Pyranyl Heterocycles from Inverse Electron Demand Hetero [4+2] Cycloaddition Reactions of Chiral Allenamides as a New Chiral Template for Constructing *C*-Glycoside Substrates

C. Rameshkumar, Richard P. Hsung*[1]

Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, U.S.A.
E-mail: hsung@chem.umn.edu

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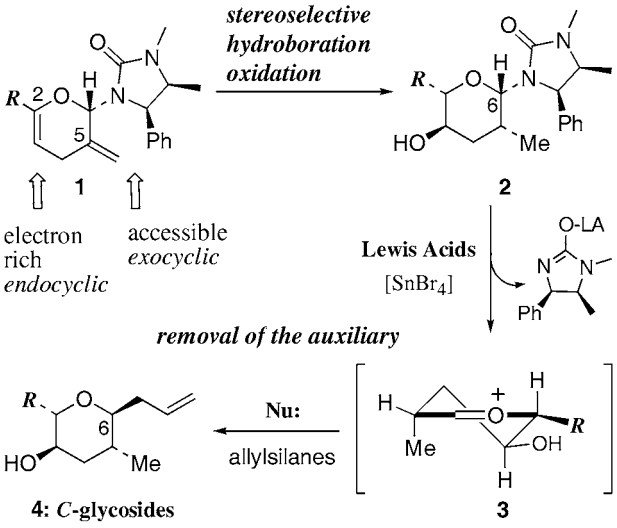
This paper is dedicated in memory of Professor Ray Lemieux for his life-long contributions to Organic Chemistry.

Abstract: A useful sequence involving stereoselective functionalization of the two olefins in pyranyl heterocycles derived from inverse electron demand hetero [4+2] cycloadditions of chiral allenamides is described here. This sequence constitutes stereoselectively dihydroxylation or hydroboration–oxidation of the sterically accessible C5 exocyclic olefin followed by hydroboration-oxidation of the endocyclic olefin at C2/C3. The ultimate success in the removal of the C6 chiral auxiliary completes the demonstration of the concept of employing these unique hetero cycloadducts as chiral templates for constructing highly functionalized pyrans or *C*-glycosides.

Key words: hetero [4+2] cycloadditions, pyranyl heterocycles, hydroboration–oxidation

We recently reported a Lewis acid mediated stereoselective removal of the chiral imidazolidinone group at the anomeric carbon of pyranyl heterocycles[2] obtained from inverse electron-demand hetero [4+2] cycloadditions of a chiral allenamide with vinyl ketones (Scheme 1).[3–7] The ability to remove this anomeric chiral urea group in the pyran **1** allows this imidazolidinone group to serve as a chiral auxiliary that can be ultimately removed and replaced stereoselectively with allyl groups. This establishes one of the two concepts needed to demonstrate that the pyran **1** could serve as a useful chiral template for synthesis of highly functionalized pyranyl heterocycles *C*-glycoside related substrates[8,9] such as **4**.

In addition, we illustrated that the C2/C3 endocyclic olefin in the pyran **1** could be subjected to a stereoselective hydroboration–oxidation after mono-hydrogenation of the C5-exocyclic olefin. This provides preliminary feasibility for the second concept: Stereoselective functionalization of the two olefins in pyran **1**. Complete realization of this second concept would constitute development of suitable sequences to stereoselectively functionalize both olefins in the pyran **1**: The endocyclic olefin at C2/C3 and the sterically accessible C5 exocyclic olefin (Scheme 1). This turned out to be not trivial especially during the ultimate removal of the chiral imidazolidinone auxiliary at C6. We report here a successful sequence constituting



Scheme 1

stereoselective oxidative transformation of both olefins in **1** followed by removal of the auxiliary.

Two transformations of the C5 exocyclic olefin were carried out promptly using the pyran **5** as the model substrate obtained from inverse electron demand hetero [4+2] cycloaddition of *N*-allenyl-*N*′-methyl-4-phenyl-5-methyl-2-imidazolidinone and 1-naphthyl vinyl ketone (Scheme 2). Hydroboration using 9-BBN was very selective for the exocyclic olefin in **5**. After oxidation of the resulting borane using 15% aqueous NaOH and 30% aqueous H_2O_2, the alcohol **6**[10] was obtained in 73% yield as a single diastereomer. Various standard protections using Ac_2O, pivaloyl chloride [Piv-Cl], and TBSCl gave pyrans **7**–**9**, respectively.

Dihydroxylation of the C5 exocyclic olefin in **5** using stoichiometric amount of OsO_4 followed by hydrolysis of the osmate ester afforded the diol **10** in 85% yield also as a single diastereomer. When a catalytic amount of OsO_4 was used, reactions were considerably slower. Pyrans **7**–**10** should provide useful functional handles serving as entry points for further elaboration at C5 and C7 using conventional methods.

Having pyrans **7**–**10** in hand, we proceeded to functionalize the endocyclic olefin at C2/C3. As shown in Scheme 3, the pyran **7** and **8**, protected with an acyl and

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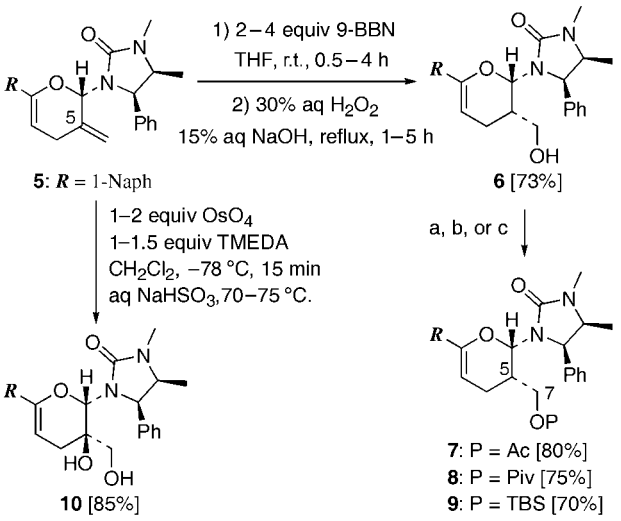
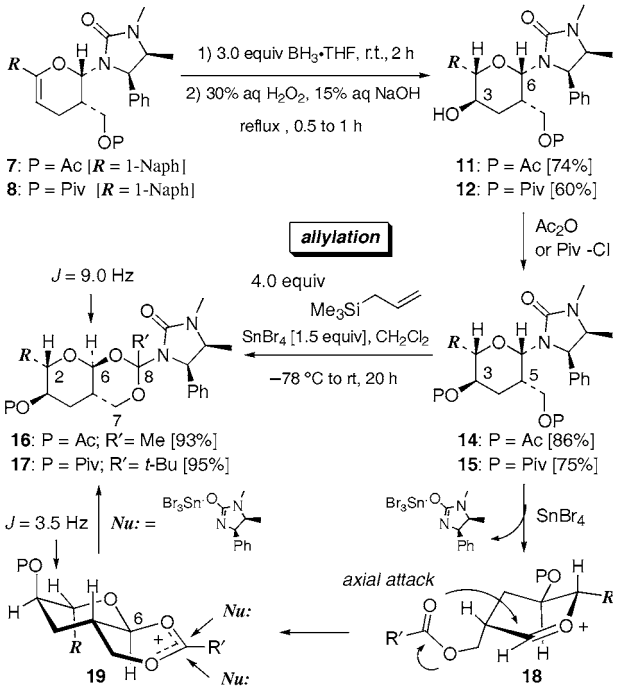


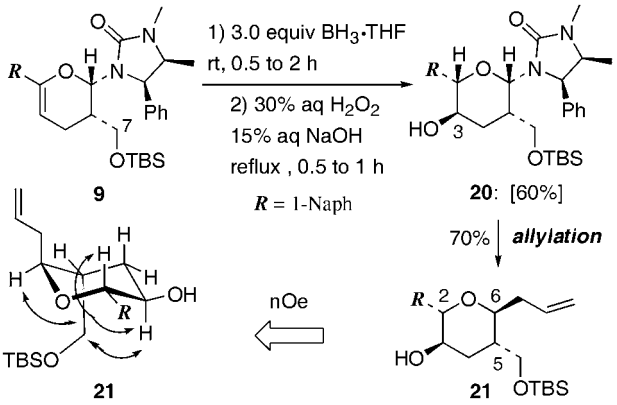
Scheme 2 a) 2.5 Equiv Ac_2O, pyridine, 0 °C to r.t., 12 h. b) 2.5 Equiv Piv-Cl, pyridine, 0 °C to r.t., 16 h. c) TBSCl, imidazole, DMF, 0 °C to r.t., 4 h.



Scheme 3

pivaloyl group, respectively, underwent hydroboration and oxidation smoothly using BH_3·THF and aqueous H_2O_2/NaOH to give alcohols **11** and **12** in 74% and 60% yields, respectively, as single diastereomers. Because removal of the C6 urea group in **11** using the allylation conditions described in the preceding paper was not clean, the C3 hydroxyl groups in **11** and **12** were protected using either Ac_2O or Piv-Cl to afford **14** and **15** in 86% and 75% yields, respectively.

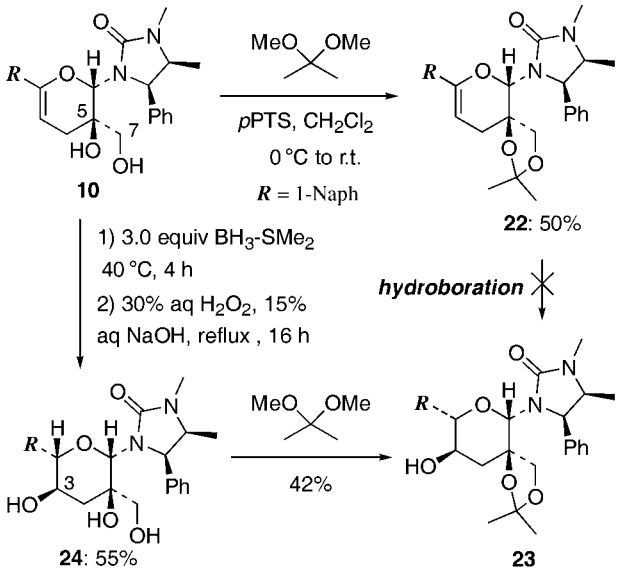
Allylations of **14** and **15** using 1.5 equivalents of $SnBr_4$ and 4.0 equivalents of allyltrimethylsilane as described in the preceding paper[2] interestingly led to the bicycles **16** and **17** in excellent yields and as single diastereomers. The stereochemistry at C6 was assigned based on the coupling constant of C6-H being 9.0 Hz, suggesting that C6-H and C5-H are di-axial, thereby providing a coupling constant of 3.5 Hz for C2-H and C3-H for they are di-equatorial. Formation of **16** and **17** is likely due to an intramolecular trapping of the oxocarbenium ion **18** by the acyl group in an anchimeric manner[8] after the loss of the chiral imidazolidinone group. Based on available stereochemical assignment, the attack of the acyl likely proceeded in an axial approach, and the resulting new oxocarbenium ion **19** was then by the scavenging urea nucleophile. Preliminary attempts to unravel the bicycle **16** or **17** using Lewis acids and excess of allyltrimethylsilane were not successful.



Scheme 4

While pyrans **16** and **17** are interesting structures, the pyran **9** in which the C5 hydroxymethyl was protected with TBS group was useful in the final removal of the C6 urea group (Scheme 4). Hydroboration–oxidation of **9** gave the alcohol **20**, and the subsequent allylation without protecting the C3-hydroxyl group gave **21** in 70% yield as a single diastereomer. The relative stereochemistry was assigned using NOE experiments.[11] This represents the first completed sequence in stereoselective functionalization of C5 exocyclic olefin and C2/C3 endocyclic olefin followed by a stereoselective removal of the C6 imidazolidinone group, thereby fully demonstrating the concept of the pyran **1** serving as a template for stereoselective constructions of complex pyranyl heterocycles.

While the pyran **9** allows the completion of the entire sequence in preparation of heterocycles such as **21**, to broaden the scope, the pyran **10** could be even more versatile given the two hydroxyl groups at C5 and C7 (Scheme 5). Standard conditions, using 2,2-dimethoxy propane, led to the acetonide **22** in 50% yield (unoptimized), but the ensuing hydroboration using BH_3·THF or BH_3·SMe_2 failed to provide the alcohol **23**. On the other hand, hydroboration of **10** without any protection steps using BH_3·SMe_2 led to the triol **24** in 55% yield after the peroxide oxidative step. Subsequent acetonide formation, using 2,2-dimethoxy propane, gave **23** in 42% yield.

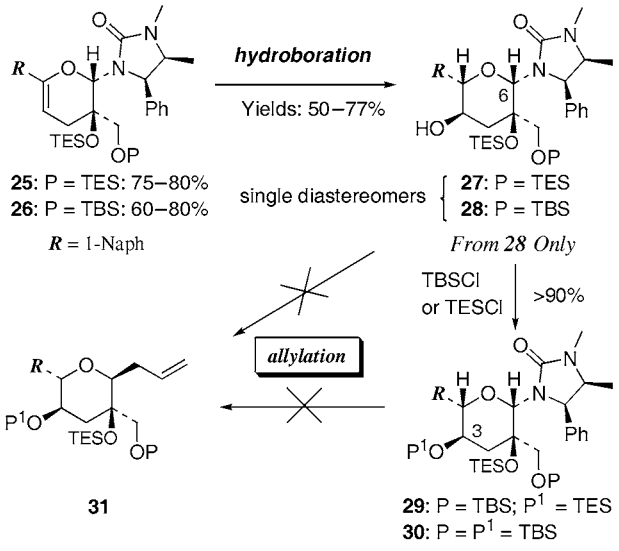


Scheme 5

However, attempts on allylation to remove the imidazolidinone group in **23** or **24** led to mostly fragmentation of the pyranyl ring or deacetonization even when the C3-OH was protected with a TBS or Ac group.

The diol **10** was then protected using various silyl group combinations to give **25** and **26** as shown in Scheme 6. While hydroboration of **25** or **26** was successful, the ensuing allylation and removal of the chiral imidazolidinone group at C6 was not successful using **27** and **28**, or using **29** and **30** (Note: Both are derived from **28**) in which the C3 secondary hydroxyl group was also silylated. Desilylation and/or decomposition of the pyranyl ring again occurred.

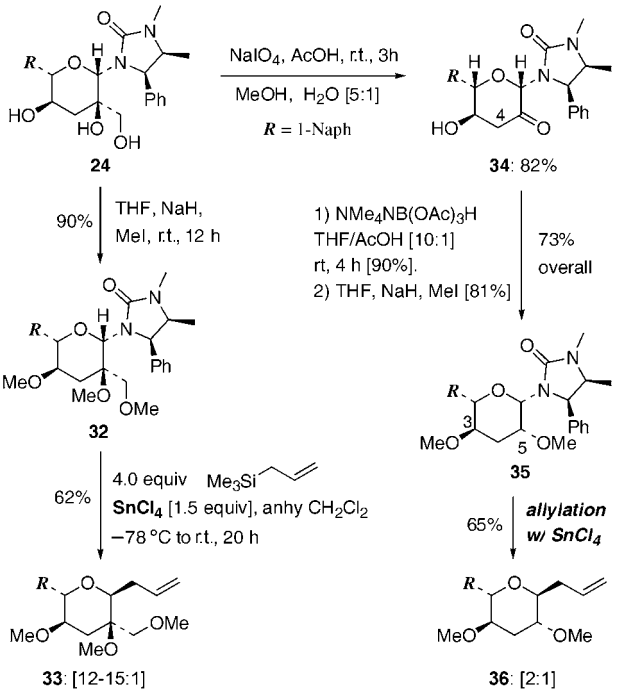
To finally achieve successful removal of the chiral imidazolidinone group at C6 position of these highly functionalized pyranyl heterocycles, two sequences were pursued



Scheme 6

as shown in Scheme 7. Successful per-methylation of the triol **24** using NaH and MeI led to the trimethoxy derivative **32** in 90% yield. After screening a variety of other Lewis acids, it was found that 1.5 equivalents of $SnCl_4$ worked effectively as the Lewis acid, and in the presence of allyltrimethylsilane, the desired allylation product **33** was isolated in 62% yield with 12-15:1 diastereomeric ratios.

Equipped with the finding that a stronger Lewis acid would now be more feasible in the removal of the imidazolidinone at C6 without destroying the pyranyl ring, the triol **24** was subjected to periodate cleavage using $NaIO_4$ in the presence of HOAc to give the ketone **34** in 82% yield. The ketone **34** represents a very important intermediate because it can be transformed into various pyranyl heterocycles that do not bear the methylene unit at C5 as those described above. In addition, the ketone **34** will allow functionalization at the C4 position.



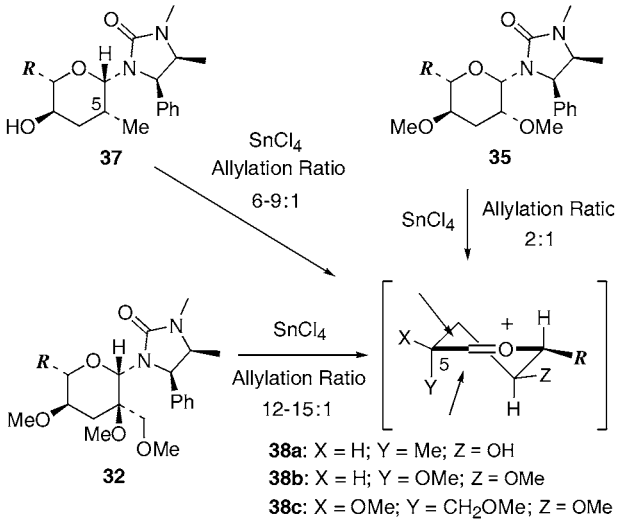
Scheme 7

Reduction of the ketone **34** using $NaBH_4$ led to a 1:1 mixture of the corresponding diol. On the other hand, a directed reduction using $NMe_4B[OAc]_3H$ gave exclusively the 3,5-*anti*-diol [90% yield], and methylation using the same condition above gave **35** in 73% overall yield. Allylation of **35** using $SnCl_4$ provided the desired pyranyl heterocycle **36** in 65% yield but with a dr of 2:1. These two sequences truly complete the demonstration that pyrans derived from hetero [4+2] cycloadditions of chiral allenamides can be employed as a chiral template for synthesis of highly functionalized oxygen heterocycles.

Although the isomeric ratio is low for **36**, mechanistically, it fits quite reasonably as shown in Scheme 8. When the oxocarbenium intermediate **38a** is derived from **37**

(X = H and Y = Me), the C5-Me group would assume a pseudo-axial position, thereby blocking the approaching of allyltrimethylsilane equatorially from bottom face. While this could further enhance the anomerically favored axial addition and lead to a diastereomeric ratio of 6-9:1,[2] the pseudo-axial C5-OMe group in the oxocarbenium intermediate **38b** derived from **35** (X = H and Y = OMe) could be less effective for it could rotate away from the bottom face.

In comparison with both cases, the oxocarbenium intermediate **38c** derived from **32** (X = OMe and Y = CH_2OMe) would provide the steric shielding of the bottom face. Additional steric interactions between the X group and Y group could also drive the CH_2OMe group further back toward the bottom face. This enhanced shielding would provide the best diastereoselectivity in the ensuing addition of allyltrimethylsilane in the case of **32**.



Scheme 8

We have described here a complete sequence suitable for stereoselective functionalization of the two olefins in pyranyl heterocycles derived from inverse electron demand hetero [4+2] cycloadditions of chiral allenamides. This sequence constitutes stereoselective dihydroxylation or hydroboration of the sterically accessible C5 exocyclic olefin followed by hydroboration–oxidation at the endocyclic olefin at C2/C3. The ultimate success in the removal of the chiral auxiliary at C6 demonstrates the concept of using these hetero cycloadducts as chiral templates for constructing highly functionalized pyrans or *C*-glycoside related substrates.

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9BBN Hydroboration-Oxidation of 5. To a solution of 29.0 mg of pyran **5** (0.071 mmol) in 3 mL of anhyd THF at r.t. was added 0.48 mL of 9BBN (2.5 equiv, 0.5 M solution in THF, 0.18 mmol). The resulting mixture was stirred at r.t. for 1 h, and was quenched with excess of 30% aq H_2O_2 and 15% aq NaOH via drop wise addition. After which, the reaction mixture was refluxed for 3 h. The solution was then cooled to r.t. and extracted with Et_2O (2 × 10 mL) and EtOAc (10 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Silica gel flash chromatography (60% EtOAc in hexanes) of the crude led to the desired alcohol **6** (22.2 mg, 73% yield).

6: R_f = 0.33 (60% EtOAc in hexanes); $[\alpha]_D^{20}$ = –95.5 (*c* 0.58, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.58 (ddd, *J* = 2.0, 12.0, 17.0 Hz, 1 H), 0.75 (d, *J* = 7.0 Hz, 3 H), 1.65 (ddd, *J* = 5.0, 9.0, 11.0 Hz, 1 H), 2.48 (m, 1 H), 2.72 (s, 3 H), 3.65 (m, 2 H), 3.89 (dq, *J* = 3.5, 9.0 Hz, 1 H), 4.64 (dd, *J* = 3.5, 11.0 Hz, 1 H), 4.73 (d, *J* = 9.0 Hz, 1 H), 4.90 (dd, *J* = 2.0, 6.0, Hz, 1 H), 6.31 (dd, *J* = 2.0, 4.0 Hz, 1 H), 7.10–8.30 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9, 150.6, 138.0, 134.1, 133.8, 130.8, 129.1, 128.3, 128.0, 127.8, 126.3, 126.0, 125.8, 125.1, 101.8, 81.9, 62.9, 58.8, 58.2, 38.8, 28.5, 19.4, 15.0. IR (thin film): 3400 (m), 3058 (w), 2925 (s), 2890 (m), 1681 (s), 1640 (w), 1434 (m)cm^{-1}. MS (EI): *m*/z (% relative intensity) = 429.2(40) [M$^+$], 411.1(100); *m*/*z* calcd for $C_{27}H_{29}N_2O_3$: 429.21782, found 429.21780.

OsO_4 Dihydroxylation of 5. To a solution of 80.0 mg of pyran **5** (0.20 mmol) in 10 mL of anhyd CH_2Cl_2 at –78 °C were added 4.0 mL of TMEDA (0.27 mmol) and drop wise via a syringe a solution of 66.7 mg of OsO_4 [0.27 mmol] in 2 mL of CH_2Cl_2. After the solution was stirred for 30 min at –78 °C, it was carefully concentrated under reduced pressure. The resulting residue was dissolved in THF (10 mL) and H_2O (1 mL). After adding 2 g of $NaHSO_3$ to the crude mixture, the reaction mixture was refluxed at 75 °C for 12 h. The solution was then cooled to r.t., and extracted with EtOAc (3 × 15 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Silica gel flash column chromatography (80% EtOAc in hexanes) of the crude furnished the desired diol **10** (70.3 mg, 85% yield) as a thick colorless oil.

10: R_f = 0.32 (80% EtOAc in hexanes). $[\alpha]_D^{20}$ = –33.0 (*c* 0.60, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 6.5 Hz, 1 H), 1.05 (d, *J* = 17.5 Hz, 1 H), 1.80 (dd, *J* = 3.5, 17.5 Hz, 1 H), 2.72 (s, 3 H), 3.33 (t, *J* = 11.0 Hz, 1 H), 3.42 (brs, 1 H), 3.90 (dq, *J* = 7.0, 13.0 Hz, 1 H), 3.96 (dd, *J* = 3.5, 12.5 Hz, 1 H), 4.77 (d, *J* = 9.0 Hz, 1 H), 4.83 (dd, *J* = 2.5, 5.5 Hz, 1 H), 4.91 (dd, *J* = 3.5, 10.5 Hz, 1 H), 5.72 (s, 1 H), 7.20–8.4 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.4, 150.1, 137.5, 134.0, 133.7, 131.3, 129.1, 128.9, 128.5, 128.4, 128.1, 127.4, 126.5, 126.2, 126.0, 125.8, 124.9, 99.2, 85.0, 70.0, 66.1, 59.4, 57.9, 28.4, 14.8. IR (thin film): 3377 (s), 3053 (w), 2925 (s), 2854 (m), 1677 (s), 1440 (m) cm^{-1}. MS (EI): *m*/*z* (% relative intensity) = 445.2(90) [M$^+$], 118.9(100); *m*/*z* calcd for $C_{27}H_{29}N_2O_4$: 445.21273. Found: 445.21270.

A General Procedure for BH_3 Hydroboration Using 9. To a solution of 12.0 mg of the TBS ether **9** (0.022mmol) in anhyd THF (1 mL) at r.t. was added BH_3·THF (0.44 mL) complex (2.0 equiv, 1 M solution in THF, 0.044 mmol). The reaction mixture was stirred for 2 h at r.t., and was quenched carefully with drop wise addition of excess of 30% aq H_2O_2 and 15% aq NaOH. The mixture was then stirred vigorously for 30 min at r.t. The resultant mixture was extracted with Et_2O [2 × 5 mL] and EtOAc [5 mL], and the combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Silica gel flash chromatography (40% EtOAc in hexanes) of the crude provided alcohol **20** (7.40 mg, 60% yield) as a colorless oil.

20: R_f = 0.20 (40% EtOAc in hexanes). ^{1}H NMR (500 MHz, toluene-d_8): δ = –0.01 (s, 3 H), 0.04 (s, 3 H), 0.34 (d, *J* = 6.5 Hz, 3 H), 1.00 (s, 9 H), 1.76 (ddd, *J* = 4.0, 11.5, 20.5 Hz, 1 H), 2.51 (s, 3 H), 2.62 (m, 1 H), 2.81 (dt, *J* = 4.0, 9.5 Hz, 1 H), 3.11 (dd, *J* = 6.0, 14.5 Hz, 1 H), 3.70 (dd, *J* = 5.5, 10.0 Hz, 1 H), 3.88 (t, *J* = 10.0 Hz, 1 H), 4.10 (m, 1 H), 4.46 (d, *J* = 8.5 Hz, 1 H), 5.05 (d, *J* = 9.0 Hz, 1 H), 5.87 (brs, 1 H), 7.01–8.45 (m, 12 H). ^{13}C NMR (75 MHz, toluene-d_8): δ = 162.5, 139.5, 135.7, 134.1, 132.4, 127.9, 127.6, 127.3, 127.4, 125.7, 125.3, 125.2, 125.0, 86.4, 82.9, 66.4, 60.2, 58.7, 57.2, 41.2, 33.2, 28.5, 25.8, 14.8, –5.5, –5.7 (missing 4 peaks due to overlap, and missing 1 additional peak). IR (thin film): 3377 (w), 3013 (w), 2954 (s), 2919 (s), 2848 (m), 1707 (m), 1507 (m), 1460 (s) cm^{-1}. MS (LCMS): *m*/*z* (% relative intensity) = 561.2 (10) [M$^+$], 191 (100).

A General Procedure for Lewis Acid Mediated Allylation Using 20.

To a solution of 5.0 mg of alcohol **20** (8.9 μmol) in 0.5 mL of anhyd CH_2Cl_2 at –78 °C were added 5.8 mg of $SnBr_4$ (1.5 equiv, 17.8 μmol) and 5.6 μL of allyltrimethylsilane (4 equiv, 35.6 μmol). The resultant mixture was warmed to r.t. and stirred for 12 h before it was quenched with sat. aq NH_4Cl (0.5 mL). The crude mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Silica gel flash chromatography (10% EtOAc in hexanes) of the crude furnished the desired pyran **21** (2.56 mg, 70% yield).

21: R_f = 0.35 (10% EtOAc in hexanes). $[\alpha]_D^{20}$ = +35.0 (*c* 0.20, CH_2Cl_3). ^{1}H NMR (500 MHz, toluene-d_8): δ = –0.02 (s, 3 H), –0.01 (s, 3 H), 0.34 (s, 9 H), 1.02 (ddd, *J* = 5.5, 8.5, 14.5 Hz, 1 H), 1.78 (m, 2 H), 2.24 (ddd, *J* = 6.5, 7.5, 13.5 Hz, 1 H), 2.33 (ddd, *J* = 6.0, 8.5, 12.5 Hz, 1 H), 2.39 (d, *J* = 2.0 Hz, 1 H), 3.34 (dd, *J* = 6.0, 9.5 Hz, 1 H), 3.39 (dd, *J* = 4.5, 9.5 Hz, 1 H), 3.91 (m, 1 H), 4.33 (ddd, *J* = 3.0, 6.0, 15.0 Hz, 1 H), 5.05 (dd, *J* = 10.0, 20.5 Hz, 1 H), 5.66 (brs, 1 H), 5.96 (m, 1 H), 6.82–8.01 (m, 7 H). ^{13}C NMR (75 MHz, toluene-d_8): δ = 145.2, 141.8, 139.8, 131.0, 129.1, 127.8, 127.5, 127.4, 125.7, 125.4, 123.3, 82.5, 80.7, 79.6, 69.8, 64.5, 46.5, 40.2, 27.9, 25.7, –5.5, –5.7 (missing 1 signal). IR (thin film): 3430 (m), 3013 (w), 2941 (m), 2873 (m), 1640 (s), 1413 (m), 1149 (s) cm^{-1}. MS (EI): *m*/*z* (% relative intensity) = 413.1 (10) [M$^+$ + H], 141.4 (45), 79.8 (100); *m*/z calcd for $C_{25}H_{36}N_3O_3SiNa$: 435.2331 [M$^+$ + Na]. Found: 435.2344.

Periodic Cleavage of 24. To a solution of 30.0 mg of the triol **24** (0.064 mmol) in of MeOH/H_2O (5 mL, 5:1) at r.t. was added 69.0 mg of $NaIO_4$ (5 equiv, 0.32 mmol) and a drop of HOAc. The reaction mixture was stirred for 3 h at r.t. before it was concentrated and dissolved in EtOAc. The crude organic solution was washed with sat. aq $Na_2S_2O_3$ (3 mL) and H_2O. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Silica gel flash chromatography (80% EtOAc in hexanes) of the crude furnished the desired ketone **34** in 84% yield (23.0 mg).

34: R_f = 0.30 (80% EtOAc in hexanes). $[\alpha]_D^{20}$ = –61.0 (*c* 0.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 6.6 Hz, 3 H), 2.57 (dd, *J* = 6.3, 16.2 Hz, 1 H), 2.83 (s, 3 H), 3.33 (dd, *J* = 3.6, 16.2 Hz, 1 H), 3.92 (dq, *J* = 6.6, 8.7 Hz, 1 H), 4.48 (ddd, *J* = 4.2, 6.6, 10.2 Hz, 1 H), 4.90 (br s, 1 H), 5.14 (d, *J* = 9.0 Hz, 1 H), 5.34 (d, *J* = 4.5 Hz, 1 H), 7.20–8.25 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.8, 161.0, 137.1, 135.2, 128.7, 128.6, 128.4, 128.3, 128.2, 126.3, 125.8, 125.6, 124.2, 123.2, 84.0, 79.0, 71.0, 56.5, 44.5, 29.7, 14.2 (missing 4 peaks due to overlap, and missing 1 additional peak). IR (thin film): 3414 (m), 3047 (w), 2977 (s), 2875 (s), 1716 (s), 1681 (s) cm^{-1}. MS (LCMS): *m*/z (% relative intensity) = 431.1 (10) [M^+], 413.1 (100).

(11) When substituents at C5 and C6 are *trans* in these pyranyl heterocycles such as **21**, we observed strong NOE between protons at C2 and C3 presumably because these two protons are not necessarily locked in di-axial relationship unlike those in pyrans where C5 and C6 substituents are *cis*.