*R*,4*R*,6*S*)-1-Acetylmethyl-2,3-di-*O*-benzyl-4-hydroxyl-6-nitrocyclohexane (9) and (1*S*,2*S*,3*R*,4*R*,6*R*)-1-Acetylmethyl-2,3-di-*O*-benzyl-4-hydroxyl-6-nitrocyclohexane (10). A solution of **6** (100 mg, 0.24 mmol) in 1% K_2CO_3−MeOH (3 mL) was kept at room temperature overnight. The mixture was partitioned between ethyl acetate and water, and the aqueous solution was extracted with ethyl acetate. The combined organic phase was dried and concentrated. Purification by chromatography (hexane/EtOAc 1:1) afforded **9** as white amorphous (68 mg, 68%) and **10** as crystals (20 mg, 20%).

For **9**: $[\alpha]_D$ −56 (*c* 0.34, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.37−7.28 (m, 10H, 2 × Ph), 5.07 (d, $J = 11.6$ Hz, 1H, $PhCH_2$), 4.76 (m, 1H, H-6), 4.68 (d, $J = 11.2$ Hz, 1H, $PhCH_2$), 4.60 (d, $J = 11.2$ Hz, 1H, $PhCH_2$), 4.40 (d, $J = 11.6$ Hz, 1H, $PhCH_2$), 4.06 (bs, 1H,

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H-3), 3.70 (bd, J = 11.2 Hz, 1H, H-2), 3.63 (m, 1H, H-4), 2.87 (m, 1H, H-1), 2.79 (m, 1H, H-1a′), 2.39 (m, 1H, H-1b′), 2.29−2.24 (m, 2H, H-5a, 5b), 2.13 (d, J = 11.2 Hz, 1H, OH), 2.02 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 207.3 (C-2′), 138.2, 137.1, 128.6, 128.2, 128.0, 127.8, 83.1 (C-6), 78.2 (C-2), 75.9 (C-3), 74.6 ($PhCH_2$), 72.2 ($PhCH_2$), 67.2 (C-4), 39.1 (C-1′), 37.1 (C-1), 34.1 (C-5), 30.4 (CH_3); HRMS calcd for $C_{23}H_{28}NO_6$ 414.1917 (M + H), found 414.1954.

For **10**: mp 99−100 °C (needles from EtOAc−hexanes); $[\alpha]_D$ −66 (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.37−7.28 (m, 10H, 2 × Ph), 5.05 (m, 1H, H-6), 4.91 (d, J = 10.8 Hz, 1H, $PhCH_2$), 4.74 (d, J = 11.6 Hz, 1H, $PhCH_2$), 4.55 (d, J = 11.6 Hz, 1H, $PhCH_2$), 4.51 (d, J = 10.8 Hz, 1H, $PhCH_2$), 4.21 (m, 1H, H-4), 4.03 (bs, 1H, H-3), 3.72 (bd, J = 10.4 Hz, 1H, H-2), 3.07 (m, 1H, H-1), 2.77 (m, 1H, H-1a′), 2.22 (m, 1H, H-1′b), 2.17 (m, 1H, H-5a), 2.07 (m, 1H, H-5b), 2.07 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 206.2 (C-2′), 138.1, 137.3, 128.7, 128.6, 128.2, 128.0, 127.9, 83.6 (C-6), 78.1 (C-2), 76.1 (C-3), 74.5 ($PhCH_2$), 72.4 ($PhCH_2$), 66.4 (C-4), 40.5 (C-1′), 34.1 (C-1), 31.9 (C-5), 30.4 (CH_3); HRMS calcd for $C_{23}H_{28}NO_6$ 414.1917 (M + H), found 414.1921.

Di-*O*-benzyl Indoline Derivative 11. A mixture of **9** (40 mg, 0.097 mmol) and zinc dust (140 mg) in acetic acid (3 mL) was stirred overnight. The filtrate was diluted by the addition of water and lyophilized to a solid residue (salt form of **11**) in quantitative yield. The amine form was obtained by dissolving the salt in dichloromethane followed by washing with aqueous sodium bicarbonate. The organic phase was dried and concentrated to give syrupy **11**: $[\alpha]_D$ −25 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.38−7.26 (m, 10H, 2 × Ph), 5.12 and 4.58 (d and d, J = 11.6 Hz, 1H each, $PhCH_2$), 4.70 and 4.62 (d and d, J = 12.0 Hz, 1H each, $PhCH_2$), 4.03 (dd, J = 2.4, 3.2 Hz, 1H, H-3), 3.55 (ddd, J = 3.2, 4.4, 9.8 Hz, 1H, H-4), 3.42 (m, 1H, H-2′), 3.22 (dd, J = 2.4, 10.8 Hz, 1H, H-2), 2.33 (ddd, J = 3.2, 11.6, 11.6 Hz, 1H, H-6), 2.13 (m, 1H, H-1), 2.06 (m, 1H, H-5a), 1.75 (m, 1H, H-1′a), 1.66 (m, 1H, H-1′b), 1.55 (ddd, J = 11.6, 11.6, 11.6 Hz, 1H, H-5b), 1.19 (d, J = 6.4 Hz, 3H, 2′-Me); ^{13}C NMR ($CDCl_3$) δ 139.0, 138.5, 128.7, 128.0, 127.9, 127.8, 81.7 (C-2), 78.7 (C-3), 75.1 ($PhCH_2$), 71.6 ($PhCH_2$), 70.4 (C-4), 60.0 (C-6), 53.3 (C-2′), 44.5 (C-1), 35.9 (C-1′), 35.0 (C-5), 23.3 (2′-CH_3); HRMS calcd for $C_{23}H_{30}NO_3$ 368.2226 (M + H), found 368.2199.

(1*S*,2*S*,3*R*,4*R*,6*S*)-1-Methoxycarbonylmethyl-2,3-di-*O*-benzyl-4-hydroxyl-6-nitrocyclohexane (17). A solution of compound **8** (27 mg) in 1% K_2CO_3−MeOH (5 mL) was kept at room temperature for 2 days. The mixture was partitioned between ethyl acetate and water, and the aqueous solution was extracted with ethyl acetate. The combined organic phase was dried and concentrated. Purification by chromatography (hexane/EtOAc 1:1) afforded **17** as a white amorphous (12 mg, 44%): $[\alpha]_D$ −25 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.39−7.26 (m, 10H, 2 × Ph), 5.08 and 4.59 (d and d, J = 11.6 Hz, 1H each, $PhCH_2$), 4.75 (m, 1H, H-6), 4.71 and 4.46 (d and d, J = 11.6 Hz, 1H each, $PhCH_2$), 4.08 (dd, J = 2.0, 2.0 Hz, 1H, H-3), 3.65−3.60 (m, 2H, H-2, 4), 3.58 (s, 3H, OMe), 2.94 (m, 1H, H-1), 2.78 (dd, J = 4.5, 17.2 Hz, 1H, H-1′a), 2.31 (dd, J = 5.2, 17.2 Hz, 1H, H-1′b), 2.30−2.25 (m, 2H, H-5a, 5b), 2.18 (d, J = 10.8 Hz, 1H, 4-OH); ^{13}C NMR ($CDCl_3$) δ 172.0 (C-2′), 138.4, 137.3, 128.9, 128.8, 128.3, 128.2, 128.1, 83.4 (C-6), 78.3 (C-2), 76.0 (C-3), 74.9 ($PhCH_2$), 72.5 ($PhCH_2$), 67.4 (C-4), 51.8 (OMe), 37.2 (C-1), 34.5 (C-5), 30.5 (C-1′); HRMS calcd for $C_{23}H_{28}NO_7$ 430.1866 (M + H), found 430.1862.

Di-*O*-benzyl Oxindole Derivative 18. To a solution of **17** (12 mg) in acetic acid (2 mL) was added zinc dust (20 mg), and the mixture was stirred at room temperature overnight. The filtrate was diluted by the addition of water and lyophilized to a residue. To a solution of the above residue in methanol (3 mL) was added K_2CO_3 (10 mg), and the mixture was stirred overnight. The reaction mixture was neutralized by the addition of acetic acid and concentrated. Purification by chromatography (EtOAc) provided **18** (9 mg, 88%) as a syrup: $[\alpha]_D$ 0 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.38−7.26 (m, 10H, 2 × Ph), 5.48 (s, 1H, NH), 5.13 and 4.58 (d and d, J = 11.2 Hz, 1H each, $PhCH_2$), 4.73 and 4.61 (d and d, J = 12.0 Hz, 1H each, $PhCH_2$), 4.09 (dd, J = 2.4, 2.8 Hz, 1H, H-3), 3.57 (m, 1H, H-4), 3.41 (dd, J = 2.4, 10.8 Hz, 1H, H-2), 2.95 (ddd, J = 3.2, 11.2, 11.2 Hz, 1H, H-6), 2.62 (m, 1H, H-1), 2.53 (m, 1H, H-1′a), 2.28 (d, J = 10.8 Hz, 1H, 4-OH), 2.09 (m, 1H, H-5a), 2.03 (m, 1H, H-1′b), 1.64 (ddd, J = 11.6, 11.6, 11.6 Hz, 1H, H-5b); ^{13}C NMR ($CDCl_3$) δ 178.2 (C-2′), 138.6, 138.0, 128.8, 128.3, 128.2, 128.1, 127.8, 79.8 (C-2), 78.6 (C-3), 75.5 ($PhCH_2$), 71.7 ($PhCH_2$), 69.5 (C-4), 54.5 (C-6), 43.0 (C-1), 35.6 (C-1′), 34.5 (C-5); HRMS calcd for $C_{22}H_{26}NO_4$ 368.1862 (M + H), found 368.1851.

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Supporting Information Available: General methods, synthetic procedures for **2**−**8** and **12**−**16**, and NMR spectra (^{1}H, ^{13}C, COSY, NOESY, HSQC) of compounds (**3**−**18**). This material is available free of charge via the Internet at http://pubs.acs.org.

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