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Asymmetric oxidopyrylium-alkene [5+2] cycloaddition: a divergent approach for the synthesis of enantiopure oxabicyclo[5.4.0]undecanes☆,☆☆

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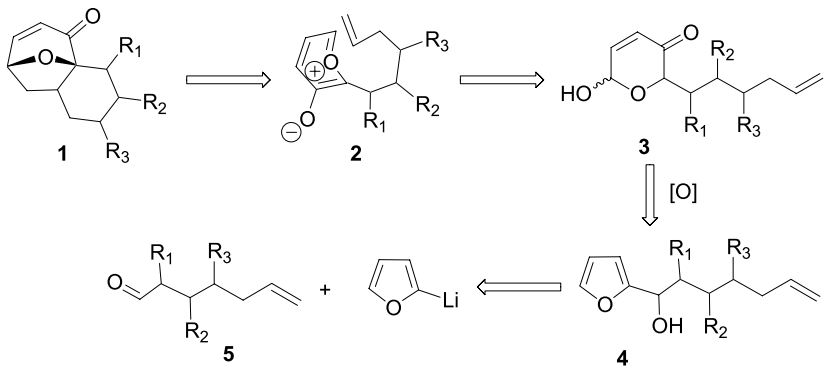
Abstract—A Chiron approach to the synthesis of enantiomeric oxabicyclic adducts **16** and **32** has been developed employing an intramolecular [5+2] cycloaddition of 3-oxidopyrylium with unsaturated sugars.

1. Introduction

3-Oxidopyrylium-alkene [5+2] cycloaddition provides an interesting and potentially versatile entry into highly functionalized oxabicyclo[3.2.1]octane frameworks from simple precursors. The rapid generation of molecular complexity in a relatively easy manner, has made this approach a highly useful tool in the synthesis of seven-membered ring containing complex natural products. Notably, Wender and coworkers have successfully applied this strategy, in an intramolecular fashion, to the total synthesis of natural products phorbol and resiniferatoxin.[1,2] However, compared to other cycloaddition strategies, one of the most important aspects that have received relatively little attention in an efficient [5+2] annulation method, is the asymmetric version of the cycloaddition reaction, despite numerous applications of this class of reactions in organic synthesis. Taking into account the various approaches reported in the literature in this context,[3] we embarked on the development of novel routes to access chiral oxabicyclo adducts. We wish to report here a chiral pool approach for the asymmetric synthesis of oxabicyclic adducts. We demonstrate that the reactions of optically active unsaturated aldehydes derivable from the appropriate sugar derivatives, with 2-lithiofuran provides useful 2-furyl-carbinol intermediates and suitable manipulations of these systems lead to a convenient and flexible route to the asymmetric synthesis of oxabicyclo[m.n.0]adducts. We also



Scheme 1.

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Keywords: D-Ribose; 3-Oxidopyrylium; Asymmetric synthesis; [5+2] Cycloaddition.
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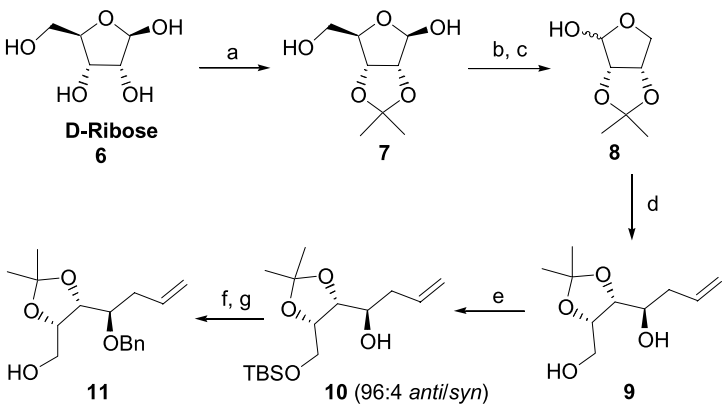


Scheme 2. (a) Me_2CO, H_2SO_4 (cat); (b) $NaBH_4$, MeOH, 2 h; (c) $NaIO_4$, H_2O, 84% (3 steps); (d) allylMgBr, −78 °C; (e) TBDMSCl, imidazole, THF, 72% (2 steps); (f) NaH, BnBr, THF, 0 °C; (g) Bu_4NF, THF, rt, 2 h.

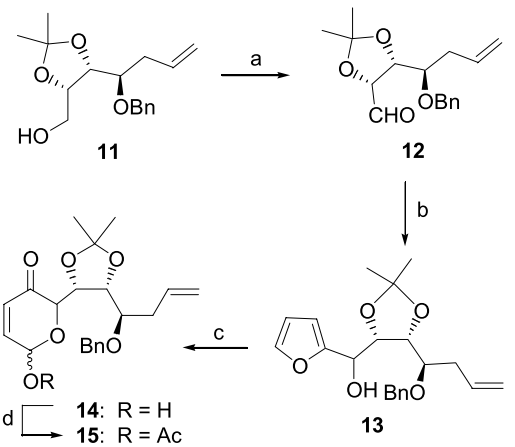
demonstrate that exploitation of the *pseudo*-symmetry of chosen sugar starting material, leads to the synthesis of the enantiomeric partners of the oxabicyclic adducts.[4]

2. Results and discussion

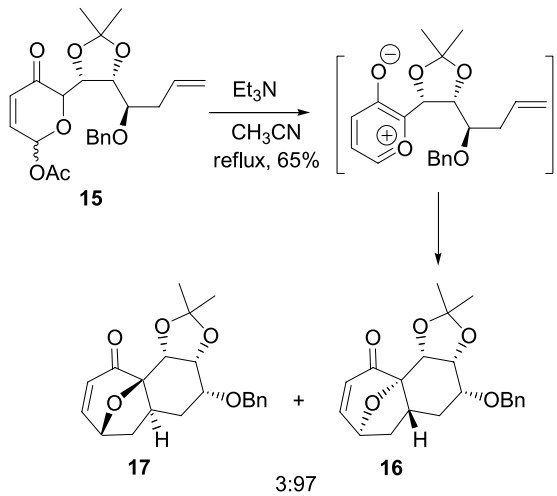
We devised a strategy with an expectation of preparing the optically active oxabicyclo[5.4.0]undecanes. Our approach involves the synthesis of cycloadduct of general type **1** by intramolecular cycloaddition of the 3-oxidopyrylium **2** with the tethered olefin. The pyrylium species **2** could be obtained from the acetoxypyranone **3**, which in turn could be obtained from the 2-furylcarbinol **4**, with requisite stereogenic centers within the tether joining the reacting partners. The synthesis of furylcarbinol (**4**) could be possible by the reaction of 2-lithiofuran with the unsaturated aldehyde **5** (Scheme 1).

The importance of carbohydrates as versatile sources of chiral information in the asymmetric synthesis of various complex organic molecules is well recognized.[5] Our initial efforts were focused on the synthesis of optically active unsaturated aldehydes from the appropriate sugar starting material. After scrutinizing various cheap and commercially available carbohydrates, we chose ribose for our purpose. Isopropylidenation of D-ribose **6** with acetone in the presence of catalytic amount of sulfuric acid gave 2,3-*O*-isopropylidene-D-ribose **7**. Compound **7** on reduction with sodium borohydride afforded the triol, which on oxidative cleavage with sodium periodate ($NaIO_4$) gave 2,3-*O*-isopropylidene-L-erythrose **8** in 84% yield from **7** (Scheme 2).[6] Grignard reaction of compound **8**, using allylmagnesium bromide at −78 °C, afforded the diol **9**. Selective monoprotection of primary alcohol (TBDMSCl/imid.) in **9** provided the compound **10** in 72% yield over 2 steps. The diastereomers (96:4, *anti*/*syn*) were separated by column chromatography and the major isomer was carried forward. The secondary hydroxyl group in **10** was protected as benzyl ether using BnBr/NaH in THF/DMF (4:1) and removal of the TBS group using tetrabutylammonium fluoride (TBAF) afforded the aldehyde precursor **11**.

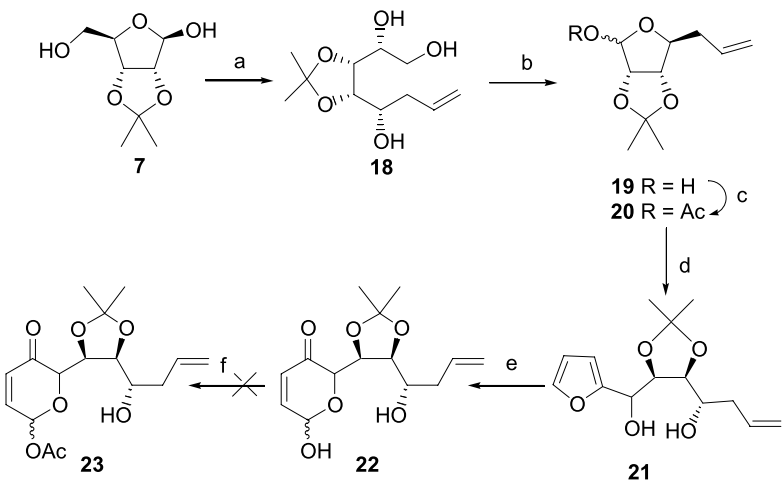
Swern oxidation of alcohol **11** furnished the corresponding aldehyde **12**. Addition of 2-lithiofuran (generated in situ by treating furan with *n*-BuLi at 0 °C) to aldehyde **12** at −78 °C afforded the furylcarbinol **13** (Scheme 3). Oxidative rearrangement of **13** using $VO(acac)_2$/*t*-BuOOH[7] in CH_2Cl_2 gave the hydroxypyranone **14** and acetylation of the anomeric hydroxyl gave the acetoxypyranone **15** in 88% yield from **13**. Oxidopyrylyum-alkene cycloaddition occurred upon treatment of the acetoxypyranone (**15**) with Et_3N (4 equiv.) in CH_3CN under reflux, affording the



Scheme 3. (a) $(COCl)_2$, DMSO, Et_3N, −78 °C; (b) *n*-BuLi, furan, THF, −78 °C, 70%; (c) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2; (d) Ac_2O, pyridine, DMAP, CH_2Cl_2, 88% (2 steps).



Scheme 4.

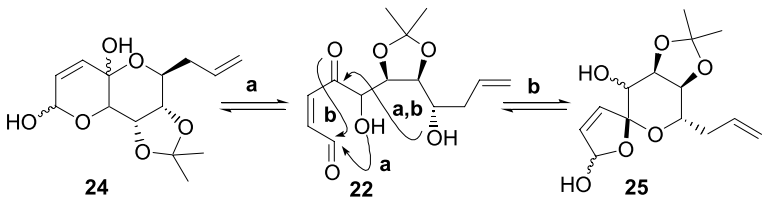


Scheme 5. (a) Diallylzinc, Et_2O, 0 °C, 5 h; (b) $NaIO_4$, water, 85% (2 steps); (c) Ac_2O, pyridine, CH_2Cl_2, 0 °C, 92%; (d) *n*-BuLi, furan, THF, −78 °C, 85%; (e) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, rt, 3.5 h; (f) Ac_2O, pyridine, CH_2Cl_2.

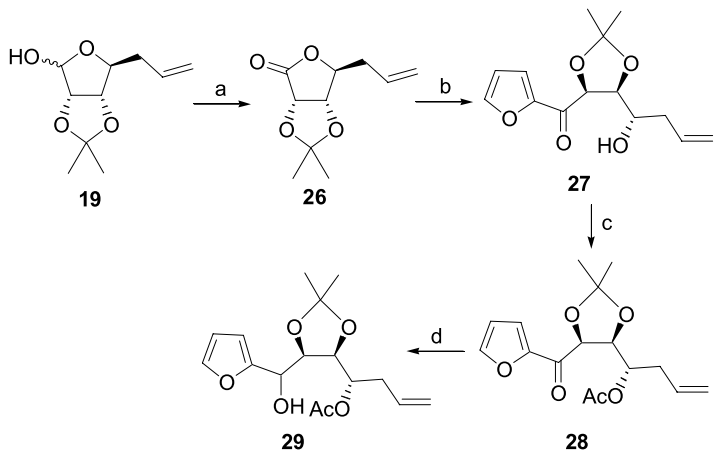
cycloadducts **16** and **17** as an inseparable mixture of diastereomers (93:7, ^{1}H NMR) in 65% yield (Scheme 4). The observed diastereoselectivity of the reaction is in accordance with that reported, which is attributed to the stereogenic center present on the tether, next to the pyrylium moiety.[1b,e,3d]

In order to synthesize other stereo-analogous [5+2] cycloadducts, we decided to exploit the *pseudo*-symmetry of ribose. It was envisioned that the introduction of the furyl unit on the lactol **19** (Scheme 5) would provide us an intermediate which facilitates the reversal of the sense of the asymmetric induction as compared to our previous intramolecular cycloaddition. Accordingly 2,3-*O*-isopropylidine-D-ribose **7** was transformed to the lactol **19** by addition of diallylzinc to **7** (diastereoselectivity 96:4 *anti*/*syn*), followed by sodium periodate cleavage of the resultant triol **18**.[8] Addition of 2-lithiofuran to the lactol **19** yielded the furylcarbinol **21**, which was then oxidatively rearranged to the hydroxypyranone **22**. However, our attempts to transform the pyranone **22** to the corresponding pyrylium ylide precursor (acetoxypyranone) (**23**), were unsuccessful. The reaction resulted in the formation of a complex mixture, which is presumably due to existence of the hydroxypyranone in the form of hemiketals (**24**) and/or spiroketals (**25**) (Scheme 6).[9]

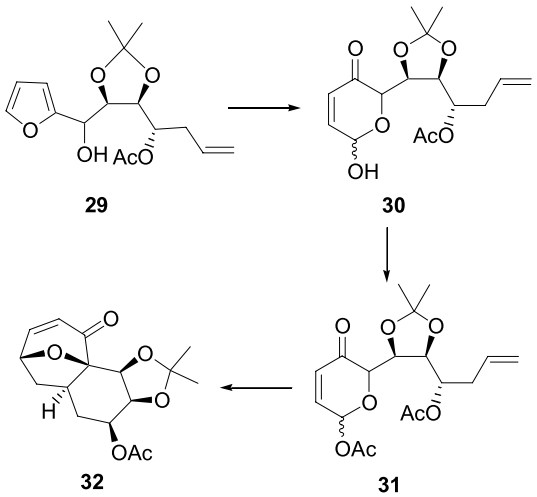
In the light of these results we have modified our synthetic strategy, which is outlined in Scheme 7. The lactol **19** was oxidized to the lactone **26** by Swern oxidation conditions.



Scheme 6.



Scheme 7. (a) $(COCl)_2$, DMSO, Et_3N, −78 °C, 90%; (b) *n*-BuLi, furan, THF, −78 °C, 6 h, 75%; (c) AcCl, pyridine, CH_2Cl_2, 0 °C-rt, 96%; (d) $NaBH_4$, MeOH, 0 °C, 93%.



Scheme 8. (a) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2; (b) Ac_2O, pyridine, DMAP, 0 °C; (c) Et_3N, CH_3CN, reflux, 83%.

Reaction of 2-lithiofuran on lactone **26** at −78 °C for 6 h afforded the monoaddition product **27** in 75% yield. The hydroxyl group in **27** was protected as acetate (AcCl/py), and the keto group was reduced with sodium borohydride to give compound **29** in 89% yield. Oxidative ring expansion of **29** using $VO(acac)_2$/*t*-BuOOH generated the pyranone **30** (Scheme 8). The pyranone **30** was transformed to the acetoxypyranone **31**, which upon treatment with Et_3N in CH_3CN under reflux conditions smoothly underwent highly diastereoselective cycloaddition to yield the cycloadduct **32** (83% yield) and the stereochemistry was unambiguously established by single-crystal X-ray analysis (Fig. 1).

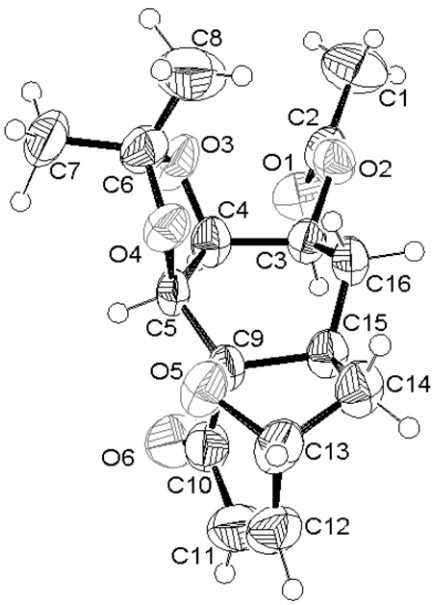


Figure 1. ORTEP drawing of the X-ray structure of **32**.

3. Conclusion

In summary, the synthesis of optically active oxabicyclo-[5.4.0]undecanes have been accomplished using D-ribose as a Chiron for asymmetric induction. We have observed that the cycloadducts **16** and **32** are *pseudo* enantiomers, having variation in the hydroxyl protection groups

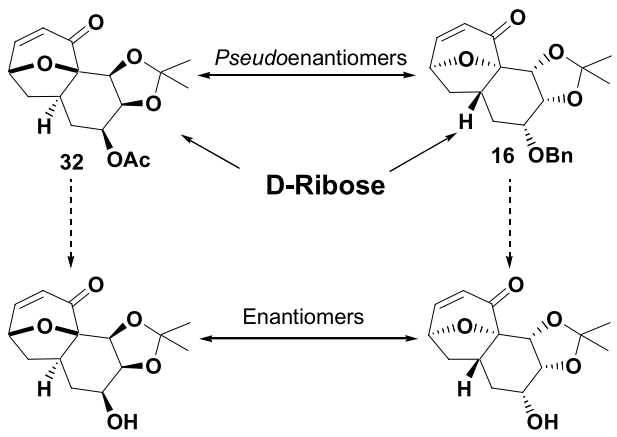


Figure 2.

(OBn, OAc), with diverse functionality around the ring (Fig. 2).

The presence of enone groups in the cycloadducts would permit introduction of other functional groups in stereocontrolled fashion by virtue of their rigid molecular architecture. It seems reasonable to believe that by choosing an appropriate sugar and its suitable manipulations the methodology might find applicability in the synthesis of various important natural products.

4. Experimental

4.1. X-ray diffraction data of 32

Crystals of **32** were obtained by slow evaporation of a solution of **32** in a mixture of petroleum ether and ethyl acetate at room temperature.

Chemical formula: $C_{16}H_{20}O_6$; formula weight: 308.32; crystal system: monoclinic; unit cell dimensions and volume with estimated standard deviations: a: 9.5590(6) Å; b=8.8780(9) Å; c=10.2790(7) Å; α: 90°; β: 114.082(5)°; γ: 90°; volume: 796.40(11) Å^3; temperature 293(2) K; space group $P2_1$; number of molecules in the unit cell (Z): 2; wavelength of radiation (λ): 0.70930 Å; linear absorption coefficient (μ): 0.098 mm^{-1}; number of reflections measured: 1311; number of independent reflections: 1311 [R_{int}=0.0000]; final R indices [$I>2\sigma(I)$]: $R1$=0.0404, $wR2$=0.0880. Crystallographic data (excluding structure factors) for the structure **32** in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC-212708. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.2. Materials and general experimental procedures

The following general procedures were used in all reactions unless otherwise noted. Oxygen- and moisture-sensitive reactions were carried out in flame-dried glassware sealed with a rubber septum under a positive pressure of dry nitrogen or argon. Sensitive liquids and solutions were transferred by syringe or cannula through rubber septa

through which a positive pressure of nitrogen was maintained. THF and Et_2O were distilled from sodium-benzophenone ketyl under nitrogen. Methylene chloride, acetonitrile and triethylamine were distilled from calcium hydride. Pyridine was refluxed over KOH pellets and distilled. Melting points were determined with a veego apparatus of Buchi type and are uncorrected. NMR spectra were measured in a Fourier transform mode on a Varian mercury-400 (^{1}H at 400 MHz, ^{13}C at 100 MHz), and Varian VXR-300s (^{1}H at 300 MHz, ^{13}C at 75 MHz) magnetic resonance spectrometer. Infrared spectra were recorded on a Nicolet Impact 400 and Thermo Nicolet Avatar 320 series Fourier transform spectrometer (FTIR) and are reported in wavenumbers (cm^{-1}). Optical rotations were determined with a JASCO DIP-370 digital polarimeter at ambient temperature.

4.2.1. 1-(5-Hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-but-3-en-1-ol (9). A dry, 100 ml, three-necked, round-bottomed flask is charged with excess of Mg (1.8 g, 0.075 g-atom) and 40 ml anhydrous Et_2O. To the stirred mixture was added dropwise a solution of allyl bromide (7.4 g, 5.3 ml, 61 mmol) in 61 ml of Et_2O at such a rate to maintain gentle reflux. After the addition is over the mixture was refluxed for 30 min. To this a solution of **8** (0.974 g, 6.1 mmol) in ether (20 ml) at −78 °C was added dropwise. The resulting mixture was stirred for 1 h at −78 °C and then allowed to warm to room temperature over 4 h. The reaction mixture was quenched by adding cold saturated NH_4Cl (100 ml) and extracted with ethyl acetate. The organic phase was washed with brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure. The crude mixture can be used directly in the next step.

$[\alpha]_D^{25}$=+51.7 (*c* 0.6, $CHCl_3$). IR (neat) ν_{max} 3422, 1645 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.89–5.82 (m, 1H), 5.22–5.18 (m, 2H), 4.34–4.30 (m, 1H), 4.0–3.96 (m, 1H), 3.89–3.76 (m, 3H), 2.85 (br s, 1H), 2.61 (m, 2H), 2.20 (m, 1H), 1.41 (s, 3H), 1.35 (s, 3H).

HRMS (EI) calculated for $C_{10}H_{18}O_5$: 202.1205 (M^+), found 202.1205.

4.2.2. 1-[5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-but-3-en-1-ol (10). To the solution of the diol **9** (0.5 g, 2.5 mmol) in THF/DMF (3:1, 5 ml) at 0 °C was added TBDMSCl (0.45 g, 2.9 mmol) and imidazole (0.43 g, 6.25 mmol). After 1 h, the mixture was poured into ether and the ether layer was washed with water, saturated $NaHCO_3$, and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash chromatography afforded the diastereomers **10** (*anti*/*syn* 96:4) in 72% yield over 2 steps.

anti Isomer: $[\alpha]_D^{25}$=−8.3 (*c* 0.6, $CHCl_3$).

IR (neat) ν_{max} 3420, 1645 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.19–5.91 (m, 1H), 5.18–5.07 (m, 2H), 4.25–4.18 (m, 1H), 4.09–4.04 (m, 1H), 3.89–3.75 (m, 3H), 3.60–3.56 (m, 1H), 2.53–2.51 (m, 1H), 2.29–2.24 (m, 1H), 1.36 (s, 3H), 1.32 (s, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H).

HRMS (FAB) calculated for $C_{16}H_{32}O_4SiNa$: 339.1968 (MNa^+), found 339.1975.

syn Isomer: $[\alpha]_D^{25}$=+8.9 (*c* 0.56, $CHCl_3$).

IR (neat) ν_{max} 3420, 1645 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.92–5.83 (m, 1H), 5.18–5.10 (m, 2H), 4.18–4.13 (m, 1H), 4.09–4.06 (m, 1H), 3.95–3.86 (m, 2H), 3.76–3.71 (m, 1H), 2.87–2.86 (d, *J*=5.1 Hz, 1H), 2.37 (m, 2H), 1.48 (s, 3H), 1.37 (s, 3H), 0.90 (s, 9H), 0.10 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.0, 117.4, 108.1, 78.9, 77.3, 68.5, 61.9, 39.0, 27.4, 25.9, 25.2, 18.4, −5.3.

4.2.3. [5-(1-Benzyloxy-but-3-enyl)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-methanol (11). To a solution of *anti*-isomer **10** (0.3 g, 0.95 mmol) in THF (5 ml) at 0 °C was added NaH (60 mg, 60%) and benzyl bromide (0.2 ml) and the resulting mixture was stirred for 3 h. The reaction mixture was quenched by addition of saturated NH_4Cl and extracted with ether. The organic phase was washed with water, brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash chromatography afforded the product.

$[\alpha]_D^{25}$=−15.7(*c* 0.83, $CHCl_3$).

IR (neat) ν_{max} 3420, 1645 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38–7.30 (m, 5H), 5.98–5.94 (m, 1H), 5.20 (m, 2H), 4.65 (d, *J*=11.1 Hz, AB system, 1H), 4.44 (d, *J*=11.1 Hz, AB system, 1H) 4.23–4.12 (m, 2H), 3.90 (dd, *J*=3.6, 11 Hz, 1H), 3.79–3.68 (m, 2H), 2.63–2.40 (m, 2H), 1.46 (s, 3H), 1.35 (s, 3H), 0.95 (s, 9H), 0.89 (s, 6H).

To this compound in THF (13 ml) at 0 °C was added *n*-Bu_4NF (0.75 ml, 1 M in THF, 0.75 mmol). After being stirred for 2 h at room temperature, water (10 ml) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash chromatography afforded the desired product **11** (0.174 g, 63% in 2 steps).

$[\alpha]_D^{25}$=−41.3° (*c* 0.63, $CHCl_3$).

IR (neat) ν_{max} 3425, 1645 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34–7.30 (m, 5H), 6.0–5.89 (m, 1H), 5.23–5.14 (m, 2H), 4.71 (d, *J*=11 Hz, AB system, 1H), 4.45 (d, *J*=11 Hz, AB system, 1H), 4.30 (dd, *J*=6, 11.7 Hz 1H), 4.15 (dd, *J*=6, 8.7 Hz, 1H), 3.79 (m, 1H),

3.70 (br m, 2H), 2.65 (m, 1H), 2.51 (m, 2H), 1.45 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.3, 133.2, 128.7, 128.2, 118.3, 108.3, 77.5, 76.3, 71.3, 61.2, 34.2, 28.0, 25.5.

HRMS (FAB) calculated for $C_{17}H_{24}O_4Na$: 315.1573 (MNa^+), found 315.1567.

4.2.4. [5-(1-Benzyloxy-but-3-enyl)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-furan-2-yl-methanol (13). To a solution of oxalyl chloride (0.044 ml, 0.63 mmol) in CH_2Cl_2 (1 ml) at −78 °C was added dropwise a solution of DMSO (0.094 ml, 1.26 mmol) in CH_2Cl_2 (0.5 ml). After 5 min, a solution of the alcohol **11** (0.14 g, 0.48 mmol) in CH_2Cl_2 (1 ml) was added. Stirring was continued for 20 min at −78 °C and Et_3N (0.33 ml, 2.39 mmol) was added dropwise. The resulting mixture was slowly allowed to warm to room temperature and stirred for 1 h. Water (5 ml) was added, and the organic layer was separated and concentrated under reduced pressure. The residue was diluted with ether (50 ml) and washed with water, brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure to give the crude aldehyde **12** (0.139 g), which was immediately used in the next step without further purification.

In a different flask, a solution of furan (0.33 ml, 4.32 mmol, freshly distilled over KOH) in THF (2.86 ml) was added dropwise a solution of *n*-BuLi (0.7 ml, 15% in hexane, 2.3 mmol) at −78 °C. After stirring for 3 h at 0 °C under argon, the mixture was cooled to −78 °C and a solution of aldehyde **12** (0.139 mg, 0.479 mmol) in THF (1 ml) was added dropwise. The resulting mixture was stirred for 3 h before being quenched by addition of saturated NH_4Cl solution (5 ml). The organic layer was separated and the aqueous layer was extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash chromatography afforded the desired compound **13** (0.86 g, 70%) as yellow oil.

$[\alpha]_D^{25}=-97°$ (*c* 0.33, $CHCl_3$).

IR (neat) ν_{max} 3460, 1645 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35–7.25 (m, 6H), 6.30 (m, 2H), 5.94 (m, 1H), 5.2 (m, 2H), 4.92 (dd, *J*=7.6, 2.4 Hz, 1H), 4.67 (d, *J*=11.2 Hz, AB system, 1H), 4.5 (m, 1H), 4.40 (d, *J*=10.8 Hz, AB system, 1H), 4.26 (m, 1H), 4.06 (m, 1H), 2.92 (d, *J*=7.6 Hz, 1H), 2.67 (m, 1H), 2.5 (m, 1H), 1.54 (s, 3H), 1.37 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.9, 141.9, 137.8, 133.4, 128.8, 128.6, 128.5, 127.9, 127.8, 118.1, 110.3, 108.4, 106.9, 77.9, 77.5, 76.7, 71.1, 65.8, 34.6, 26.9, 24.7.

4.2.5. Synthesis of cycloadducts 16 and 17. To a solution of furylcarbinol **13** (0.48 g, 0.134 mmol) in dry CH_2Cl_2 (1 ml) at −20 °C was added *t*-BuOOH (0.03 ml) and $VO(acac)_2$ (1.69 mg, 0.008 mmol)) under argon atmosphere. The resulting dark solution was stirred at −20 °C for 1 h and then at room temperature for 3 h. The pale yellow solution was diluted with CH_2Cl_2, washed with water brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure (ν_{max} 3415, 1694, 1639 cm^{-1}). The resultant residue was taken in CH_2Cl_2 (2 ml) containing pyridine (0.06 ml) at 0 °C, and treated with acetic anhydride (0.24 ml) and 4-dimethylaminopyridine (DMAP) (catalytic). The resulting mixture was stirred for 1 h at 0 °C. CH_2Cl_2 was added and the organic layer was treated with 5% hydrochloric acid, saturated $NaHCO_3$, water and dried over Na_2SO_4. Evaporation of the solvent followed by flash column chromatography afforded the desired compound **15** in quantitative yield. This crude material was used as such in the next step.

IR (neat) ν_{max} 1749, 1701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33–7.25 (m, 5H), 6.90 (dd, *J*=10, 3.6 Hz, 1H), 6.58 (d, *J*=3.6 Hz, 1H), 6.22 (d, *J*=10 Hz, 1H), 5.72 (m, 1H), 5.15 (m, 2H), 4.88 (d, *J*=6.4 Hz, 1H), 4.74 (m, 2H), 4.35 (m, 2H), 4.0 (m, 1H), 2.76 (m, 1H), 2.45 (m, 1H), 2.1 (s, 3H), 1.32 (s, 3H), 1.25 (s, 3H).

To a solution of pyranone acetate **15** (0.38 g, 0.09 mmol) in CH_3CN (0.5 ml) was added Et_3N (0.005 ml) at room temperature. The reaction mixture was heated at reflux for 20 h. After being cooled to 25 °C, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography to afford the cycloadduct **16** and **17** as 93:7 inseparable mixtures of diastereomers in 65% yield.

$[\alpha]_D^{25}=+38.5°$ (*c* 0.91, $CHCl_3$). IR (neat) ν_{max} 1693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.4–7.2 (m, 5H), 7.2 (dd, *J*=9.6, 4.4 Hz, 1H), 5.9 (d, *J*=9.6 Hz, 1H), 5.0 (d, *J*=6.8 Hz, 1H), 4.9 (m, 1H), 4.70 (d, *J*=12 Hz, AB system, 1H), 4.59 (d, *J*=12.4 Hz, AB system, 1H), 4.65 (m, 1H), 3.40 (m, 1H), 1.9–1.7 (m, 5H), 1.4 (s, 3H), 1.3 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.0, 152.3, 138.0, 128.3, 127.6, 127.5, 125.5, 109.6, 84.1, 75.1, 72.9, 72.6, 70.6, 38.5, 35.5, 28.2, 26.3, 24.9.

HRMS (EI) calculated for $C_{21}H_{25}O_5$: 356.1624 (M^+), found 356.1628.

4.2.6. 6-Allyl-2,2-dimethyl-dihydro-furo[3,4-*d*][1,3]-dioxol-4-one (26). To a solution of oxalyl chloride (1.56 ml, 17.94 mmol) in CH_2Cl_2 (40 ml) at −78 °C was added dropwise a solution of DMSO (3.12 ml, 44.1 mmol) in CH_2Cl_2 (14 ml). (3.13 g, 15.63 mmol). After 5 min, a solution of the lactol **19**[8] in CH_2Cl_2 (24 ml) was added. Stirring was continued for 20 min at −78 °C and Et_3N (11.5 ml) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 1 h. Water (25 ml) was added, and the organic layer was separated and concentrated under reduced pressure. The residue was diluted with ether (50 ml) and washed with water, brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash chromatography afforded the lactone **26** (2.8 g, 90%) as oil.

$[\alpha]_D^{25}$=+52.5° (*c* 0.4, $CHCl_3$).

IR (neat) ν_{max} 3446, 1785, 1641 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 5.76–5.69 (m, 1H), 5.24 (m, 2H), 4.71 (d, *J*=6.1 Hz, 1H), 4.65 (t, *J*=6.1 Hz, 1H), 4.58 (d, *J*=6.1 Hz, 1H), 2.5 (m, 2H), 1.47 (s, 3H), 1.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 130.3, 120.8, 113.7, 81.9, 78.8, 74.9, 37.5, 26.9, 25.8.

HRMS (FAB) calculated for $C_{10}H_{14}NaO_4$: 199.0970 (MNa^+), found 199.0982.

4.2.7. Acetic acid 1-[5-(furan-2-carbonyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-but-3-enyl ester (28). To a solution of furan (0.29 ml, 3.795 mmol) in ether (8 ml) was added dropwise a solution of *n*-BuLi (1.25 ml, 15% in hexane) at −78 °C. After stirring for 3 h at 0 °C under argon, the mixture was cooled to −78 °C and a solution of lactone **26** (0.5 g, 2.53 mmol) in ether (10 ml) was added dropwise. The resulting mixture was stirred at −78 °C for 6 h before being quenched by addition of methanol (1 ml). After warming to room temperature the solution was extracted with ether. The organic phases were washed with NH_4Cl and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure to afford the furyl ketone **27** along with some amount of unreacted lactone **26**. This mixture was difficult to separate by column chromatography and hence it was carried through the next step.

To a solution of **26** (0.25 g, 0.94 mmol) in dry CH_2Cl_2 (4 ml) at 0 °C was added pyridine (0.27 ml, 3.29 mmol) and freshly distilled acetyl chloride (0.14 ml, 1.9 mmol). The resulting suspension was stirred at 0 °C for 1 h, then warmed to room temperature and stirred for a further 2 h. The reaction was diluted with CH_2Cl_2 and the organic layer was washed with saturated sodium bicarbonate solution, 5% hydrochloric acid, brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash chromatography afforded the desired product **28** in 72% over 2 steps.

$[\alpha]_D^{25}$=−23.4° (*c* 0.47, $CHCl_3$).

IR (neat) ν_{max} 1741, 1685 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ: 7.61 (d, *J*=1.5 Hz, 1H), 7.36 (d, *J*=3.9 Hz, 1H), 6.55 (dd, *J*=3.9, 1.5 Hz, 1H), 5.74–5.60 (m, 1H), 5.31 (d, *J*=6.9 Hz, 1H), 5.0 (m, 2H), 4.79 (m, 1H), 4.61 (m, 1H), 2.5 (m, 1H), 2.3 (m, 1H), 1.7 (s, 3H), 1.68 (s, 3H), 1.43 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 182.5, 168.9, 151.5, 146.7, 132.5, 118.5, 118.2, 112.5, 110.4, 78.7, 77.7, 70.7, 34.7, 27.2, 25.3, 20.5.

HRMS (FAB) calculated for $C_{16}H_{20}NaO_6$: 331.1158 (MNa^+), found 331.1172.

4.2.8. Acetic acid 1-[5-(furan-2-yl-hydroxy-methyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-but-3-enyl ester (29). To a solution of furyl ketone **28** (0.2 g, 0.65 mmol) in MeOH (3 ml) at 0 °C was added sodium borohydride (40 mg, 1.05 mmol). The reaction mixture was stirred at 0 °C for 1 h, and then quenched by addition of water and extracted with CH_2Cl_2. The organic phase was washed with brine and dried over Na_2SO_4, filtered and evaporated. Purification of the resultant residue by flash chromatography afforded the desired adduct **29** (0.193 g, 93%) as yellow oil.

$[\alpha]_D^{25}$=41.2° (*c* 0.34, $CHCl_3$).

IR (neat) ν_{max} 3466, 1737, 1641 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ: 7.41 (s, 1H), 6.34 (m, 2H), 5.98–5.74 (m, 1H), 5.27–5.07 (m, 3H), 4.7 (d, *J*=8.4 Hz, 1H), 4.5 (m, 1H), 4.43 (m, 1H), 2.5 (m, 1H), 2.3–2.2 (m, 2H), 2.1 (s, 3H), 1.4 (s, 3H), 1.3 (s, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ: 170.0, 153.8, 142.2, 132.8, 118.1, 110.2, 108.6, 107.9, 78.0, 76.9, 70.4, 65.7, 35.9, 27.6, 25.4, 21.2.

HRMS (FAB) calculated for $C_{16}H_{23}O_6$: 311.1494 (MH^+), found 311.1511.

4.2.9. Synthesis of cycloadduct 32. To a solution of furylmethanol **29** (0.1 g, 0.32 mmol) in dry CH_2Cl_2 (2.4 ml) at −20 °C was added *t*-BuOOH (0.074 ml) and $VO(acac)_2$ (2.69 mg, 0.012 mmol) under argon atmosphere. The resulting dark solution was stirred at −20 °C for 1 h and then at room temperature for 3 h. The pale yellow solution was diluted with CH_2Cl_2, washed with water brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure (ν_{max} 3453, 1738, 1702, 1641 cm^{-1}). The resultant residue was (0.135 g, 0.41 mmol) was taken in CH_2Cl_2 (2 ml) containing pyridine (0.07 ml, 0.85 mmol) at 0 °C, was treated with acetic anhydride (0.47 ml) and 4-dimethylaminopyridine (catalytic). The resulting mixture was stirred for 1 h at 0 °C. CH_2Cl_2 was added and the organic layer was treated with 5% hydrochloric acid, saturated $NaHCO_3$, water and dried over Na_2SO_4. Evaporation of the solvent followed by flash column chromatography afforded the desired compound **31** (ν_{max} 1738, 1699, 1647 cm^{-1}) which was carried to the next step without further purification.

To a solution of pyranone acetate **31** (0.1 g, 0.27 mmol) in CH_3CN (1.5 ml) was added Et_3N (0.05 ml) at room temperature. The reaction mixture was heated at reflux for 6 h. after being cooled to 25 °C, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography to afford the cycloadduct **32** (0.70 g, 83%).

$[\alpha]_D^{25}$=−183.3° (*c* 0.42, $CHCl_3$).

IR ($CHCl_3$) ν_{max} 1738, 1693 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 7.22 (dd, *J*=9.6, 4 Hz, 1H), 5.97 (d, *J*=9.6 Hz, 1H), 5.0 (m, *J*=6.4, 3.2 Hz, 1H), 4.93 (dd, *J*=4.8, 4 Hz, 1H), 4.64 (m, 2H), 2.20–1.87 (m, 5H), 2.1 (s, 3H), 1.56 (s, 3H), 1.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.3, 170.0, 151.9, 125.3, 109.6, 109.5, 83.7, 72.9, 72.8, 72.0, 70.6, 37.8, 35.3, 27.8, 26.2, 24.9, 21.0.

HRMS (EI) calculated for $C_{16}H_{20}O_6$: 308.1260 (M^+), found 308.1271.

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