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Locked Nucleosides Based on Oxabicyclo[3.2.1]octane and Oxabicyclo[2.2.1]heptane Skeletons

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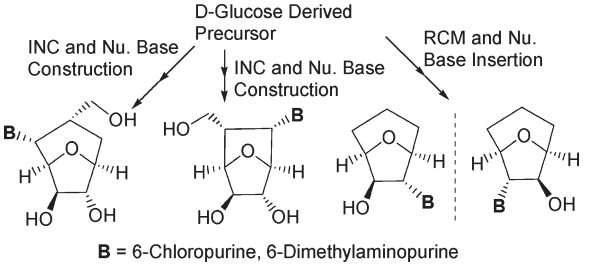

Intramolecular nitrone cycloaddition (INC) reaction on a D-glucose derived substrate carrying an allyl group at C-1 and an enose-nitrone at C-5 or an aldehyde-nitrone at C-1 and vinyl group at C-4 furnished a tricyclo[6.2.1.$0^{2,6}$]-undecane or a tricyclo[5.2.1.$0^{2,6}$]decane ring structure. These tricycles were converted to bicylic nucleosides with oxabicyclo[3.2.1]octane and oxabicyclo[2.2.1]heptane rings in three steps. An oxabicyclo[3.2.1]octane ring compound could alternatively be formed by RCM reaction between C-1−allyl and C-4−vinyl moieties and transformed to nucleoside analogues through a nucleophilic substitution reaction. Participation of a neighboring benzyl ether substituent in one case paved the way for an enantiodivergent synthesis.

The conformation of the sugar moiety in nucleosides is believed to play a crucial role in modulating biological activity. However, the attempt to correlate a specific type of sugar conformation to bioactivity is beset with the twin problem that the pentose ring is quite flexible in solution and its conformation can differ sharply in the solid state. Consequently, any structure−activity study based on solid-state conformation would be imperfect. Thus, aiming at the generation of nucleoside analogues for which both solution and solid-state conformations could be very similar, various conformationally locked bicyclic nucleosides (1′,2′-linked,[1] 1′,3′−linked,[2] 2′,3′-linked,[3] 2′,4′-linked,[4] 3′,4′-linked,[5] and 3′,5′-linked[6]) have been targeted for synthesis. These have restricted geometrical shape, are potentially useful as inhibitors of certain enzymes,[7] and are building blocks of oligonucleotides.[8]

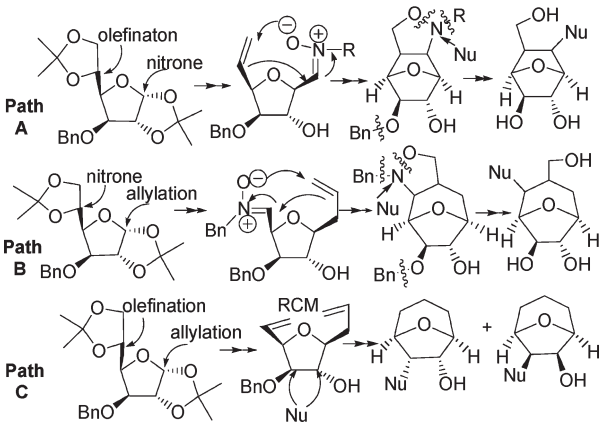

FIGURE 1. Strategies for locked bicyclic nucleosides synthesis.

We have been working for some time on the syntheses of various nucleoside analogues from the cheap and readily available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose exploiting the intramolecular nitrone cycloaddition (INC) reaction as a synthetic tool.[9] As a part of our program to construct a new class of C(1)→C(5)-linked bicycles, we envisioned two strategies (Figure 1), which entailed inclusion of an olefin functionality at C-5 and an aldehyde unit at C-1 (path A), or an allyl moiety at C-1 and an aldehyde group at

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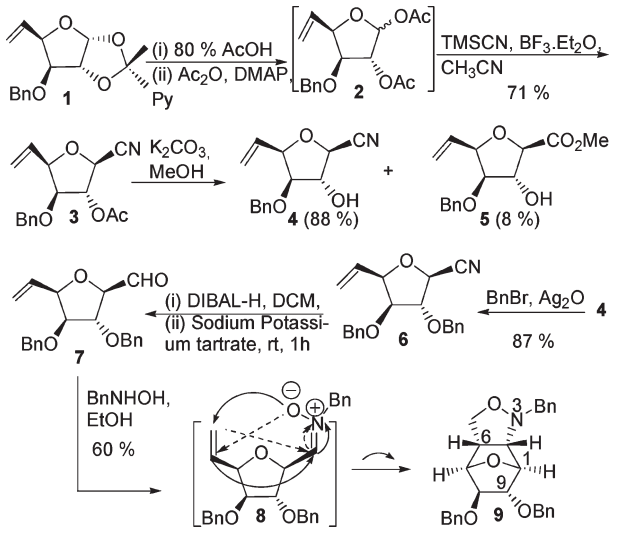
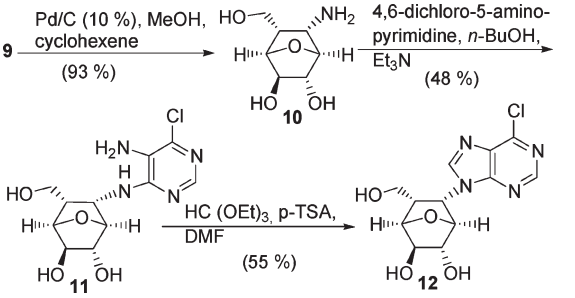
SCHEME 1. An Approach to the Tricyclic Decane System in 9



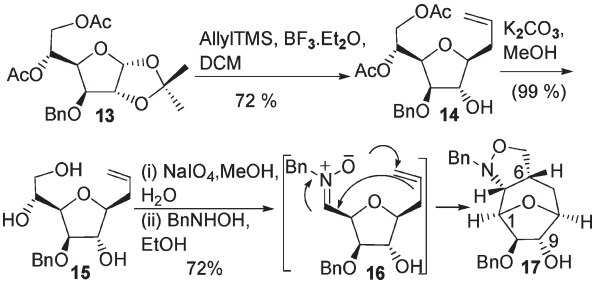
C-4 (path B) followed by INC reaction with *N*-alkyl hydroxylamine to synthesize hitherto unknown tricyclic ring systems. In another strategy, a ring closing metathesis reaction between an allyl group at C-1 and an olefin unit at C-5 (path C) could produce a locked bicyclic ring. It was important to ensure that the generated C (1)-substituent involved in ring closure be β oriented so that cyclization with the C-5 olefin substituent may proceed in the desired manner to achieve our target. Once the desired isoxazolidino bicyclic rings are derived, conversion to their corresponding nucleosides having bicyclo[3.2.1]octane and bicyclo[2.2.1]-heptane could follow through cleavage of the isoxazolidine rings and construction of the nucleoside base. For the RCM reaction product, nucleophilic attack by a nucleoside base on an appropriate center of the furanose moiety could afford locked bicyclic carbanucleoside analogues. The importance of these nucleosides lacking glycosidic linkages lies in the fact that they are metabolically stable toward cleavage by phosphorylases and hydrolases.

Synthesis of Oxabicyclo[2.2.1]heptane Nucleoside (Path A). I. Preparation of the Tricyclic Decane System 9 via INC Reaction. Toward the insertion of an aldehyde group in β-orientation and eventual transformation to nitrone, introducing β-cyano moiety at C-1 was necessary. For this, removal of acetonide protection from the D-glucose-derived product **1**[10] by acid treatment and subsequent acetylation were carried out, affording **2** as an anomeric mixture. This was treated with trimethylsilyl cyanide in the presence of borontrifluoride−etherate to produce the cyanide **3** exclusively in 71% yield. The peak at 2244 cm^{-1} in its IR spectrum clearly indicated the presence of the cyano group, while the β-orientation was evident from the appearance of the H-1 signal as singlet at δ 5.47 (coupling constant $J_{1,2} = 0$ Hz) in the ^{1}H NMR spectrum. Acetyl deprotection of **3** with potassium carbonate in methanol furnished the desired product **4** (88%) along with the minor ester derivative **5** (8%), separated easily by column chromatography (Scheme 1). Protection of C-2 OH of **4** by benzylation delivered **6** (87%), which was treated with DIBAL-H in dry DCM to yield the corresponding aldehyde **7** as hydrate. Without purification this was reacted with *N*-benzyl hydroxylamine in refluxing ethanol to produce the tricyclic product **9** through the in situ generated enose-nitrone **8** in good yield (60% in two steps). The absence of upfield proton and carbon signals expected for a methylene group in the NMR spectra clearly excluded the alternate structure. The structure of **9** was elaborated by 2D NMR spectroscopy. The energetically favored cis ring juncture stereochemistry is expected in this tricyclo[5.2.1.$0^{2,6}$]decane system. The signals for H-2 (δ 3.01) and H-9 (δ 3.85) indeed show a characteristic NOESY relationship in agreement with the observed distance between them (2.38 Å) in the energy-minimized structure (obtained using Chem Office 6.0).

SCHEME 2. Synthesis of Bicyclic Nucleoside 12



SCHEME 3. Synthesis of Tricyclic Undecane Ring in 17



II. Transformation of 9 to Oxabicyclo[2.2.1]heptane Nucleoside Analogue 12. Transfer hydrogenolysis of **9** with Pd/C/cyclohexene (Scheme 2) removed the isoxazolidine ring as well as benzyl protections to produce the bicyclic trihydroxyamino compound **10** (93%), which was coupled with 5-amino-4,6-dichloropyrimidine to furnish **11** (48%). Construction of purine ring on **11** by treatment with triethyl orthoformate smoothly afforded the desired bicyclic chloropurine nucleoside **12** (55%).

Synthesis of Oxabicyclo[3.2.1]octane Nucleoside (Path B). I. Construction of the Tricyclic Undecane System 17 by INC Reaction. For this goal, the synthon **13**[11] was reacted with allyl trimethylsilane in the presence of boron trifluoride-etherate to smoothly furnish the C-1 allylated product **14** (72%). Deacetylation to **15** followed by vicinal diol cleavage generated an aldehyde, which without purification was treated with *N*-benzyl hydroxylamine in refluxing ethanol to furnish (Scheme 3) the tricyclic product **17** through nitrone **16**.

The absence of signals for olefinic protons and the occurrence of signals for the *N*-benzylic group in the ^{1}H NMR spectrum of **17** proved that cyclization involving the olefin and the nitrone moieties had indeed taken place. The formation of the product through the other possible cyclization

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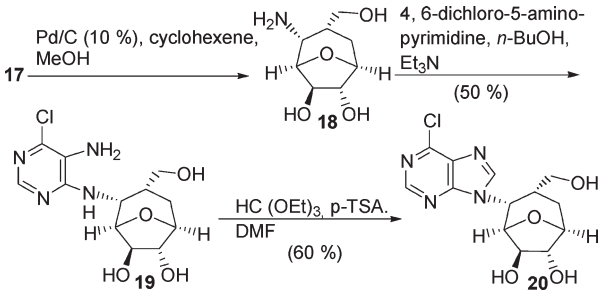
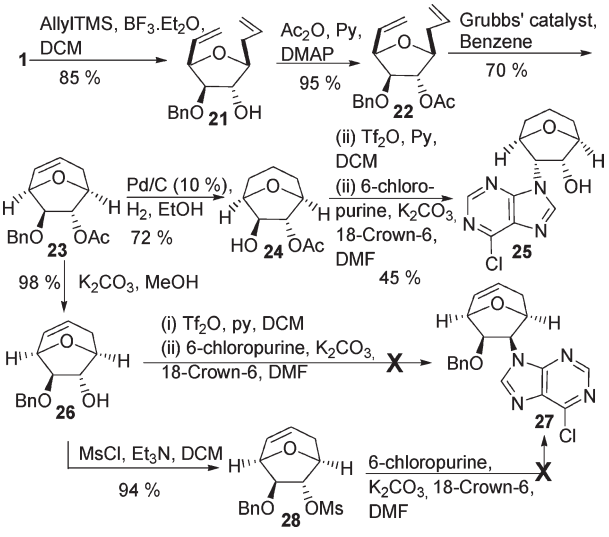
SCHEME 4. Synthesis of Locked Bicyclic Nucleoside 20



SCHEME 5. Synthesis of Bicyclic Nucleoside 25

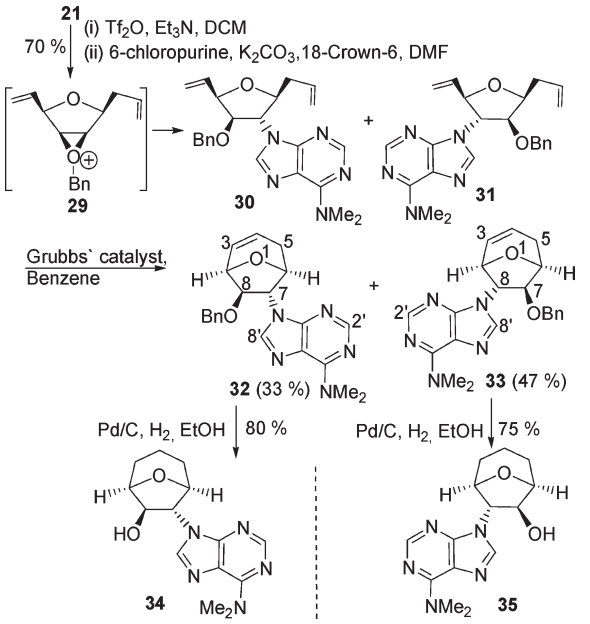


mode was not observed. The $^1H-^1H$ COSY, $^1H-^{13}C$ HSQC, and $^1H-^{13}C$ HMBC spectra clearly identified most of the signals establishing the disposition of the atoms in the tricyclic framework. The newly generated ring juncture stereochemistry, which is expected to be cis, could be either α,α or β,β in the tricyclo[6.2.1.$0^{2,6}$]undecane system. The distance between H-6 (δ 2.80) and H-9 (δ 4.13) is 2.32 Å in the energy-minimized structure of the β,β-isomer (steric energy 26.5 kcal/mol) suggesting that their signals should show correlation in the NOESY spectrum. This was indeed observed. The other cis structure has 32.2 kcal/mol steric energy and is not expected to show the NOESY relationship between H-6 and H-9. Therefore, the formation of this structure could be ruled out.

II. Conversion of 17 to Oxabicyclo[3.2.1]octane Nucleoside Analogue 20. Hydrogenolytic cleavage (Scheme 4) of **17** produced **18**, which without further purification was converted to **19** (50%) and subsequently to **20** (60%) through the familiar sequence of reactions, viz. coupling with 5-amino-4,6-dichloropyrimidine and then conversion to the bicyclic carbanucleoside analogues.

Synthesis of Oxabicyclo[3.2.1]octane Nucleoside (Path C). I. RCM Reaction and Nucleosidation To Produce 25. In this route, the C-allylated product **21** (Scheme 5) was prepared in 85% yield by treatment of **1** with allyl trimethylsilane in the presence of boron trifluoride-etherate. Acetylation of **21** furnished **22**, which upon RCM reaction with Grubbs' catalyst (2nd generation) afforded the cyclized compound **23** in 70% yield.

SCHEME 6. Synthesis of Enantiomeric Nucleosides 34 and 35



Hydrogenation of the olefin moiety as well as debenzylation with hydrogen gas in the presence of Pd/C produced **24** (72%). Protection of the hydroxyl group of this product as triflate and subsequent nucleophilic attack by 6-chloropurine furnished the bicyclic nucleoside **25** (45%). The formation of N-9-linked nucleoside[12] was confirmed by the presence of a signal at δ 129.7 (C-5′) in the ^{13}C NMR spectrum. The N-7-linked nucleoside would have generated instead a signal at δ ~125.0. Further, C-8′ of **25** resonates at δ 145.1 rather than at δ ~155.0 as expected for the N-7 isomer.

In a separate experiment, conversion of **23** to **26** by K_2CO_3 treatment followed by attempted installation of nucleoside base at the hydroxyl bearing carbon through its triflate to generate **27** was unsuccessful, possibly due to the hindrance offered by the β-oriented ring residue to the approach of the base from the β-side. Therefore, it was decided to insert the nucleoside base before the formation of the bicyclic ring by RCM reaction.

II. Nucleosidation and RCM Reaction to Enantiomeric Oxabicyclo[3.2.1]octane Nucleoside Analogues 34 and 35. Toward this end, formation of the triflate of **21** followed by nucleosidation with 6-chloropurine in refluxing DMF furnished an inseparable mixture of **30** and **31** (Scheme 6). The crude NMR spectrum of this mixture indicated the presence of four distinct aromatic proton signals at δ ~8.0−8.4 attributed to the formation of the two nucleoside derivatives. The chloro group was replaced by dimethylamino group by reaction with dimethylamine formed in situ from DMF. The formation of the mixture of **30** and **31** from **21** could only be explained by invoking the participation of the neighboring benzyloxy substituent during elimination of the triflate substituent. This generated a nonisolable epoxonium intermediate **29**, which suffered nucleophilic attack by nucleoside base from either side of the epoxide ring. This mixture (of **30** and **31**) without purification was subjected to

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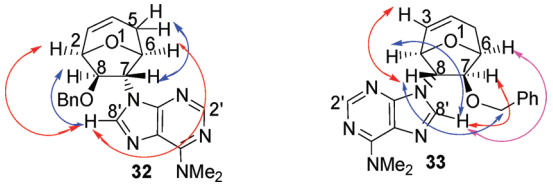

FIGURE 2. Characteristic NOESY relationship in **32** and **33**.

RCM reaction with Grubbs' catalyst (second generation) to provide the cyclized derivatives **32** and **33** separated by chromatography. Hydrogenation reaction of both compounds afforded the nucleoside derivatives **34**, $[\alpha]^{25}_{D}$ −19.8, and **35**, $[\alpha]^{25}_{D}$ +19.0. Their enantiomeric nature was anticipated from the optical rotations, which were almost identical in magnitude but opposite in sign. Besides, they exhibited virtually identical ^{1}H and ^{13}C NMR spectra.

For the structure elucidation of **32** and **33**, the ipso proton signal for the carbon carrying the heterocyclic group was initially identified through HMBC correlation with the C-8′ signal. With **32**, this signal (δ 5.11) showed further HMBC correlation with the peak for C-5 (δ 32.7) but not with those of the olefinic carbons. The reverse was true for **33** where the ipso proton signal (δ 5.23) indeed showed correlation with the peak for C-3 (δ 127.7) besides those for the neighboring ones. The crucial evidence for the stereochemistry shown came thereafter from NOESY studies. For **32**, the H-7 signal showed a NOESY relationship (Figure 2) with one of the C-5 proton signals (δ 2.25) while the H-8′ (δ 7.87) peak was correlated with H-8 (δ 4.49), H-6 (δ 4.45), and H-2 (δ 4.61) peaks indicating their cis orientation. With **33** on the other hand, similar evidence showed the closeness in space of H-8 (δ 5.23) with H-3 (δ 6.05) as well as benzylic protons (δ 4.49 and 4.89), and of H-8′ (δ 7.99) with H-7 (δ 4.19), H-2 (δ 4.40), and H-6 (δ 4.84).

In conclusion, the work described herein unravels a synthetic route to a new class of conformationally locked bicyclic carbanucleosides with bicyclo[3.2.1]octane and bicyclo[2.2.1]heptane ring systems. The steps involve the application of both INC and RCM reactions on easily prepared D-glucose-derived substrates. The simplicity of the strategy for precursor assembly for INC as well as RCM reactions makes the procedure both efficient and useful. The success of the strategy to synthesize enatiomeric pair of bicyclo[3.2.1]octane nucleoside analogs is an added advantage.

Experimental Section

(1*S*,2*S*,6*S*,7*R*,8*S*,9*S*)-3-Aza-3-benzyl-8,9-bisbenzyloxy-4,10-dioxatricyclo[5.2.1.0^{2,6}]decane (9). *N*-Benzyl hydroxylamine (0.85 g, 6.87 mmol) was added to a refluxing dry ethanolic solution of **7** (1.75 g, 5.72 mmol) and the heating was continued for 5 h. The solvent was evaporated in vacuo to obtain a residue, which was extracted with $CHCl_3$ (2 × 25 mL). The $CHCl_3$ solution was dried (Na_2SO_4) and the solvent was evaporated to afford a crude product, which was purified by silica gel column chromatography with use of EtOAc−petroleum ether (7:93) to furnish **9** as a sticky gum (1.37 g, 60% yield): $[\alpha]^{25}_{D}$ +69.9 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.01 (d, 1H, *J* = 7.8 Hz), 3.24 (s, 1H), 3.31 (q-like, 1H, *J* = 7.8 Hz), 3.61 (t, 1H, *J* = 7.5 Hz), 3.76 (d, 1H, *J* = 12.3 Hz), 3.85 (br d, 2H, *J* = 6.9 Hz), 4.09 (t, 1H, *J* = 8.4 Hz), 4.21 (d, 1H, *J* = 12.0 Hz), 4.25−4.29 (m, 2H), 4.34 (d, 1H, *J* = 12.3 Hz), 4.43 (s, 2H), 7.21−7.43 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.8 (CH), 62.0 (CH_2), 68.8 (CH_2), 70.7 (CH_2), 70.8 (CH), 72.4 (CH_2), 78.2 (CH), 83.3 (2 × CH), 85.3 (CH), 127.6 (CH), 127.7 (3 × CH), 127.8 (2 × CH), 127.9 (CH), 128.2 (2 × CH), 128.3 (2 × CH), 128.4 (2 × CH), 129.4 (2 × CH), 136.2 (C), 137.3 (C), 137.4 (C); ESIMS, *m*/*z* 466 (M + Na)$^+$. Anal. Calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.57; H, 6.38; N, 3.01.

(1*R*,5*S*,6*R*,7*S*)-7-(6-Chloropurin-9-yl)-8-oxabicyclo[3.2.1]octan-6-ol (25). Triflic anhydride (0.31 mL, 1.85 mmol) was added to a solution of **24** (250 mg, 1.34 mmol) in DCM (15 mL) containing pyridine (0.3 mL) at 0 °C and the solution was stirred for 1 h. Evaporation of the solvent furnished a residue (250 mg). To the solution of the residue in dry DMF (15 mL) were added K_2CO_3 (130 g, 0.94 mmol), 6-chloropurine (183 mg, 1.18 mmol), and 18-crown-6 (235 mg, 0.79 mmol), and the mixture was heated at 80 °C for 5 h. Usual workup and purification by silica gel chromatography with EtOAc−petroleum ether (3:2) as eluent furnished **25** (169 mg, 45%) as a foamy solid: $[\alpha]^{25}_{D}$ +5.6 (*c* 0.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33−1.50 (m, 4H), 1.86−1.91 (m, 2H), 3.86 (m, 1 H), 4.08 (d, 1H, *J* = 7.6 Hz), 4.13 (d, 1H, *J* = 7.6 Hz), 4.31 (dd, 1H, *J* = 6.8, 13.5 Hz), 8.24 (s, 1H), 8.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.9 (CH_2), 24.7 (CH_2), 30.1 (CH_2), 67.6 (CH), 73.9 (CH), 77.6 (CH), 80.0 (CH), 129.7 (C), 145.1 (CH), 148.9 (C), 152.3 (CH), 155.0 (C); ESIMS, *m*/*z* 303 (M + Na)$^+$ for Cl^{35} and 305 (M + Na)$^+$ for Cl^{37}. Anal. Calcd for $C_{12}H_{13}ClN_4O_2$: C, 51.34; H, 4.67; N, 19.96. Found: C, 51.21; H, 4.45; N, 19.73.

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Supporting Information Available: General and experimental details and copies of ^{1}H and ^{13}C NMR spectra of **3**, **6**, **9**−**12**, **14**, **17**, **19**−**21**, **23**−**25**, and **32**−**35**. This material is available free of charge via the Internet at http://pubs.acs.org.