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Densely Functionalized Chiral Pyrroles from Endocyclic, Exocyclic, and Acyclic Vinyl Sulfone-Modified Carbohydrates

Rahul Bhattacharya, Ananta Kumar Atta, Debanjana Dey, and Tanmaya Pathak*

Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India

tpathak@chem.iitkgp.ernet.in

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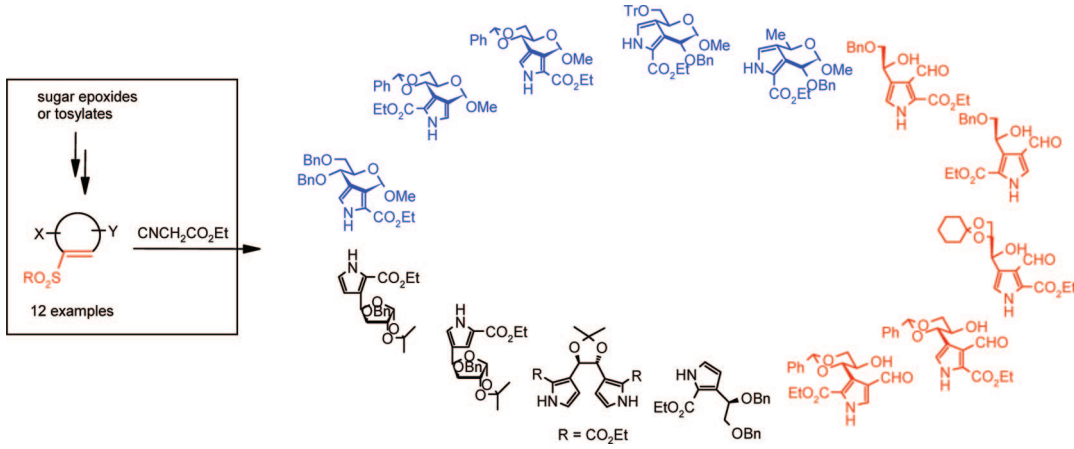

A wide range of vinyl sulfone-modified carbohydrates have been prepared as starting materials for the synthesis of polysubstituted chiral pyrroles. All these vinyl sulfones reacted efficiently with ethylisocyanoacetate to generate a plethora of new pyrrole derivatives. Furanosyl rings opened up during pyrrole synthesis, and pyranosyl rings were opened up by reacting the pyrrole with $POCl_3$/DMF. This paper also reports one of the most efficient and practical routes for the synthesis of β-substituted pyrroles.

Introduction

Pyrrole-containing compounds play crucial roles in nature.[1] Substituted pyrroles are important for research in pharmaceutical and material sciences.[2] Although a variety of synthetic approaches for the synthesis of pyrroles have been developed over the years, a perusal of the literature reveals that even now the synthesis of highly functionalized pyrroles remains a synthetic challenge in terms of regioselectivity and chemoselectivity.[3] Moreover, synthesis of β-substituted pyrroles was reported to be particularly difficult because the direct alkylation or acylation of pyrroles produced the desired products as minor components. Although methods using the directing effects of N-protecting groups or permanent α-substituents did produce the β-substituted products, designing of a general and practical method for the synthesis of β-substituted pyrroles still remains a difficult challenge.

Conjugate addition of the anion generated from an isocyanoacetate to vinyl sulfones was put forward as a methodology for the synthesis of pyrrole-2-esters.[4] Since the strategy was crucially dependent on the availability of functionalized vinyl sulfones, highly specialized methods were devised in the past decade for the synthesis of the derivatized vinyl sulfones.[3−6] Although these vinyl sulfones were reacted with isocyanoacetates for the synthesis of pyrroles, the strategy stagnated over the years for the nonavailability of straightforward and general

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methodologies for the synthesis of polysubstituted vinyl sulfones. A detailed analysis of these synthetic strategies revealed that virtually all vinyl sulfones as starting materials for pyrroles were derived from either symmetrical olefins via the addition of PhSCl across the double bond[5] or methods having no potential for generating regioisomers.[6] The serious shortcomings of currently available methods for the synthesis of polysubstituted pyrroles were compounded[7] by the fact that strategies for the synthesis of pyrroles attached to chiral moieties are virtually nonexistent.[8] The usefulness of such chirally substituted pyrroles in biological and material sciences can be studied only after suitable methodologies are available for their synthesis in relatively large amounts.

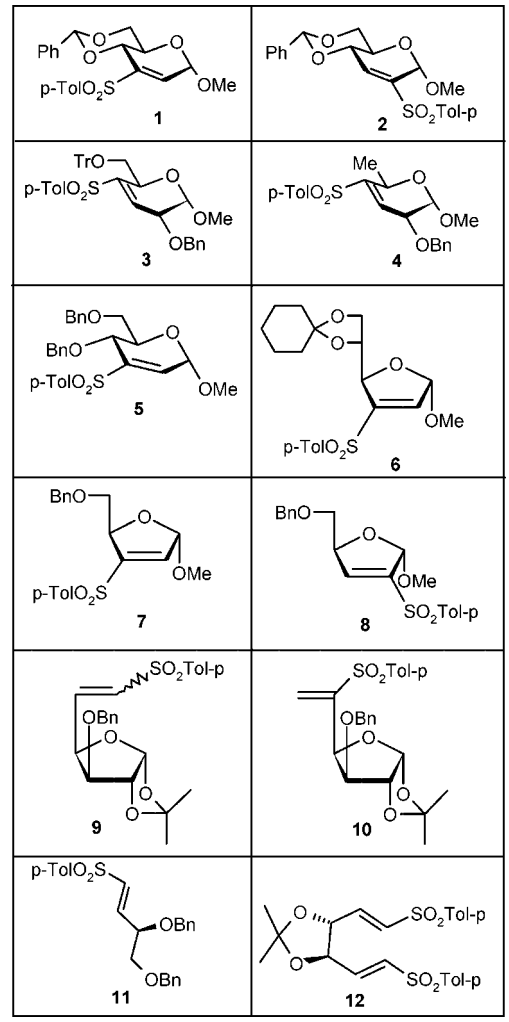
Results and Discussion

We opined that the utility of the powerful strategy used in vinyl sulfone-mediated pyrrole synthesis can be immensely increased if the substituted vinyl sulfones are synthesized through regiocontrolled routes. We observed that the C−S bond formation in the synthesis of furanosyl and pyranosyl thiosugars is regiocontrolled, and therefore the orientation of the vinyl sulfone group derived from these thiosugars in the required vinyl sulfone-modified carbohydrates is predefined.[9] However, C−S bond formation in exocyclic and acyclic sugar can also be made regiocontrolled by suitably incorporating a leaving group or an epoxide ring. We opined that vinyl sulfones derived from carbohydrates would act as excellent and efficient acceptors for the carbanion generated from ethylisocyanoacetate. Moreover, the inbuilt chiral environments of the sugar residue would be automatically transferred to the newly synthesized pyrroles. Therefore, we selected the endocyclic, exocyclic, and acyclic vinyl sulfone-modified carbohydrates **1**−**8**, **9**, **10**, **11**, and **12**, respectively, as substrates for the synthesis of pyrroles (Table 1).

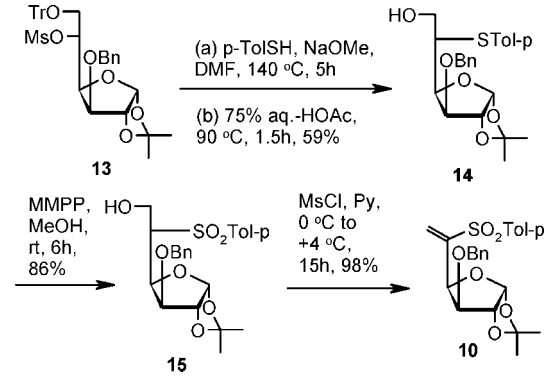
For the synthesis of endocyclic vinyl sulfone-modified carbohydrates **1**−**8**, C−S bonds were formed by opening an epoxide in a regioselective fashion or by displacing a suitably designed sulfonate ester.[9] The exocyclic vinyl sulfone-modified carbohydrate 6-*C*-tolysulfonyl-hex-5-enofuranoside **9** was also obtained by reacting a 5,6-*O*-anhydro derivative with tolyl thiol.[10] For the synthesis of 5-C-tolysulfonyl-hex-5-enofuranoside **10**, the regioisomer of **9**, the fully protected mesylate **13**[11] was treated with tolylthiol/NaOMe followed by aq. acetic acid to obtain the sulfide **14**. The sulfide was oxidized with MMPP to the sulfone **15**, which on treatment with mesyl chloride in pyridine afforded the desired vinyl sulfone-modified carbohydrate **10** (Scheme 1).

We then turned our attention to the synthesis of the acyclic vinyl sulfone **11** and the acyclic bisvinyl sulfone **12**. Thus the epoxide ring of an easily available tetrosyl epoxide **16**[12] was regioselectively opened with the sulfur nucleophile to obtain the alcohol **17**. Oxidation of the sulfide **17**, followed by one-pot mesylation of the sulfone **18** and the elimination of sulfonic acid, afforded the acyclic vinyl sulfone **11** (Scheme 2). The synthesis of the bisvinyl sulfone **12** started from the known ditosylate **19** derived from mannitol.[13] The ditosylate derivative **19**, on treatment with tolylthiol/TMG, generated the bissulfide **20**. Oxidation of the bissulfide **20** afforded the bissulfone **21**.

TABLE 1. Vinyl Sulfone-Modified Carbohydrates as Precursors of Densely Functionalized Chiral Pyrroles



SCHEME 1. Synthesis of Exo-Cyclic Vinyl Sulfone



(7) ". .even 150 years after its isolation and synthesis, and more than 100 years after the classical pyrrole syntheses were developed, the synthesis of highly substituted pyrroles is anything but straightforward."[3c]

(8) There are scant reports on the synthesis of sugar linked pyrroles. In these cases the aldehydo group of sugar molecule was directly reacted with pyrrole, see: Yadav, J. S.; Reddy, B. V. Subba; Satheesh, G. *Tetrahedron Lett.* **2004**, *45*, 3673. Casiraghi, G.; Cornia, M.; Zanardi, F.; Rassu, G.; Ragg, E.; Bortolini, R. *J. Org. Chem.* **1994**, *59*, 1801.

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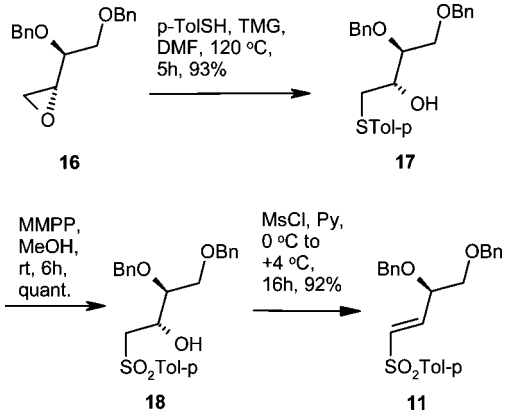
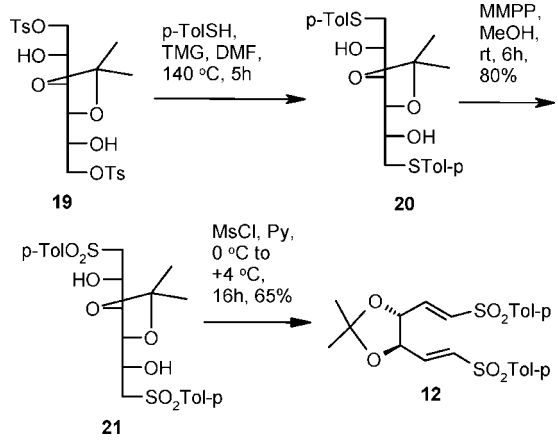
SCHEME 2. Synthesis of Acyclic Vinyl Sulfone



SCHEME 3. Synthesis of Acyclic Bisvinyl Sulfone



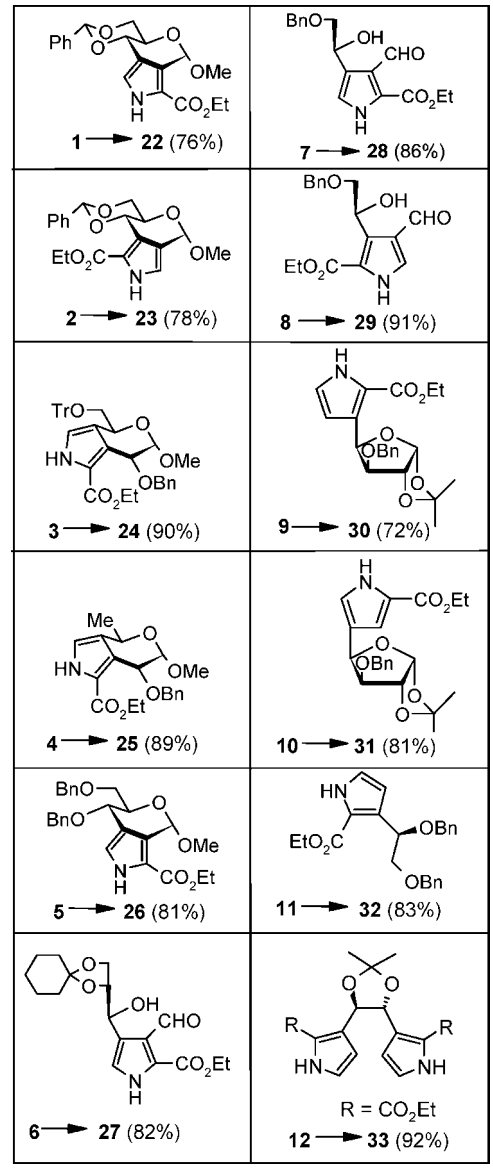
Mesylation of the sulfone **21** in pyridine and concomitant elimination of sulfonic acid afforded the acyclic bisvinyl sulfone **12** (Scheme 3).

All vinyl sulfones were treated with ethyl isocyanoacetate in the presence of ^{t}BuOK in dry THF at the reflux temperature for 5 h to afford clean products. The results and the yields are summarized in Table 2. The conversion is usually efficient with the yields varying between 70 and 90%. Interestingly in the case of furanosyl analogues **6**−**8**, the sugar ring opened up in situ to afford three different trisubstituted pyrroles **27**−**29**, respectively.

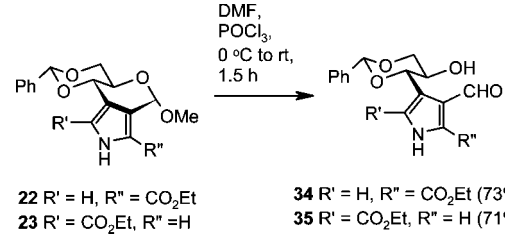
Although this serendipitous reaction fulfilled our requirement for opening the furanosyl sugar rings to afford polysubstituted pyrroles **27**−**29**, we continued to search for a reaction condition for opening the pyranosyl rings of **22**−**26**. We attempted several reaction conditions for opening the sugar ring, and in almost all cases, either the unreacted starting materials or the breakdown products was obtained. To our surprise, while scanning reaction conditions for the formylation of the pyrrole rings, we observed that the $POCl_3$·DMF complex smoothly opened the pyranosyl rings of **22** and **23** to afford the trisubstituted pyrroles **34** and **35**, respectively, in high yields (Scheme 4). Peaks ranging between δ 9.96−10.87 (^{1}H NMR) and δ 187.0−188.9 (^{13}C NMR) confirmed the presence of a free −CHO group in compounds **27**−**29**, **34**, and **35**.

In conclusion, we have reported a straightforward and general method for the synthesis of a wide range of polysubstituted pyrroles from vinyl sulfone-modified carbohydrates. Our general and regioselective approach to the synthesis of the vinyl sulfones

TABLE 2. Chiral Pyrroles from Vinyl Sulfone-Modified Carbohydrates



SCHEME 4. Reactions of Pyranosyl Derivatives of Pyrroles with $POCl_3$/DMF



was pivotal for accessing these crucially important intermediates. In the case of furanosyl compounds, the five-membered ring opened up in situ to afford directly the densely functionalized pyrroles substituted with chiral functional groups, and the pyranosyl compounds underwent ring opening with $POCl_3$ in DMF. A perusal of the structure of pyrroles in Table 2 also suggests that a myriad of functional groups have been attached to the β-position of pyrrole rings. Some of these groups, such as chiral acyclic chains (**27**, **28**, **29**, **32**, **33**) or sugar residues

(**30**, **31**) would be very difficult, if not impossible, to introduce at the β-position of a pyrrole ring with the currently available methods. Wider applications of the new polysubstituted chiral pyrroles are currently under study.

Experimental Section

General Methods.[10] **3-*O*-Benzyl-5-deoxy-(5-C-*p*-tolylsulfide)-1,2-*O*-isopropylidene-β-L-ido-1,4-furanose 14.** To a well-stirred solution of *p*-thiocresol (5.54 g, 44.69 mmol) and NaOMe (1.93 g, 35.75 mmol) in dry DMF (20 mL) was added a solution of compound **13** (2.81 g, 4.46 mmol) in dry DMF (10 mL), and the resulting solution was heated at 120−130 °C under N_2 for a period of 5 h. The reaction mixture was cooled to room temperature and poured into a satd. aq. $NaHCO_3$ soution (150 mL). The aqueous phase was extracted with EtOAc (3 × 30 mL). Organic layers were pooled together, dried over anhyd. Na_2SO_4, and evaporated under reduced pressure. The crude mass was purified over silica gel. To a solution of this compound in EtOH (10 mL) was added aq. HOAc (75%, 25 mL). The reaction mixture was heated at 90 °C for 1.5 h and cooled to room temperature. Volatile matters were evaporated under reduced pressure to near dryness, and the residual acid was coevaporated with toluene (3 × 10 mL) to get the crude mass. The crude residue was purified over silica gel to yield **14** (1.1 g, 59%).

Colorless jelly. $[\alpha]_D^{30}$: − 52.2 ° (*c* 1.14, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.31 (s, 3H); 1.42 (s, 3H); 2.32 (s, 3H); 3.34−3.39 (m, 1H); 3.43−3.49 (m, 1H); 3.50−3.55 (m, 1H); 3.89 (d, 1H, J = 3.2 Hz); 4.03−4.07 (m, 1H); 4.47 (d, 1H, J = 11.6 Hz); 4.64−4.70 (m, 2H); 5.98 (d, 1H, J = 3.6 Hz); 7.10 (d, 2H, J = 8.0 Hz); 7.29−7.35 (m, 5H); 7.44 (d, 2H, J = 8.0 Hz). ^{13}C NMR: δ 21.2, 26.3, 26.7, 51.0, 60.5 (CH_2), 71.8 (CH_2), 78.9, 81.6, 81.8, 104.4, 111.7, 127.6, 128.0, 128.2, 128.6, 134.9, 136.9, 138.5. HRMS (ES^+), *m*/*z* calcd. for $(M + Na)^+$ $C_{23}H_{28}O_5SNa$: 439.1555. Found: 439.1556.

3-*O*-Benzyl-5-deoxy-(5-C-*p*-tolylsulfonyl)-1,2-*O*-isopropylidene-β-L-ido-1,4-furanose 15. To a solution of **14** (0.84 g, 1.94 mmol) in dry MeOH (20 mL) was added MMPP (3.85 g, 7.78 mmol), and the reaction mixture was stirred at room temperature for 6 h under N_2. The reaction mixture was filtered through a celite bed, and the filtrate was evaporated under reduced pressure. The crude mass obtained was dissolved in EtOAc (30 mL), and the organic layer was washed with satd. aq. solution of $NaHCO_3$ (3 × 30 mL). The organic layer was dried over anhyd. Na_2SO_4 and filtered, and the filtrate was evaporated under reduced pressure to get a residue. The crude residue was purified over silica gel to yield **15** (0.78 g, 86%). Colorless jelly. $[\alpha]_D^{30}$: −31.5 ° (*c* 0.625, $CHCl_3$). H NMR ($CDCl_3$): δ 1.28 (s, 3H); 1.42 (s, 3H); 2.42 (s, 3H); 3.53−3.62 (m, 1H); 3.95−4.04 (m, 3H; 4.36 (dd, 1H, J = 3.0, 9.6 Hz); 4.46 (d, 1H, J = 11.4 Hz); 4.54 (d, 1H, J = 3.8 Hz); 4.64 (d, 1H, J = 11.4 Hz); 5.76 (d, 1H, J = 3.8 Hz); 7.26−7.39 (m, 7H); 7.84 (d, 2H, J = 8.4 Hz). ^{13}C NMR: δ 21.7, 26.3, 26.7, 58.5 (CH_2), 66.9, 71.9 (CH_2), 76.0, 80.8, 82.0, 104.7, 111.9, 128.0, 128.4, 128.7, 129.3, 129.4, 136.2, 136.6, 144.8. HRMS (ES^+), *m*/*z* calcd. for $(M + H)^+$ $C_{23}H_{29}O_7S$: 449.1634. Found: 449.1635.

3-*O*-Benzyl-5,6-didehydro-5,6-dideoxy-1,2-*O*-isopropylidene-(5-C-*p*-tolylsulfonyl)-α-D-gluco-1,4-furanose 10. To a solution of **15** (0.54 g, 1.23 mmol) in dry pyridine (15 mL) was added a solution of methanesulfonyl chloride (0.28 mL, 3.69 mmol) in dry pyridine (5 mL) at 0 °C. The mixture was left overnight at 4 °C. The reaction mixture was poured into satd. aq $NaHCO_3$ (70 mL), and the aqueous phase was extracted with dichloromethane (3 × 30 mL). Organic extracts were collected together, dried over anhyd. Na_2SO_4, and filtered. Et_3N (5 mL) was added to the filtrate, and after stirring for 15 min, the solvent was evaporated under reduced pressure. The resulting residue was purified over silica gel to yield **10** (0.5 g, 98%). Colorless jelly. $[\alpha]_D^{30}$: −8.7 ° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.28 (s, 3H); 1.39 (s, 3H); 2.42 (s, 3H); 4.15 (d, 1H, J = 2.8 Hz); 4.49 (s, 2H); 4.57 (d, 1H, J = 3.8 Hz); 4.79 (bd, 1H, J = 2.6 Hz); 5.90 (d, 1H, J = 3.8 Hz); 6.27 (d, 1H, J = 1.4 Hz); 6.57 (d, 1H, J = 0.6 Hz); 7.26−7.37 (m, 7H); 7.77 (d, 2H, J = 6.6 Hz). ^{13}C NMR: δ 21.5, 26.2, 26.7, 72.6 (CH_2), 76.9, 82.2, 83.2, 104.2, 111.9, 127.6 (CH_2), 127.6, 127.8, 128.2, 128.3, 129.9, 135.9, 137.4, 144.8. HRMS (ES^+), *m*/*z* calcd. for $(M + H)^+$ $C_{23}H_{27}O_6S$: 431.1528. Found: 431.1527.

(2*S*,3*S*)-3,4-Dibenzyloxy-(1-C-*p*-tolylsulfonyl)butan-2-ol 18. To a solution of **16** (1.2 g, 4.22 mmol) in DMF (15 mL) were added thiocresol (2.62 g, 21.13 mmol) and TMG (1.46 g, 12.66 mmol). The reaction mixture was heated for 5 h at 120−130 °C, cooled to room temperature, and poured into satd. aq. NaCl solution (50 mL). The mixture was extracted with EtOAc (3 × 30 mL). The EtOAc layer was washed with satd. aq. $NaHCO_3$ (2 × 25 mL), dried over anhyd. Na_2SO_4, and evaporated under reduced pressure. The resulting syrup was purified over silica gel to yield **17** (1.61 g, 93%). To a solution of **17** (1.6 g, 3.92 mmol) in methanol (30 mL) was added MMPP (7.76 g, 15.68 mmol). The reaction mixture was stirred for 6 h at room temperature and filtered. The filtrate was evaporated under reduced pressure. The resulting residue was neutralized with satd. aq. $NaHCO_3$ (70 mL). The mixture was extracted with EtOAc (3 × 30 mL). The organic layer was separated and dried over anhyd. Na_2SO_4 and filtered, and the filtrate was concentrated to dryness under reduced pressure to get the residue. The crude residue was purified over silica gel to yield **18** (1.7 g, quantitative). White solid. Mp: 126−129 °C. $[\alpha]_D^{28}$: +34.5 ° (0.625, THF). ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H); 3.26−3.36 (m, 2H); 3.62−3.69 (m, 3H); 4.26−4.29 (m, 1H); 4.47−4.51 (m, 3H); 4.67 (d, 1H, J = 12.0 Hz); 7.22−7.37 (m, 12H); 7.76 (d, 2H, J = 8.0 Hz). ^{13}C NMR: δ 21.6, 59.2 (CH_2), 66.8, 69.0 (CH_2), 72.6 (CH_2), 73.5 (CH_2), 78.0, 127.6, 127.8, 127.9, 128.0 (2 × C), 128.4 (2 × C), 129.8, 136.4, 137.6 (2 × C), 144.8. HRMS (ES^+), *m*/*z* calcd. for $(M + H)^+$ $C_{25}H_{29}O_5S$: 441.1736. Found: 441.1735.

1-{[(3*R*)-3,4-Dibenzyloxy-but-1-en-1-yl]sulfonyl}-4-methylbenzene 11. To a solution of **18** (1.5 g, 3.40 mmol) in dry pyridine (25 mL) was added a solution of methanesulfonyl chloride (0.79 mL, 10.23 mmol) in dry pyridine (15 mL) at 0 °C. The mixture was left overnight at 4 °C. The reaction mixture was poured into satd. aq $NaHCO_3$ (70 mL), and the aqueous phase was extracted with dichloromethane (3 × 30 mL). Organic extracts were collected together, dried over anhyd. Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure. The resulting residue was purified over silica gel to yield **11** (1.33 g, 92%). White solid. Mp: 99−102 °C. $[\alpha]_D^{28}$: −31.2 ° (0.625, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.43 (s, 3H); 3.53−3.62 (m, 2H); 4.25−4.28 (m, 1H); 4.51−4.61 (m, 4H); 6.63 (d, 1H, J = 14.8 Hz); 6.94 (dd, 1H, J = 4.4, 14.8 Hz); 7.24−7.35 (m, 12H); 7.74 (d, 2H, J = 8.0 Hz). ^{13}C NMR: δ 21.7, 71.5 (CH_2), 72.1 (CH_2), 73.5 (CH_2), 76.4, 127.6, 127.7, 127.8 (2 × C), 128.0, 128.5 (2 × C), 130.0, 132.3, 137.2, 137.4, 137.7, 143.1, 144.5. HRMS (ES^+), *m*/*z* calcd. for $(M + H)^+$ $C_{25}H_{27}O_4S$: 423.1630. Found: 423.1633.

3,4-Isopropylidine-1,6-bis-*p*-tolylsulfonyl-D-mannitol 21. To a well-stirred solution of the ditosylate **24** (4.00 g, 7.54 mmol) in DMF (40 mL) was added *p*-thiocresol (9.34 g, 75.4 mmol) and NaOMe (2.03 g, 37.70 mmol). The mixture was heated at 120−130 °C with stirring under N_2. After 5 h, the reaction mixture was poured into satd. aq. solution of $NaHCO_3$, and the product was washed with EtOAc (3 × 10 mL). The combined organic layer was dried over anhyd. Na_2SO_4 and filtered through a short silica gel column to afford the sulfide **20**. To a solution of **20** (2.61 g, 6.01 mmol) in dry MeOH (40 mL) was added MMPP (17.83 g, 36.06 mmol), and the reaction mixture was stirred at room temperature for 6 h under N_2. The reaction mixture was then filtered through a celite bed, and the filtrate was evaporated under reduced pressure. The crude mass obtained was then dissolved in EtOAc (30 mL), and the organic layer was washed with satd. aq. solution of $NaHCO_3$ (3 × 30 mL). Organic layers were collected and dried over anhyd. Na_2SO_4 and filtered, and the filtrate was evaporated under reduced pressure to get a residue. The crude residue was purified over silica gel to yield **21** (3.00 g, 80%). White solid. Mp: 116−117 °C. $[\alpha]_D^{28}$:

+36.5 ° (0.625, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.17 (s, 6H); 2.44 (s, 6H); 3.15−3.28 (m, 2H); 3.52 (dd, 2H, J = 1.6, 14.6 Hz); 3.74−3.78 (m, 2H); 3.95 (d, 2H, J = 2.2 Hz); 4.07−4.16 (m, 2H); 7.35 (d, 4H, J = 8.0 Hz); 7.80 (d, 4H, J = 8.0 Hz). ^{13}C NMR: δ 21.6, 26.7, 59.5 (CH_2), 67.8 (CH_2), 80.8, 110.3, 128.0, 129.9, 136.4, 145.0. HRMS (ES^+), m/z calcd. for $(M + H)^+$ $C_{23}H_{31}O_8S_2$: 499.1460. Found: 499.1468.

(4*R*,5*R*)-2,2-Dimethyl-4,5-bis[(*E*)-2-(*p*-tolylsulfonyl)ethenyl]-1,3-dioxolane 12. To a well-stirred solution of the sulfone **21** (2.00 g, 4.01 mmol) in pyridine (15 mL) was added a solution of methanesulfonyl chloride (1.9 mL, 24.06 mmol) in pyridine (10 mL) dropwise at 0 °C under N_2. The reaction mixture was kept overnight at +4 °C. The reaction mixture was poured into a satd. aq. solution of $NaHCO_3$, and the product was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over anhyd. Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure to get a residue. The residue was purified over silica gel to afford **12** (1.20 g, 65%). White solid. Mp: 177−179 °C. $[\alpha]_D^{28}$: +24.5 ° (0.625, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.39 (s, 6H); 2.42 (s, 6H); 4.31 (bs, 2H); 6.70 (d, 4H, J = 14.8 Hz); 6.89 (d, 2H, J = 15.2 Hz); 7.33 (d, 4H, J = 8.0 Hz); 7.76 (d, 2H, J = 8.0 Hz). ^{13}C NMR: δ 21.5, 26.6, 78.3, 111.3, 127.8, 130.0, 133.2, 136.5, 138.6 144.8. HRMS (ES^+), m/z calcd. for $(M + H)^+$ $C_{23}H_{27}O_6S_2$: 463.1249. Found: 463.1248.

General Procedure for the Synthesis of Pyrroles from Vinyl Sulfone-Modified Carbohydrates. To a suspension of 90% ^{t}BuOK (6 equiv) in dry THF (2 mL/mmol) at 0 °C was added ethyl isocyanoacetate (5 equiv), and the resulting solution was stirred for 15 min under N_2. A solution of the appropriate vinyl sulfone-modified carbohydrates (1 equiv) in dry THF (1 mL/mmol) was added dropwise to the reaction mixture. The resulting solution was heated under reflux with continuous stirring under N_2 for 5 h. The reaction mixture was cooled to room temperature, and the volatile matters were evaporated under reduced pressure. The residue obtained was triturated with EtOAc (30 mL). The organic layer was washed with satd. aq. solution of NH_4Cl (3 × 30 mL) and separated. The organic layer was dried over anhyd. Na_2SO_4 and filtered, and the filtrate was evaporated under reduced pressure to get a crude mass. The crude residue was purified over silica gel to get the pure product. Eluent:Pet.ether-EtOAc (3:1).

Ethyl (2*R*,4a*R*,6*S*,9b*S*)-6-Methoxy-2-phenyl-4a,6,8,9b-tetrahydro-4*H*-[1,3]dioxino[4′,5′:5,6]pyrano[3,4-c]pyrrole-7-carboxylate 22. Following the general procedure, compound **1** (0.15 g, 0.37 mmol) was converted to yield compound **22** (Yield: 0.99 g, 76%). White crystal. Mp: 117−119 °C. $[\alpha]_D^{28}$: +15.2 ° (c 0.625, THF). ^1H NMR (DMSO-d_6): δ 1.27 (t, 3H, J = 7.0 Hz); 3.42 (s, 3H); 3.85−3.95 (m, 2H); 4.15−4.26 (m, 3H); 4.69 (d, 1H, J = 8.4 Hz); 5.62 (s, 1H); 5.80 (s, 1H); 6.89 (d, 1H, J = 2.8 Hz); 7.36−7.47 (m, 5H); 11.99 (bs, 1H). ^{13}C NMR: δ 14.7, 55.9, 60.2 (CH_2), 64.6, 68.9 (CH_2), 74.6, 96.6, 101.3, 118.0, 118.5, 119.8, 124.2, 126.8, 128.5, 129.3, 138.2. 160.3. HRMS (ES^+), m/z calcd. for $(M + Na)^+$ $C_{19}H_{21}NO_6Na$: 382.1267. Found: 382.1269.

Ethyl (2*R*,4a*R*,6*S*,9b*S*)-6-Methoxy-2-phenyl-4a,6,8,9b-tetrahydro-4*H*-[1,3]dioxino[4′,5′:5,6]pyrano[3,4-c]pyrrole-9-carboxylate 23. Following the general procedure, compound **2** (0.2 g, 0.5 mmol) was converted to yield compound **23**. (Yield: 0.135 g, 78%). White solid. Mp: 137−139 °C. $[\alpha]_D^{28}$: +54.1 ° (c 0.625, THF). ^1H NMR (DMSO-d_6): δ 1.02 (t, 3H, J = 7.0 Hz); 3.38 (s, 3H); 3.79−3.85 (m, 1H); 3.92−3.98 (m, 1H); 4.06−4.12 (m, 2H); 4.23−4.27 (m, 1H); 4.81 (d, 1H, J = 8.8 Hz); 5.05 (s, 1H); 5.82 (s, 1H); 6.94 (d, 1H, J = 2.8 Hz); 7.34−7.37 (m, 3H); 7.46−7.47 (m, 2H); 11.94 (bs, 1H). ^{13}C NMR: δ 14.4, 55.1, 60.1 (CH_2), 64.9, 68.8 (CH_2), 75.0, 96.0, 101.2, 118.0, 120.6 (2 × C), 122.8, 126.6, 128.3, 129.1, 138.5. 160.6. HRMS (ES^+), m/z calcd. for $(M + Na)^+$ $C_{19}H_{21}NO_6Na$: 382.1267. Found: 382.1259.

Ethyl (4*S*,6*S*,7*R*)-7-(Benzyloxy)-6-methoxy-4-(triphenylmethyloxymethyl)-2,4,6,7-tetrahydropyrano[3,4-c]pyrrole-1-carboxylate 24. Following the general procedure, compound **3** (0.4 g, 1.03 mmol) was converted to yield compound **24** (Yield: 0.32 g, 90%). Colorless jelly. $[\alpha]_D^{28}$: +39.8 ° (c 0.32, THF). ^1H NMR (DMSO-d_6): δ 1.16−1.20 (m, 3H); 3.14−3.17 (m, 1H); 3.24−3.29 (m, 1H); 3.38 (s, 3H); 4.13−4.23 (m, 2H); 4.55−4.63 (m, 1H); 4.71−4.78 (m, 3H); 4.87−4.93 (m, 1H); 6.61 (s, 1H,); 7.22−7.39 (m, 20H); 11.83 (bs, 1H). ^{13}C NMR: δ 14.7, 56.4, 60.1 (CH_2), 66.1 (CH_2), 69.8, 72.3 (CH_2), 86.6, 98.9, 117.5, 119.1, 120.0, 123.6, 127.4, 127.5, 127.6, 128.3, 128.6, 139.8, 144.1, 160.8. HRMS (ES^+), m/z calcd. for $(M + Na)^+$ $C_{38}H_{37}NO_6Na$: 626.2519. Found: 626.2512.

Ethyl (4*R*,6*S*,7*R*)-7-(Benzyloxy)-6-methoxy-4-methyl-2,4,6,7-tetrahydropyrano[3,4-c]pyrrole-1-carboxylate 25. Following the general procedure, compound **4** (0.4 g, 1.03 mmol) was converted to yield compound **25** (Yield: 0.32 g, 89%). Colorless jelly. $[\alpha]_D^{28}$: +39.8 ° (0.32, THF). ^1H NMR (DMSO-d_6): δ 1.20 (t, 3H, J = 7.0 Hz); 1.35 (d, 3H, J = 6.4 Hz); 3.39 (s, 3H); 4.11−4.26 (m, 2H); 4.62−4.84 (m, 4H); 4.92−4.97 (m, 1H); 6.79 (d, 1H, J = 2.8 Hz); 7.21−7.29 (m, 5H); 11.82 (bs, 1H). ^{13}C NMR: δ 14.7, 21.8, 56.0, 60.0 (CH_2), 65.6, 70.6, 72.1 (CH_2), 97.9, 117.3, 118.8, 122.8, 125.1, 127.4, 127.4, 128.3, 139.9. 160.8. HRMS (ES^+), m/z calcd. for $(M + Na)^+$ $C_{19}H_{23}NO_5Na$: 368.1474. Found: 368.1479.

Ethyl (4*S*,6*R*,7*S*)-7-Benzyloxy-6-(benzyloxymethyl)-4-methoxy-2,4,6,7-tetrahydropyrano[3,4-c]pyrrole-3-carboxylate 26. Following the general procedure, compound **5** (0.2 g, 0.40 mmol) was converted to yield compound **26** (Yield: 0.148 g, 81%). Colorless jelly. $[\alpha]_D^{28}$: +34.2 ° (c 0.325, THF). ^1H NMR ($CDCl_3$): δ 1.31−1.37 (m, 3H); 3.59 (s, 3H); 3.88 (d, 2H, J = 10.0 Hz); 4.26−4.36 (m, 3H); 4.55−4.61 (m, 3H); 4.71−4.80 (m, 2H); 5.79 (s, 1H); 6.64 (d, 1H, J = 2.0 Hz); 7.27−7.41 (m, 10H); 9.58 (bs, 1H). ^{13}C NMR: δ 14.4, 55.8, 60.5 (CH_2), 69.1 (CH_2), 69.3, 69.9, 71.2 (CH_2), 73.4 (CH_2), 95.7, 117.9, 118.9, 121.9, 125.2, 127.6), 127.7 (2 × C), 127.8, 128.3, 128.4, 138.2, 138.4, 160.7. HRMS (ES^+), m/z calcd. for $(M + Na)^+$ $C_{26}H_{29}NO_6Na$: 474.1893. Found: 474.1893.

Ethyl 4-[(*S*)-1,4-Dioxaspiro[4.5]dec-2-yl(hydroxy)methyl]-3-formyl-1*H*-pyrrole-2-carboxylate 27. Following the general procedure, compound **6** (0.16 g, 0.40 mmol) was converted to yield compound **27** (Yield: 0.114 g, 82%). Colorless jelly. $[\alpha]_D^{28}$: +55.3 ° (c 0.725, THF). ^1H NMR (DMSO-d_6): δ 1.24 (t, 3H, J = 7.0 Hz); 1.27−1.56 (m, 10H); 3.51 (d, 1H, J = 9.6 Hz); 3.87−3.98 (m, 3H); 4.13−4.21 (m, 2H); 6.71 (s, 1H); 10.87 (s, 1H); 11.97 (bs, 1H). ^{13}C NMR: δ 14.6, 23.9 (CH_2), 24.1 (CH_2), 25.1 (CH_2), 34.9 (CH_2), 36.5 (CH_2), 60.1 (CH_2), 65.9, 66.1 (CH_2), 78.1 (CH_2), 120.4, 109.4, 114.6, 122.1, 130.2, 132.1, 159.9, 188.9. HRMS (ES^+), m/z calcd. for $(M + Na)^+$ $C_{17}H_{23}NO_6Na$: 360.1423. Found: 360.1419.

Ethyl 4-[(1*S*)-2-(Benzyloxy)-1-hydroxyethyl]-3-formyl-1*H*-pyrrole-2-carboxylate 28. Following the general procedure, compound **7** (0.10 g, 0.27 mmol) was converted to yield compound **28** (Yield: 0.74 g, 86%). Colorless jelly. $[\alpha]_D^{28}$: +68.6 ° (c 1.0, THF). ^1H NMR (DMSO-d_6): δ 1.30 (t, 3H, J = 7.0 Hz); 3.50−3.53 (m, 2H); 4.28−4.34 (m, 2H); 4.46−4.55 (m, 2H); 5.18−5.21 (m, 2H); 7.01 (d, 1H, J = 2.0 Hz); 7.24−7.33 (m, 5H); 10.39 (s, 1H); 12.48 (bs, 1H). ^{13}C NMR: δ 14.6, 61.3 (CH_2), 66.2, 72.3 (CH_2), 75.4 (CH_2), 122.1, 124.3, 127.0, 127.6, 127.8, 128.5, 129.1, 139.1, 159.9, 188.8. HRMS (ES^+), m/z calcd. for $(M + Na)^+$ $C_{17}H_{19}NO_5Na$: 340.1161. Found: 340.1166.

Ethyl 3-[(1*S*)-2-(Benzyloxy)-1-hydroxyethyl]-4-formyl-1*H*-pyrrole-2-carboxylate 29. Following the general procedure, compound **8** (0.15 g, 0.40 mmol) was converted to yield compound **29** (Yield: 0.116 g, 91%). Colorless jelly. $[\alpha]_D^{28}$: +43.8 ° (c 0.82, THF). ^1H NMR (DMSO-d_6): δ 1.26 (t, 3H, J = 7.0 Hz); 3.46−3.61 (m, 2H); 4.25 (q, 2H, J = 7.0 Hz); 4.47 (s, 2H); 5.57−5.65 (m, 2H); 7.18−7.34 (m, 5H); 7.73 (s, 1H); 9.96 (s, 1H); 12.53 (bs, 1H). ^{13}C NMR: δ 14.6, 60.8 (CH_2), 66.0, 72.3 (CH_2), 75.3 (CH_2), 120.4, 126.0, 127.5, 127.6, 128.5, 131.4, 133.3, 138.9, 160.8, 188.8 (CH). HRMS (ES^+), m/z calcd. for $(M + Na)^+$ $C_{17}H_{19}NO_5Na$: 340.1161. Found: 340.1163.

Ethyl 3-[(3a*R*,5*R*,6*S*,6a*R*)-6-Methoxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl]-1*H*-pyrrole-2-carboxylate 30. Following the general procedure, compound **9** (0.14 g, 0.32 mmol) was

converted to yield compound **30** (Yield: 0.91 g, 72%). Colorless jelly. $[\alpha]_D^{28}$: +34.5 ° (*c* 0.625, THF). ^{1}H NMR (DMSO-d_6): δ 1.17 (t, 3H, J = 7.0 Hz); 1.27 (s, 3H); 1.41 (s, 3H); 3.95 (d, 1H, J = 2.8 Hz); 4.07−4.15 (m, 3H); 4.33 (d, 1H, J = 12.4 Hz); 4.70 (d, 1H, J = 3.6 Hz); 5.61 (d, 1H, J = 2.8 Hz); 5.99 (d, 1H, J = 3.6 Hz); 6.28 (s, 1H); 6.94−6.96 (m, 3H); 7.19−7.21 (m, 3H); 11.74 (bs, 1H). ^{13}C NMR: δ 14.5, 26.5, 26.9, 59.9 (CH_2), 71.0 (CH_2), 76.6, 82.0 (CH), 83.1, 104.3, 110.8, 111.1,117.9, 123.1, 126.5, 127.6,127.7, 128.4, 138.3. 160.7. HRMS (ES^+), *m*/*z* calcd. for (M + Na)$^+$ $C_{21}H_{25}NO_6Na$: 410.1580. Found: 410.1578.

Ethyl 4-[(3a*R*,5*R*,6*S*,6a*R*)-6-Methoxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl]-1*H*-pyrrole-2-carboxylate 31. Following the general procedure, compound **10** (0.248 g, 0.57 mmol) was converted to yield compound **31** (Yield: 0.18 g, 81%). White crystal. Mp: 87−89 °C (decomposed). $[\alpha]_D^{28}$: +39.3 ° (*c* 1.0, THF). ^{1}H NMR (DMSO-d_6): δ 1.23−1.26 (m, 6H); 1.43 (s, 3H); 3.81 (d, 1H, J = 2.4 Hz); 4.17−4.28 (m, 3H); 4.49 (d, 1H, J = 12.0 Hz); 4.75 (d, 1H, J = 3.6 Hz); 5.05 (d, 1H, J = 2.4 Hz); 5.90 (d, 1H, J = 3.6 Hz); 6.84 (s, 1H); 7.02 (s,1H); 7.13−7.15 (m, 2H); 7.25−7.27 (m, 3H); 11.78 (bs, 1H). ^{13}C NMR: δ 14.7 (CH_3), 55.9 (CH_3), 60.2 (CH_2), 64.6 (CH), 68.9 (CH_2), 74.6 (CH), 96.6 (CH), 101.3 (CH), 118.0 (CH), 118.5 (C), 119.8 (C), 124.2 (C), 126.8 (CH), 128.5 (CH), 129.3 (CH), 138.2 (C). 160.3 (C). HRMS (ES^+), *m*/*z* calcd. for (M + Na)$^+$ $C_{21}H_{25}NO_6Na$: 410.1580. Found: 410.1572.

Ethyl 3-[(1*R*)-1,2-Dimethoxyethyl]-1*H*-pyrrole-2-carboxylate 32. Following the general procedure, compound **11** (0.53 g, 1.25 mmol) was converted to yield compound **32** (Yield: 0.395 g, 83%). White solid. Mp: 144−145 °C. $[\alpha]_D^{28}$: +18.7 ° (*c* 0.725, THF). ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H, J = 7.0 Hz); 3.63−3.66 (m, 1H); 3.73−3.78 (m, 1H); 4.26 (q, 2H, J = 7.2 Hz); 4.47 (d, 1H, J = 12.0 Hz); 4.60−4.65 (m, 3H); 5.37−5.40 (m, 1H); 6.43−6.44 (m, 1H); 6.91−6.92 (m, 1H); 7.29−7.37 (m, 10H); 9.03 (bs, 1H). ^{13}C NMR: δ 14.4, 60.4 (CH_2), 70.8 (CH_2), 73.0 (CH_2), 73.8, 74.4 (CH_2), 109.8, 111.1,119.5, 122.7, 127.4 (2 × C), 127.6,127.8, 128.1, 128.3 (2 × C), 129.7, 138.7, 138.9, 160.4. HRMS (ES^+), *m*/*z* calcd. for (M + Na)$^+$ $C_{23}H_{25}NO_4Na$: 402.1681. Found: 402.1672.

Diethyl 3,3′-[(4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]bis(1*H*-pyrrole-2-carboxylate) 33. Following the general procedure, compound **12** (0.1 g, 0.21 mmol) was converted to yield compound **33** (Yield: 0.75 g, 92%). Colorless jelly. $[\alpha]_D^{28}$: +31.5 ° (*c* 0.625, THF). ^{1}H NMR (DMSO-d_6): δ 1.17 (t, 6H, J = 7.0 Hz); 1.45 (s, 6H); 3.96−4.05 (m, 2H); 4.07−4.15 (m, 2H); 5.51 (s, 2H); 6.31 (d, 2H, J = 2.4 Hz); 6.91 (d, 2H, J = 2.4 Hz); 11.74 (bs, 2H). ^{13}C NMR: δ 14.6, 27.7, 26.9, 59.8 (CH_2), 76.3, 107.7, 109.5, 120.1, 123.3, 126.6, 160.8. HRMS (ES^+), *m*/*z* calcd. for (M + Na)$^+$ $C_{19}H_{24}N_2O_6Na$: 399.1532. Found: 399.1530.

Ethyl 3-Formyl-4-[(2*R*,4*S*,5*R*)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl]-1*H*-pyrrole-2-carboxylate 34. To an ice cold solution of $POCl_3$ (0.02 mL, 0.21 mmol) in dry DMF (2 mL) was added a solution of compound **32** (0.051 g, 0.14 mmol) in dry DMF (2 mL). The reaction mixture was allowed to warm up to room temperature, and the reaction was continued for 1.5 h under stirring at N_2. The reaction mixture was poured slowly into cold satd. aq. $NaHCO_3$ solution (30 mL). The mixture was extracted with EtOAc (3 × 15 mL) and separated. The EtOAc layer was dried over anhyd. Na_2SO_4 and filtered, and the filtrate was evaporated under reduced pressure. The resulting syrup was purified over silica gel to yield **34** (0.034 g, 73%). Colorless jelly. $[\alpha]_D^{28}$: + 61.6 ° (*c* 0.375, THF). ^{1}H NMR (DMSO-d_6): δ 1.17 (t, 3H, J = 7.0 Hz); 3.58−3.64 (m, 1H); 3.85−3.88 (m, 1H); 4.17−4.20 (m, 1H); 4.21−4.29 (m, 2H); 5.10 (d, 1H, J = 5.6 Hz); 5.52 (d, 1H, J = 9.2 Hz); 5.63 (s, 1H); 7.33−7.43 (m, 5H); 7.62 (d, 1H, J = 3.2 Hz); 10.12 (s, 1H); 12.53 (bs, 1H). ^{13}C NMR: δ 14.6, 60.7 (CH_2), 66.7, 72.1 (CH_2), 77.4, 101.4, 122.4, 125.5, 126.7, 128.2, 128.5, 129.0, 129.2, 138.6, 160.7, 187.0. HRMS (ES^+), *m*/*z* calcd. for (M + Na)$^+$ $C_{18}H_{19}NO_6Na$: 368.1110. Found: 368.1119.

Ethyl 4-Formyl-3-[(2*R*,4*S*,5*R*)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl]-1*H*-pyrrole-2-carboxylate 35. Compound **33** (0.051 g, 0.14 mmol) was converted to **35** (0.035 g, 73%, colorless jelly) following the procedure described for the synthesis of **34**. $[\alpha]_D^{28}$: +59.3 ° (*c* 0.62, THF). ^{1}H NMR (DMSO-d_6): δ 1.17 (t, 3H, J = 7.0 Hz); 3.57−3.62 (m, 1H); 3.78−3.84 (m, 1H); 4.14−4.18 (m, 1H); 4.30−4.35 (m, 2H); 5.05−5.11 (m, 2H); 5.59 (s, 1H); 7.21 (s, 1H); 7.30−7.38 (m, 5H); 10.46 (s, 1H); 12.58 (bs, 1H). ^{13}C NMR: δ 14.6, 61.3 (CH_2), 65.2, 71.8 (CH_2), 76.5, 100.8, 123.3, 124.0, 126.1, 126.5, 127.0, 128.3, 128.9, 138.6, 160.0, 188.5. HRMS (ES^+), *m*/*z* calcd. for (M + Na)$^+$ $C_{18}H_{19}NO_6Na$: 368.1110. Found: 368.1115.

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Supporting Information Available: Experimental procedures, full spectroscopic data of selected compounds,and CIF files of **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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