

**Regioselective Reductive Cleavage of Bis-benzylidene Acetal: Stereoselective Synthesis of Anticancer Agent OGT2378 and Glycosidase Inhibitor 1,4-Dideoxy-1,4-imino-L-xylitol**

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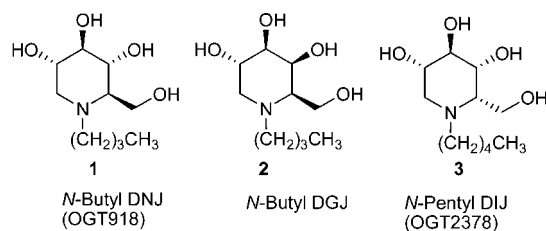
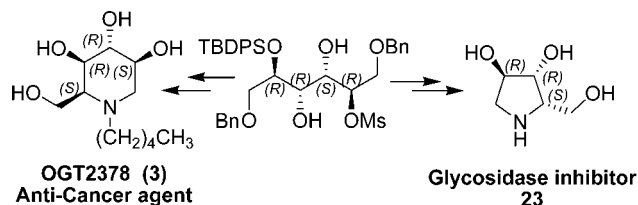


FIGURE 1. Structures of NB-DNJ (1), NB-DGJ (2), and NP-DIJ (3).



A highly regioselective reductive cleavage of the bis-benzylidene acetal of D-mannitol was performed using a  $\text{BF}_3 \cdot \text{Et}_2\text{O}/\text{Et}_3\text{SiH}$  reagent system. A chiral intermediate **6** thus obtained was efficiently utilized in the stereoselective synthesis of the anticancer agent OGT2378 (**3**) and glycosidase inhibitor derivative *N*-tosyl 1,4-dideoxy-1,4-imino-L-xylitol (**22**). Chemoselective reduction of azido epoxide **10** followed by regioselective intramolecular cyclization of amino epoxide **11** resulted in the exclusive formation of deoxydonojirimycin derivative **12**. By changing the order of deprotection, the chiral intermediate **6** was readily transformed to glycosidase inhibitor derivative **22**.

Generating a high level of skeletally and stereochemically diverse intermediates from a common substrate is an especially challenging and innovative task for synthetic organic chemists. Meeting this formidable task is the goal of diversity-oriented synthesis.<sup>1</sup> Many strategies have been developed for the diversity-oriented synthesis of biologically active and pharmaceutically important molecules.<sup>2</sup> The polyhydroxylated piperidines and pyrrolidines have been studied in the most detail,

owing to their ability to mimic their analogous pyranoses and furanoses in interactions with carbohydrate-processing enzymes. Thus, because of their biomimetic properties, iminosugars are becoming important lead compounds for drug development in a variety of therapeutic areas, including diabetes, viral infections, and tumor metastasis.<sup>3,4</sup>

Butters and co-workers have shown that the hydrophobic substituent on iminosugars increases the enzyme inhibitory activities.<sup>5</sup> *N*-Alkylated analogues of glucose and galactose isomers have additional inhibitory activities toward ceramide glucosyltransferase, an enzyme involved in the biosynthesis of glycosphingolipids (Figure 1).<sup>6,7</sup>

Recently, Ladisch et al. identified a new iminosugar, *N*-pentyl deoxydonojirimycin (NP-DIJ) (**3**), also known as OGT2378, as a novel and potent anticancer agent that inhibits the synthesis of gangliosides in cancer cells with no cytotoxic or antiproliferative effects.<sup>8</sup>

Very recently, we reported a highly regioselective method for the reductive cleavage of bis-benzylidene acetals of D-mannitol using a  $\text{BF}_3 \cdot \text{Et}_2\text{O}/\text{Et}_3\text{SiH}$  reagent system under mild conditions, which resulted in the formation of highly functionalized chiral intermediates in good yields (Scheme 1).<sup>9</sup>

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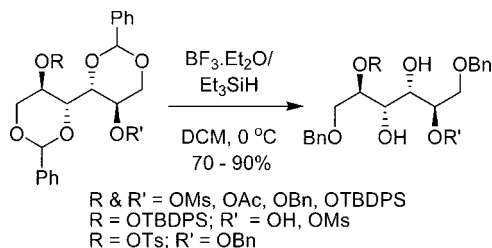
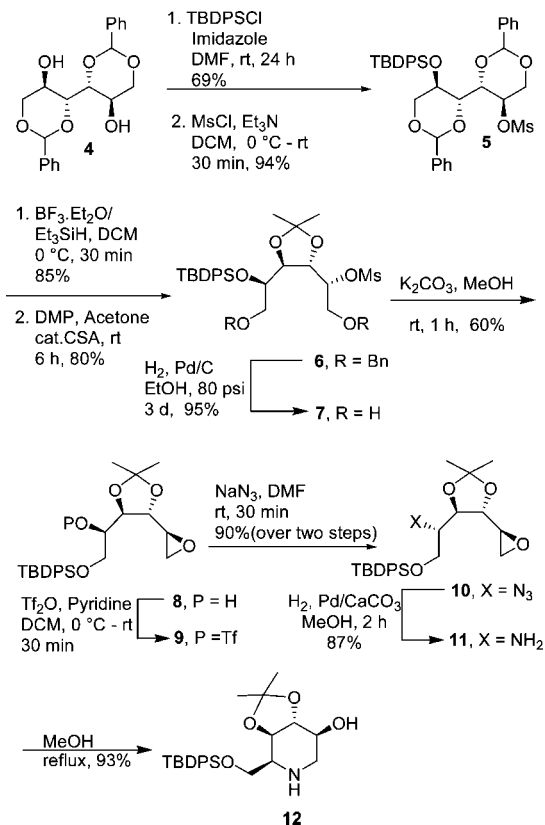
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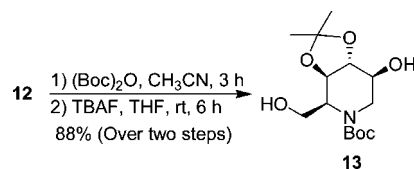
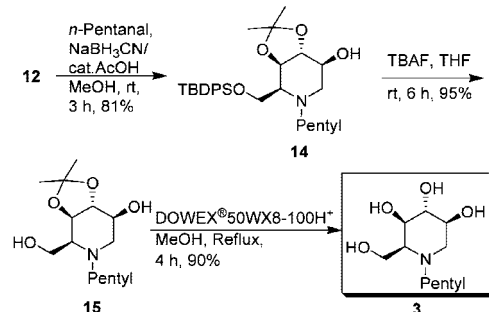
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**SCHEME 1. Regioselective Reductive Cleavage of Bis-benzylidene Acetals of D-Mannitol**

**SCHEME 2. Synthesis of Deoxydonojirimycin Derivative 12**


Herein we report our diversity-oriented approach for the synthesis of the anticancer agent *N*-pentyl-deoxydonojirimycin (OGT2378) (**3**) and glycosidase inhibitor derivative *N*-tosyl 1,4-dideoxy-1,4-imino-L-xylitol (**22**) from a common chiral intermediate derived through the regioselective reductive cleavage of the bis-benzylidene acetal of D-mannitol.

Our approach toward the stereo- and regioselective synthesis of anticancer agent *N*-pentyl-deoxydonojirimycin (OGT2378) starting from the chiral intermediate **6** is shown in Schemes 2–4.<sup>10</sup> Selective monoprotection of one of the hydroxy functional groups of bis-benzylidene acetal **4** was achieved using TBDPSCI in DMF, and the other hydroxy group was converted to the corresponding mesylate **5** in good yield. Regioselective reductive cleavage of bis-benzylidene acetal **5** with the BF<sub>3</sub>·Et<sub>2</sub>O and Et<sub>3</sub>SiH reagent system resulted in the formation in 85% yield of a diol, which was further converted to the corresponding acetone **6** using 2,2-DMP. Debenzylation of **6** under catalytic

(10) The first and only synthesis of OGT2378 was reported in the patent literature: Butters, T. D.; Dwek, R. A.; Fleet, G.; Orchard, M. G.; Platt, F. M. *PCT Int. Appl. WO 2002055498*, 2002.

**SCHEME 3. Synthesis of *N*-Boc Deoxydonojirimycin Derivative 13**

**SCHEME 4. Synthesis of Anticancer Agent OGT2378 (3)**


hydrogenation conditions furnished diol **7** in very good yield. Exposure of diol derivative **7** to K<sub>2</sub>CO<sub>3</sub> in MeOH resulted in a smooth S<sub>N</sub>2 displacement of mesylate leading to an epoxide with concomitant migration of the TBDPS group from the secondary to the primary hydroxyl group.<sup>11</sup> Interestingly, this migration paved the way for the synthesis of deoxydonojirimycin with the desired stereochemistry (vide infra). Chemoselective conversion of epoxy alcohol **8** to epoxy azide **10** was achieved under very mild conditions, by converting the hydroxyl group to the corresponding triflate **9** and then treating it with sodium azide at room temperature. Chemoselective reduction of azide **10** in the presence of epoxide was readily achieved under catalytic hydrogenation conditions using Lindlar's catalyst<sup>12</sup> to yield amino epoxide **11**, which on refluxing in methanol underwent facile regioselective cyclization via 6-*endo-tet* mode<sup>13</sup> to furnish deoxydonojirimycin derivative **12** as the only product in 93% yield.

The structure and the relative stereochemistry of the cyclized product **12** was established by 2D NMR experiments and further unambiguously confirmed by single crystal X-ray analysis on the corresponding *N*-Boc deoxydonojirimycin derivative **13** (Scheme 3 and Figure 2).

Reductive alkylation of deoxydonojirimycin derivative **12**, with pentanal in combination with NaBH<sub>3</sub>CN, yielded *N*-pentyl derivative **14**, which was desilylated using TBAF to give diol **15**. Finally, the deprotection of the acetone in **15** was readily achieved using DOWEX50WX8-100H<sup>+</sup>, which resulted in the isolation of anticancer agent OGT2378 (**3**) in 90% yield (Scheme 4).

1,4-Dideoxy-1,4-iminopentitols have been attracting the attention of synthetic chemists as a result of their potential

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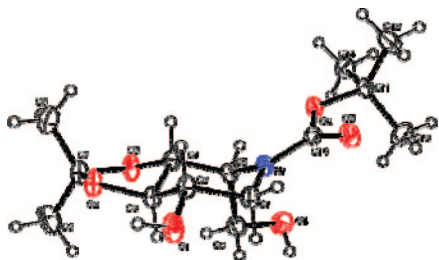
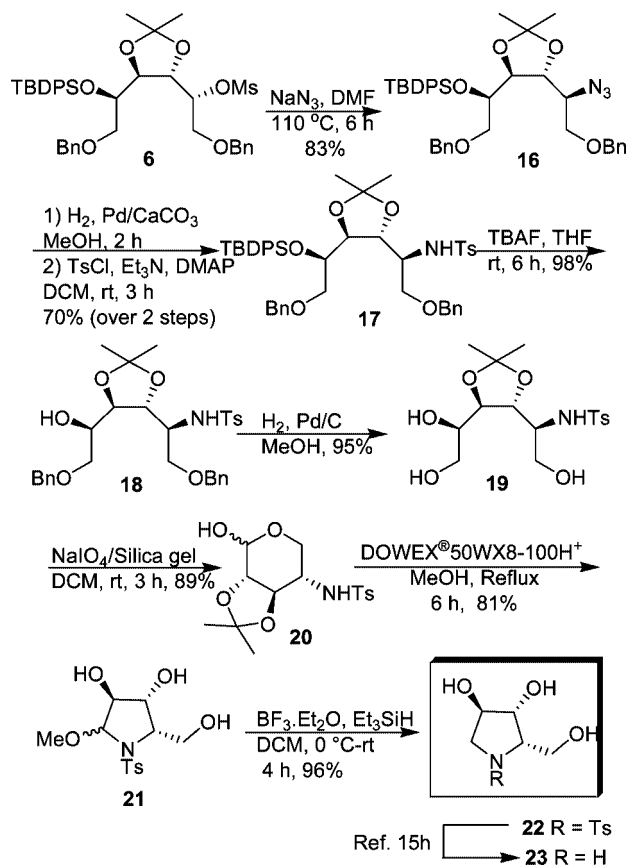


FIGURE 2. ORTEP diagram of *N*-Boc deoxydonojirimycin derivative 13.

SCHEME 5. Stereoselective Synthesis of 1,4-Dideoxy-1,4-imino-L-xylitol (23)



biological activities.<sup>14</sup> The versatility of our chiral intermediate **6** in the diversity-oriented synthesis of iminosugars is further exemplified in the stereoselective synthesis of the glycosidase inhibitor 1,4-dideoxy-1,4-imino-L-xylitol (**23**)<sup>15</sup> by changing the order of deprotection as well as functional group interconversions (FGI) (Scheme 5). Thus, acetone **6** on treatment with  $\text{NaN}_3$  yielded azido derivative **16**, which on catalytic hydrogenation with Lindlar's catalyst and subsequent tosylation fur-

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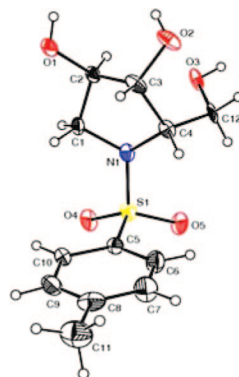


FIGURE 3. ORTEP diagram of *N*-tosyl derivative 22.

nished *N*-tosyl derivative **17** in good yield. Deprotection of silyl ether with TBAF gave the corresponding hydroxy derivative **18**, which was debenzylated under catalytic hydrogenation conditions to yield the corresponding triol **19** in 95% yield. Oxidative cleavage of the vicinal diol under heterogeneous conditions using  $\text{NaIO}_4$  supported on silica gel yielded lactol **20**, which upon refluxing in methanol with DOWEX50WX8-100H<sup>+</sup> furnished 2-methoxy-iminopentitol **21** in good yield. 2-Methoxy-iminopentitol derivative **21** upon treatment with  $\text{BF}_3 \cdot \text{Et}_2\text{O}/\text{Et}_3\text{SiH}$  yielded *N*-tosyl 1,4-dideoxy-1,4-imino-L-xylitol (**22**) in good yield.

The structure and relative stereochemistry of compound **22** was further confirmed by single crystal X-ray analysis (Figure 3). The conversion of *N*-tosyl 1,4-dideoxy-1,4-imino-L-xylitol (**22**) to 1,4-dideoxy-1,4-imino-L-xylitol (**23**) in the presence of  $\text{NaNH}_2$  in liquid ammonia has already been reported in the literature.<sup>15h</sup>

In conclusion, the highly functionalized chiral intermediate **6** obtained through regioselective reductive cleavage of the bis-benzylidene acetal of D-mannitol was efficiently utilized in the stereoselective synthesis of the anticancer agent OGT2378 (**3**) and glycosidase inhibitor derivative *N*-tosyl 1,4-dideoxy-1,4-imino-L-xylitol (**22**) with overall yields of 12.6% and 16.5%, respectively. Salient features of our synthesis are (i) facile migration of the TBDPS group from the secondary to primary hydroxyl group, which paved the way for the stereoselective synthesis of deoxydonojirimycin scaffold; (ii) chemoselective reduction of azido epoxide **10** to amino epoxide **11** in the presence of Lindlar's catalyst; and (iii) highly regioselective intramolecular cyclization of amino epoxide **11** to deoxydonojirimycin scaffold (**12**), which was unambiguously established by single crystal X-ray analysis. In addition, by changing the order of deprotection and FGI, stereoselective synthesis of glycosidase inhibitor derivative **22** was readily achieved from the chiral intermediate **6**. The success of our diversity-oriented approach in the stereoselective synthesis of iminosugars underscores the power of the chiral intermediates derived through the regioselective reductive cleavage of bis-benzylidene acetal of D-mannitol.

## Experimental Section

(*R*)-2-(*tert*-Butyldiphenylsilyloxy)-1-((4*R*,5*R*)-2,2-dimethyl-5-((*S*)-oxiran-2-yl)-1,3-dioxolan-4-yl)ethanol (**8**). To a stirred solution of compound **7** (400 mg, 0.74 mmol) in dry MeOH (10 mL) was added  $\text{K}_2\text{CO}_3$  (112 mg, 0.81 mmol), and the resultant mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to remove MeOH. The residue

was diluted with water (10 mL) and extracted with EtOAc ( $2 \times 10$  mL). The combined organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude compound was purified by column chromatography over deactivated silica gel (gradient elution with 20–30% EtOAc in hexane) to yield the pure title compound **8** (197 mg, 60%) as a viscous liquid.  $[\alpha]_{\text{D}}^{30} -3.9$  (*c* 1.0,  $\text{CHCl}_3$ ); IR (neat) 3520, 3072, 2944, 2832, 1462, 1427, 1376, 1260, 1216, 1174, 1110, 1062, 739, 704, 505  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.08 (s, 9H), 1.32 (s, 3H), 1.37 (s, 3H), 2.77–2.82 (m, 2H), 2.99–3.14 (m, 1H), 3.65 (m, 1H), 3.79 (dd,  $J = 10.2$ , 5.6 Hz, 1H), 3.84–3.91 (m, 2H), 3.96–3.99 (m, 1H), 7.37–7.45 (m, 6H), 7.65–7.67 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.2, 26.5, 26.8, 27.0, 44.8, 52.2, 65.1, 73.1, 77.1, 80.0, 109.9, 127.8, 127.8, 129.9, 129.9, 132.8, 132.9, 135.5, 135.5; HRMS(ESI) calcd for  $\text{C}_{25}\text{H}_{34}\text{O}_5\text{SiNa}$  ( $\text{M} + \text{Na}$ ) $^+$  465.2073, found 465.2085.

**(3aR,4S,7S,7aR)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2-dimethylhexahydro-[1,3]dioxolo[4,5-*c*]pyridin-7-ol (12).** A solution of compound **11** (140 mg, 0.32 mmol) in MeOH was refluxed for 4 h. The reaction mixture was then concentrated in vacuum, and the residue was purified by column chromatography over silica gel (gradient elution with 40–50% EtOAc in hexane) to yield deoxydonojirimycin derivative **12** (130 mg, 93%) as a viscous liquid.  $[\alpha]_{\text{D}}^{26} -28.5$  (*c* 1,  $\text{CHCl}_3$ ); IR (neat) 3472, 2928  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.06 (s, 9H), 1.29 (s, 3H), 1.39 (s, 3H), 2.40 (dd,  $J = 12.0$ , 9.9 Hz, 1H), 2.94 (dd,  $J = 12.1$ , 5.1 Hz, 1H), 3.37 (t,  $J = 9.4$  Hz, 1H), 3.52–3.55 (m, 1H), 3.60 (dd,  $J = 9.5$ , 5.4 Hz, 1H), 3.76–3.83 (m, 3H), 7.36–7.43 (m, 6H), 7.65–7.68 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.2, 26.5, 26.7, 26.8, 45.7, 56.0, 58.9, 70.7, 76.0, 79.5, 109.9, 127.7, 127.8, 129.7, 129.8, 133.2, 133.3, 135.5, 135.5; HRMS (ESI) calcd for  $\text{C}_{25}\text{H}_{36}\text{NO}_4\text{Si}$  ( $\text{M} + \text{H}$ ) $^+$  442.2414, found 442.2419.

**2-(Hydroxymethyl)-1-pentylpiperidine-3,4,5-triol (3).** To a stirred solution of compound **15** (51 mg, 0.09 mmol) in dry MeOH (3 mL) was added DOWEX50WX8-100H $^+$  (51 mg), and the resultant mixture was refluxed for 2 h. The reaction mixture was treated with aqueous ammonia and filtered, and the filtrate was concentrated under reduced pressure to yield pure OGT2378 (**3**) (39 mg, 90%) as a viscous liquid.  $[\alpha]_{\text{D}}^{27} +2.1$  (*c* 1,  $\text{CH}_3\text{OH}$ ); IR (neat) 3376, 2348, 2327, 1677, 1413, 1356, 1077  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ )  $\delta$  0.86 (t,  $J = 6.4$  Hz, 3H), 1.25–1.33 (m, 4H),

1.48–1.55 (m, 2H), 2.59–2.78 (m, 3H), 2.92 (dd,  $J = 12.4$ , 4.8 Hz, 1H), 3.18–3.20 (m, 1H), 3.47 (t,  $J = 8.8$  Hz, 1H), 3.63 (dt,  $J = 9.6$ , 4.4 Hz, 1H), 3.77 (dd,  $J = 9.4$ , 5.6 Hz, 1H), 3.82–3.88 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$ )  $\delta$  15.9, 24.5, 28.3, 31.5, 53.8, 56.5, 58.1, 65.0, 71.7, 73.1, 76.4; HRMS (ESI) calcd for  $\text{C}_{11}\text{H}_{24}\text{NO}_4$  ( $\text{M} + \text{H}$ ) $^+$  234.1705, found 234.1713.

**(2S,3R,4R)-2-(Hydroxymethyl)-1-tosylpyrrolidine-3,4-diol (22).** To a stirred solution of compound **21** (70 mg, 0.22 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (5 mL) was added  $\text{Et}_3\text{SiH}$  (52 mg, 0.44 mmol) followed by  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (157 mg, 1.1 mmol). The reaction mixture was stirred for 4 h at room temperature. The reaction mass was then diluted with  $\text{CH}_2\text{Cl}_2$  (10 mL) and water (5 mL). The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 10$  mL). The combined organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to yield the crude compound. Column chromatographic purification of the crude compound over silica gel using gradient elution with 0–10% MeOH in EtOAc yielded the pure title compound **22** (63 mg, 96%) as a colorless solid.  $[\alpha]_{\text{D}}^{26} +19.3$  (*c* 1.3, EtOH); IR (neat) 3339, 2926, 1328  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  2.44 (s, 3H), 3.21 (dd,  $J = 11.2$ , 3.2 Hz, 1H), 3.60 (dd,  $J = 10.8$ , 6.4 Hz, 1H), 3.65 (dd,  $J = 11.0$ , 4.8 Hz, 1H), 3.89–3.96 (m, 2H), 4.00 (dd,  $J = 11.0$ , 4.0 Hz, 1H), 4.09–4.10 (m, 1H), 7.42 (d,  $J = 8.0$  Hz, 2H), 7.76 (d,  $J = 8.0$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  21.3, 55.0, 61.8, 63.4, 74.4, 77.6, 128.6, 130.2, 144.1; HRMS (ESI) calcd for  $\text{C}_{12}\text{H}_{17}\text{NO}_5\text{SiNa}$  ( $\text{M} + \text{Na}$ ) $^+$  310.0725, found 310.0731.

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**Supporting Information Available:** General experimental procedures, experimental data, and  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all new compounds and X-ray crystallographic data of **13** and **22** in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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