JOC*Note*

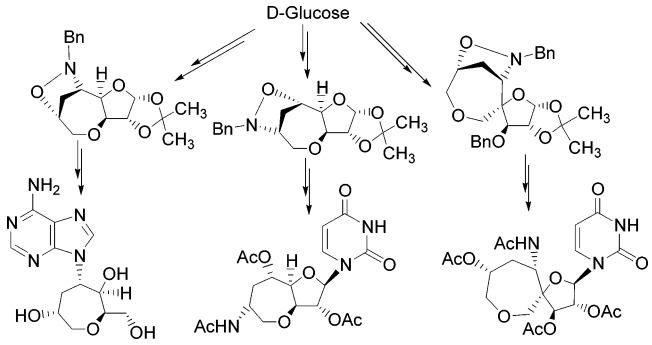
Synthesis of Oxepane Ring Containing Monocyclic, Conformationally Restricted Bicyclic and Spirocyclic Nucleosides from D-Glucose: A Cycloaddition Approach

Subhankar Tripathi,[†,§] Biswajit G. Roy,[†,§] Michael G. B. Drew,[‡] Basudeb Achari,[†] and Sukhendu B. Mandal*[,†]

Department of Chemistry, Indian Institute of Chemical Biology, 4, Raja S. C. Mullick Road, Jadavpur, Kolkata 700 032, India, and Department of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, United Kingdom

sbmandal@iicb.res.in

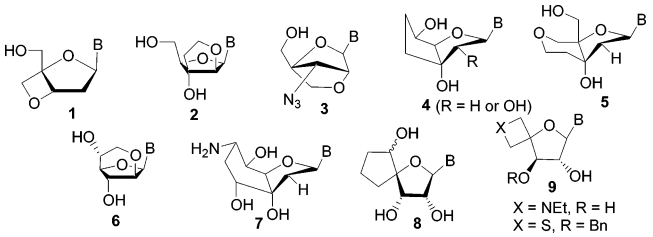
Received April 23, 2007



Carbohydrate-derived substrates having (i) C-5 nitrone and C-3-*O*-allyl, (ii) C-4 vinyl and a C-3-*O*-tethered nitrone, and (iii) C-5 nitrone and C-4-allyloxymethyl generated tetracyclic isoxazolidinooxepane/-pyran ring systems upon intramolecular nitrone cycloaddition reactions. Deprotection of the 1,2-acetonides of these derivatives followed by introduction of uracil base via Vorbrüggen reaction condition and cleavage of the isooxazolidine rings as well as of benzyl groups by transfer hydrogenolysis yielded an oxepane ring containing bicyclic and spirocyclic nucleosides. The corresponding oxepane based nucleoside analogues were prepared by cleavage of isoxazolidine and furanose rings, coupling of the generated amino functionalities with 5-amino-4,6-dichloropyrimidine, cyclization to purine rings, and finally aminolysis.

The natural nucleosides experience rapid flipping between the two preferential conformations of the ribose ring,[1,2] viz. the C-3′-*endo* (N-type) and the C-2′-*endo* (S-type), due to the low-energy barriers. If this conformational flipping is stopped or restricted to some extent, the nucleoside analogues are expected to become more selective and less toxic potential therapeutic agents[3] for cancer and deadly viral diseases. Recent years have therefore seen a surge in interest in the synthesis of unnatural nucleoside analogues having conformational restrictions in the pentofuranose moiety.[4,5]

To impart some degree of conformational restriction to the natural nucleosides, several possibilities have been suggested. These include (i) synthesis of locked bicyclic nucleoside analogues by inserting an extra ring fused to the furanose moiety, (ii) synthesis of spironucleosides,[6−10] and (iii) synthesis of nucleosides of varied ring structures.[11] Some examples of conformationally constrained synthetic bicyclic and spirocyclic nucleosides are shown in structures **1**−**9**. We have therefore



taken up a scheme to synthesize new classes of bicyclic nucleosides and C-4′ spiroannulated nucleosides. The present Note deals with the application of 1,3-dipolar nitrone cycloaddition reactions (INC) toward this goal, which also delivered, with suitable modification of the scheme, newer nucleosides based on oxepanes.

An interesting and flexible strategy[12] suitable for the construction of oxepane-fused furano sugars involves an INC reaction between C-5 nitrone and C-3 olefin (C-3-*O*-allyl) of D-glucose derived substrates (Scheme 1, Path I). We rationalized that cyclization involving a C-4 vinyl and a C-3 tethered nitrone

* Address correspondence to this author. Fax: +91 (33) 24735197.
† Indian Institute of Chemical Biology.
§ These authors contributed equally to this paper.
‡ University of Reading.

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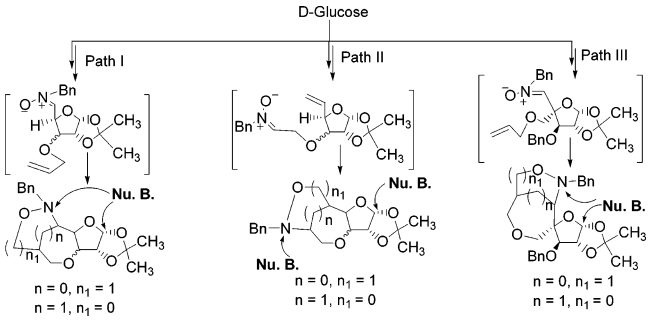
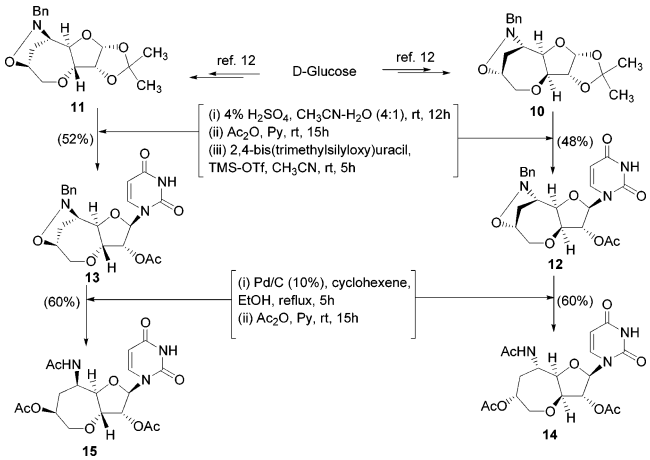
10.1021/jo070846m CCC: $37.00
Published on Web 08/23/2007

SCHEME 1. Methods for the Construction of Oxepane/ Pyran Fused Nucleoside Analogues



SCHEME 2. Conversion of Tetracyclic Oxepano Derivatives 10 and 11 to the Bicyclic Nucleosides



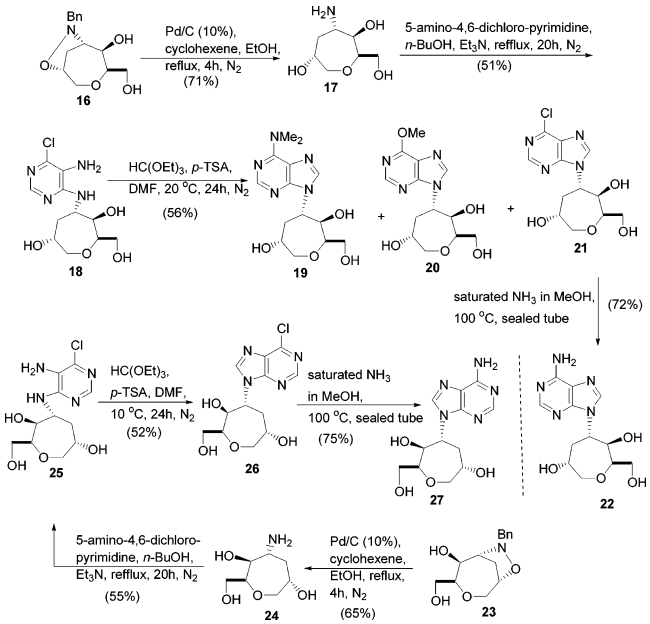
(generated from a C-3-*O*-formylmethyl derivative) could constitute (Path II) an additional strategy to produce oxepanes/ pyrans of different substitution patterns upon INC reaction. On the other hand, the same reaction performed on substrates having nitrone functionality at C-5 and olefin at C-4 (e.g., C-allyloxymethyl) would be expected (Path III) to generate a spirocyclic ring structure depending on the mode of cyclization. The products may then be used to synthesize the projected classes of nucleosides through established routes.

Bicyclic Nucleosides 14 and 15 (Path I). INC reactions of 3-*O*-allyl-6-nor furanose aldehydes have been reported by Bhattacharjya and his group[12] to culminate in bridged oxepanoisoxazolidines (**10** and **11**) in both the glucose and allose derived substrates. Deprotection of the 1,2-acetonide moiety (Scheme 2) of the products with dilute sulfuric acid followed by peracetylation with acetic anhydride−pyridine and subsequent nucleosidation under Vorbrüggen condition[13] with uracil base furnished **12** (52%) and **13** (48%), respectively. Cleavage of the isoxazolidine rings by transfer hydrogenolysis afforded the corresponding aminoalcohols, purified as acetates.

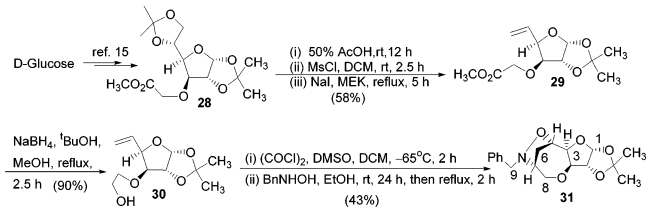
The structure and stereochemistry of **10** has been conclusively settled by X-ray crystal structural determination.[14] Spectroscopic analyses (^{1}H, ^{13}C NMR, MS) of **12**−**15** helped deduce their structures.

Oxepanyl Nucleosides 19−22, 26, and 27 (Path I). Isoxazolidinooxepane **16**, derived from **10** following the reported procedure,[12] yielded (Scheme 3) the aminoalcohol **17** upon

SCHEME 3. Synthesis of Oxepanyl Nucleosides 19−22, 26, and 27



SCHEME 4. Synthesis of Tetracyclic Oxepane Derivative 31



transfer hydrogenolysis. The aminoxepane was coupled with 5-amino-4,6-dichloropyrimidine to produce the aminopyrimidinyl oxepane **18** (51%). Transformation of the pyrimidine ring to the purine ring by reaction with triethyl orthoformate generated a mixture of purine nucleosides **19**−**21** (56%). Our earlier observations in related systems suggested that use of higher temperatures may be the cause for the undesirable transformation to the dimethylaminopurine nucleoside **19**, while the minor methoxypurine nucleoside **20** is generated during purification of nucleosides by reversed-phase HPLC with use of H_2O−MeOH. Repeating the reaction at lower temperature, to our gratification, gave the chloropurine **21** as the sole product in 60% yield. Substitution of the chloro group of the adenine ring by an amino group furnished **22** (72%). On the other hand, the isoxazolidinooxepane **23**[12] could be similarly converted (via **24** and **25**) to **26** and **27** in good yields. The enantiomeric nucleoside pairs **21**/**26** and **22**/**27** exhibited optical rotations virtually identical in magnitude but opposite in sign. All the nucleosides exhibited ^{1}H NMR and mass spectra fully in conformity with the structures.

Cyclization Involving C-3-*O*-Tethered Nitrone and C-4 Vinyl (Path II). Selective removal of the 5,6-*O*-isopropylidene protection of **28**[15] by dilute acetic acid treatment (Scheme 4) followed by mesylation of the hydroxy groups set up the substrate for successive steps of iodination and deiodination, affording the olefinic ester **29**. Reduction of the carbomethoxy group with $NaBH_4$−^{t}BuOH−MeOH reagent to furnish **30**

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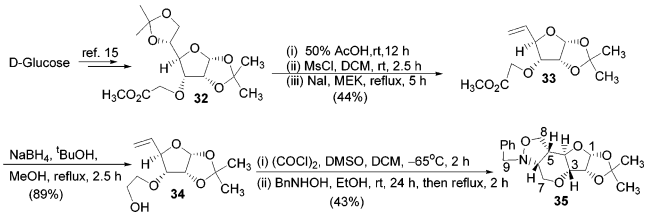
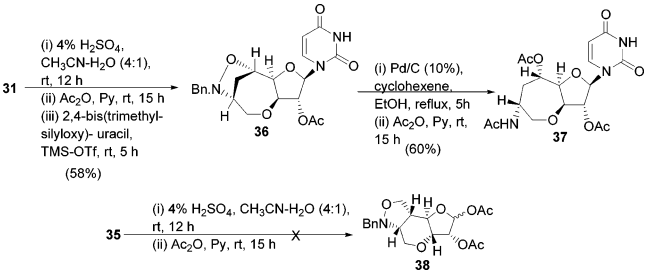
SCHEME 5. Synthesis of Tetracyclic Pyran Derivative 35



SCHEME 6. Conversion of 31 to Bicyclic Oxepanyl Nucleoside 37



followed by Swern oxidation furnished an aldehyde, which without purification was subjected to nitrone formation−cyclization by treatment with *N*-benzylhydroxylamine, affording the tetracyclic oxepane **31**.

Retracing the above reaction route beginning with **32**[15] (C-3 epimer of **28**) furnished (Scheme 5) the tetracyclic pyran derivative **35** (19% overall yield) via **33** and **34**.

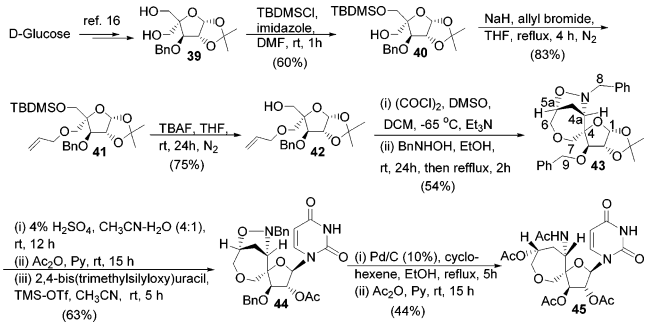
The structures of **29**−**35** were deduced with NMR and mass spectral analysis. The stereochemistry of the newly generated ring juncture in **31** and **35** was, however, determined from the NOESY correlation of the energy-minimized structures (Figures 1−4 in the Supporting Information).

With the full structure of **31** and **35** thus established, introduction of uracil on the anomeric center of **31** was carried out by the Vorbrüggen procedure[13] (Scheme 6) to afford **36**, which was converted to the nucleoside **37** by adopting the earlier described procedure. However, an attempt to install a nucleoside base on **35** was unsuccessful. This may be due to the trans ring juncture of the pyranofuranose ring, which upon deprotection generated a furanose moiety that preferred to remain in the open chain form. Therefore a complex mixture of acetates resulted instead of **38**.

Synthesis of Spirocyclic Nucleosides (Path III). Toward this goal, we chose to utilize **39**.[16] Selective TBDMS protection by using slightly less than 1 equiv of TBDMSCl (Scheme 7) afforded the monosilyl ether **40** as the major product. Allylation of the free hydroxy group of **40** to **41** and subsequent desilylation produced the desired monoallyl ether **42**. Swern's oxidation of the free primary hydroxyl group proved to be the most satisfactory in regard to the yield of the aldehyde, which without any purification was treated with *N*-benzylhydroxylamine to precipitate a dipolar cycloaddition reaction. The product on careful purification delivered the oxepanospirocycle **43** in 54% yield. Lewis acid-catalyzed nucleoside base coupling then led to isoxazolidinospironucleoside **44** (63%). Finally, the isooxazolidine ring was cleaved and the product was acetylated to the fully protected C-4′ spironucleoside **45**.

The structure of **43** was deduced originally from ^{1}H, ^{13}C NMR and mass spectroscopic evidence and finally settled by single-

SCHEME 7. Synthesis of Spirocyclic Nucleoside 45 from the Precursor 39



crystal X-ray analysis.[14] This information clinched the structures of **44** and **45** with the help of NMR analyses.

In conclusion, this study describes both linear and convergent approaches in which conformationally constrained oxepane-fused bicyclic and C-4′ oxepane-spiroannulated nucleosides can be synthesized from D-glucose derived substrates through the application of INC reactions followed by nucleosidation. The results may be extended to other systems utilizing different substitution patterns judiciously derived from carbohydrates.

Experimental Section

(1*S*,2*R*,4*R*,5*R*,6*S*,9*R*)- 5-Acetoxy-11-benzyl-4-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-3,7,10-trioxa-11-azatricyclo[7.2.1.0^{2,6}]-dodecane (12). A solution of **10** (1.20 g, 3.60 mmol) in a $CH_3CN-H_2O-H_2SO_4$ mixture (18:6:1, 25 mL) was stirred at room temperature for 20 h. Solid $CaCO_3$ was added portionwise to neutralize the acidic solution and the precipitate was filtered off. The solvent was evaporated to a gummy mass, which was acetylated at room temperature by using pyridine (3 mL) and Ac_2O (1 mL) to furnish the anomeric mixture of diacetates. A mixture of uracil (345 mg), hexamethyldisilazane (10 mL), and freshly distilled TMSCl (2−3 drops) was heated at reflux under N_2 for 12 h. Excess solvent was distilled off; a solution of the residue in DCE (5 mL) was added to a stirred DCE solution (25 mL) of the above diacetates containing TMS−OTf (0.4 mL) and the stirring was continued for 5 h. The reaction mixture was neutralized by solid $NaHCO_3$ and H_2O (2−3 drops). The solvent was evaporated and the residue was extracted with 2% MeOH in $CHCl_3$ (3 × 20 mL). The solvent was washed with brine (20 mL), dried (Na_2SO_4), and concentrated to a mass, which was purified over a silica gel (60−120 mesh) column with 3% MeOH in $CHCl_3$ as eluent to furnish **12** (224 mg, 48%) as a foam: $[\alpha]^{20}_D$ −84.0 (*c* 0.61, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.41−2.50 (m, 1H), 2.56 (d, 1H, J = 12.7 Hz), 3.70 (d, 1H, J = 12.9 Hz), 3.74−3.81 (m, 3H), 3.92 (br s, 1H), 4.07 (d, 1H, J = 1.5 Hz), 4.10 (d, 1H, J = 12.7 Hz), 4.68 (br d, 1H, J = 8.1 Hz), 4.93 (d, 1H, J = 1.6 Hz) 5.75 (dd, 1H, J = 1.8, 8.1 Hz), 5.99 (d, 1H, J = 1.6 Hz), 7.34 (m, 5H), 7.72 (d, 1H, J = 8.1 Hz), 8.83 (br d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 (CH_3), 27.9 (CH_2), 62.4 (CH), 62.6 (CH_2), 73.4 (CH_2), 78.6 (CH), 81.5 (CH), 81.7 (CH), 82.3 (CH), 87.6 (CH), 103.8 (CH), 128.3 (CH), 129.0 (2 × CH), 129.5 (2 × CH), 136.8 (C), 141.2 (CH), 150.5 (C), 163.1 (C), 169.7 (C). FABMS, *m/z* 430 $(MH)^+$. Anal. Calcd for $C_{21}H_{23}N_3O_7$: C, 58.74; H, 5.40; N, 9.79. Found: C, 58.54; H, 5.23; N, 9.55.

(2*R*,3*R*,4*S*,6*R*)-4-(6-Chloro-9*H*-purin-9-yl)-2-hydroxymethyl-oxepane-3,6-diol (21). To a solution of **18** (350 mg, 1.15 mmol) in DMF (10 mL) were added $HC(OEt)_3$ (8 mL) and *p*-TSA (60 mg), and the mixture was stirred at 10 °C for 24 h under N_2. The solvent was evaporated in vacuo; the gummy residue was dissolved in MeOH and neutralized by stirring with Dowex-1 OH^- resin for 1 h at room temperature. The resin was filtered off and the solvent

(16) Youssefyeh, R. D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1979**, *44*, 1301−1309.

was evaporated to give a crude foamy material. Purification by reverse phase (LiChroprep RP-18, particle size 25−40 μm) flash chromatography with H_2O as the eluent furnished **21** (216 mg, 60%) as a foamy solid: $[\alpha]^{26}_D$ +14.5 (*c* 0.32, MeOH). ^{1}H NMR (D_2O, 300 MHz) δ 2.16 (br d, 1H, J = 13.5 Hz), 2.69 (dd, 1H, J = 12.0 Hz), 3.28 (t, 1H, J = 11.5 Hz), 3.62 (d, 2H, J = 5.5 Hz), 3.97−4.10 (m, 2H), 4.26 (dd, 1H, J = 5.7, 12.0 Hz), 4.35 (dd, 1H, J = 3.4, 8.5 Hz), 4.69 (1H, overlapped by HOD proton signal), 8.51 (s, 1H), 8.60 (s, 1H). ^{13}C NMR (D_2O, 75 MHz) δ 37.7 (CH_2), 59.4 (CH), 62.2 (CH_2), 68.8 (CH), 74.3 (CH), 77.6 (CH_2), 84.9 (CH), 131.5 (C), 147.5 (CH), 150.4 (C), 151.6 (C), 151.8 (CH). ESIMS, *m/z* 315 (MH^+, for Cl^{35}) 317 (MH^+, for Cl^{37}). Anal. Calcd for $C_{12}H_{15}ClN_4O_4$: C, 45.80; H, 4.80; N, 17.80. Found: C, 45.62; H, 4.66; N, 17.53.

(3a*R*,3b*S*,6*R*,9*S*,9a*S*,10a*R*)-7-Benzyl-2,2-dimethylperhydro-6,9-methano-1,3-dioxolo[4′,5′:4,5]furo[2,3-*d*][1,5,2]dioxazocine (31). Oxalyl chloride (0.3 mL, 3.14 mmol) was added to dry CH_2Cl_2 (5 mL) in a two-necked round-bottom flask under N_2 and the mixture was cooled to −65 °C. To this was added a solution of dry DMSO (0.48 mL) in dry CH_2Cl_2 (3 mL) dropwise and the mixture was stirred for 10 min. A solution of **30** (700 mg, 3.04 mmol) in CH_2Cl_2 (7 mL) was then added to the above solution, which was then stirred for 1 h. The mixture was allowed to stir for 15 min, Et_3N (1 mL) was added to it, and the solution was allowed to reach room temperature. The reaction was quenched by addition of H_2O (1 mL) and extracted with $CHCl_3$ (2 × 15 mL). The combined extract was washed with H_2O (2 × 10 mL) to remove DMSO, dried (Na_2SO_4), and concentrated to a crude aldehyde (500 mg), which was used in the next step without purification. BnNHOH (568 mg, 1.5 equiv) was added to the above aldehyde dissolved in dry EtOH (20 mL), and the mixture was stirred at room temperature for 24 h and then heated at reflux for 2 h. The solvent was evaporated and the gummy mass was extracted with $CHCl_3$ (3 × 15 mL). The $CHCl_3$ solution was washed with saturated brine solution (3 × 10 mL), dried (Na_2SO_4), and concentrated to furnish a gum, which was purified by silica gel column chromatography with ethyl acetate−petroleum ether (1:4) as eluent to afford **31** (440 mg, 43%): $[\alpha]^{26}_D$ −7.7 (*c* 0.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.48 (s, 3H), 2.19−2.23 (m, 1H), 2.64 (d, 1H, J = 12.2 Hz), 3.39 (t-like, 1H, J = 6.7, 7.2 Hz), 3.48 (d, 1H, J = 12.6 Hz), 3.78 (dd, 1H, J = 6.0, 12.6 Hz), 3.80 (d, 1H, J = 12.6 Hz), 4.09 (br s, 1H), 4.12−4.13 (m, 1H, partially merged), 4.14 (d, 1H, J = 12.9 Hz), 4.43 (d, 1H, J = 3.6 Hz), 4.72 (dd, 1H, J = 4.2, 7.5 Hz), 5.89 (d, 1H, J = 3.6 Hz), 7.27−7.39 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6 (CH_3), 27.1 (CH_3), 28.9 (CH_2), 63.9 (CH), 64.1(CH_2), 74.6 (CH_2), 76.9 (CH), 78.6 (CH), 83.6 (CH), 84.8 (CH), 105.1 (CH), 112.2 (C), 127.9 (CH), 128.9 (2 × CH), 129.6 (2 × CH), 137.5 (C). ESIMS, *m/z* 334 $(MH)^+$, 356 $(MNa)^+$. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.55; H, 7.02; N 4.10.

Acknowledgment. The authors acknowledge the CSIR for providing Research Fellowships (to S.T. and B.G.R.) and an Emeritus Scientist scheme (to B.A.). We thank EPSRC and the University of Reading for funds for the Oxford Diffrraction X-Calibur CCD System.

Supporting Information Available: Stereochemical discussion of **31** and **35**, general and detailed experimental procedures, ORTEP diagrams, and CIF files for **10** and **43**, experimental details for X-ray data, and ^{1}H and ^{13}C NMR spectra (copies) of all new compounds, except **18** (^{1}H NMR only). This material is available free of charge via the Internet at http://pubs.acs.org.

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