Some routes to C2-alkoxymethyl hex-2-enopyranosides[1]

Gordon Wong and Bert Fraser-Reid[2]

Paul M. Gross Chemical Laboratory, Duke University, Durham, NC 27708, U.S.A.

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This paper is dedicated to Professors David B. MacLean and Ian Spenser

Gordon Wong and Bert Fraser-Reid. Can. J. Chem. **72**, 69 (1994).

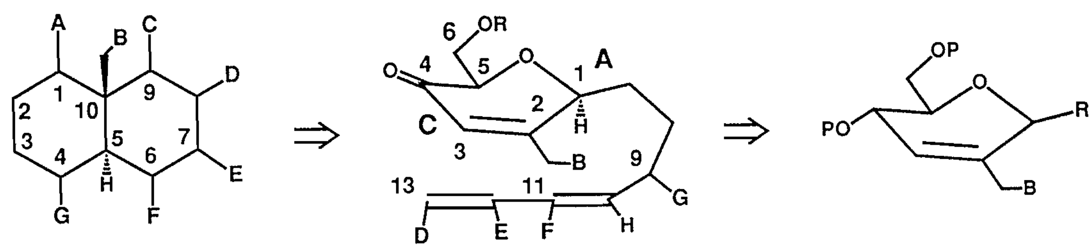
Several procedures for installing a C2 alkoxy group at C2 of a hex-2-enopyranoside have been investigated. The one that is most convenient for large-scale preparation begins with a 2-keto pyranoside, which is converted into the corresponding *exo* methylene derivative. An S_N2' rearrangement is effected with thionyl chloride, and the resulting primary allylic chloride is displaced with sodium benzylate.

Gordon Wong et Bert Fraser-Reid. Can. J. Chem. **72**, 69 (1994).

On a examiné diverses méthodes d'introduire un groupe alcoxyle en position C2 d'un hex-2-énopyranoside. Celle qui semble la plus appropriée pour des préparations sur une haute échelle fait appel à un 2-cétopyranoside qui est transformé en dérivé exométhylène correspondant. On effectue ensuite un réarrangement S_N2' à l'aide du chlorure de thionyle avant de déplacer le chlorure allylique primaire qui en résulte avec du benzylate de sodium.

[Traduit par la rédaction]

A recent report from our laboratory described a route to the *trans*-decalin core, symbolized by **1***a*, via an intramolecular Diels–Alder (IMDA) reaction of a hex-2-enopyranoside of type **2** (1). This approach to **1** seemed attractive since all of the functional groups represented by labels **A** → **G** could be installed in, or derived from, precursor **2** (1). The success of the early venture, with preparation of a key intermediate for forskolin (1), prompted us to explore more expeditious methods for obtaining **2**. Use of a normal hexose precursor would require attaching carbon substituents at C1 and C2 of the pyranose precursor. In the reported synthesis (1), the latter had proved to be more problematic, and we therefore examined alternative methods. In doing so we have been mindful that in many naturally occurring terpenes the angular C19 methyl group, which corresponds to the C2 substituent of **2**, is functionalized (3) and hence provisions for this possibility ought to be made. The alkoxymethyl analog **2***b* was conceived as a valuable synthon. Its precursor would be alkene **3***b*. In this manuscript, we describe our efforts to prepare alkenes related to **3***b*.



1 — *a* B= H; *b* B= OR' — Terpenoid numbering

2 — *a* B= H; *b* B= OR' — Sugar numbering

3 — *a* B= H; *b* B= OR'

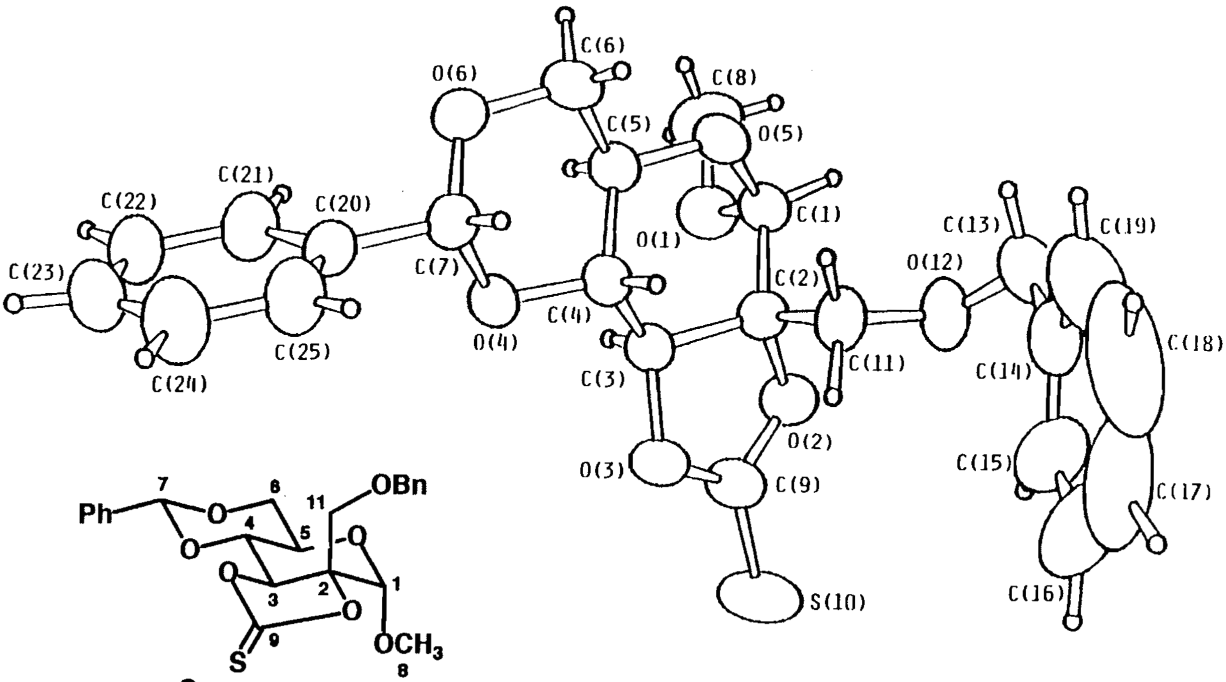
In our recent work (1), the Corey–Winter reductive elimination strategy (3) had proven to be the method of choice for the preparation of C2-CH_3 alkenes of type **3***a*. Accordingly, our initial approaches to the alkoxymethyl analog **3***b* were undertaken with this reaction in mind. A particularly encouraging feature of the prototype study was the fact that the Corey–Winter reaction had succeeded with both diastereomeric *cis*- and *trans*-diol precursors of **3***a* (1). In the light of this precedent, the known uloside **4***a* (4), seemed a plausible starting material whose reaction with an alkoxymethyl anion would provide the required C2-functionalized carbon.

Benzyloxymethyl magnesium chloride (5) was tested first, but problems were encountered with its preparation from commercially available benzyloxymethyl chloride and also with its lack of stability. The lithio analog, obtained most conveniently by treating benzyloxymethyl tributylstannane with butyllithium as described by Still (6) was successful, giving the expected adduct **5***a* along with substantial amounts of the product from silyl migration, both of which underwent desilylation without event to give **5***b* in 74% overall yield. A more direct route to **5***b* arose from addition of an excess of the benzyloxymethyllithium to the known 3-*O*-acetyl uloside **4***b* (7).

In contrast to the previously described (2) results for the C2-CH_3 analog **3***a*, treatment of **5***b* with thiocarbonyl diimidazole gave nearly equal amounts of the corresponding thionocarbonate **8** and its uncyclized precursor, which could be partially pro-

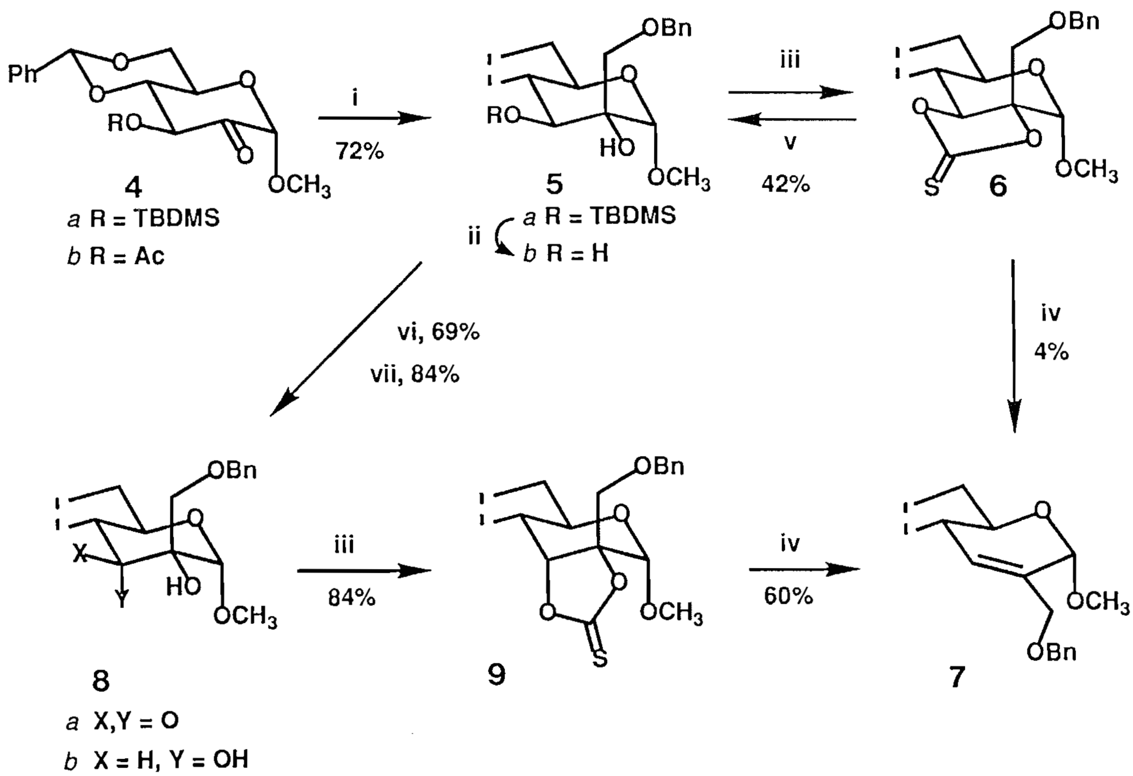
[1]This paper is dedicated to Professors Dave MacLean and Ian Spenser with grateful thanks for their many kindnesses and help when one of us (B.F.R) was at the then fledgling University of Waterloo.

[2]Author to whom correspondence may be addressed.



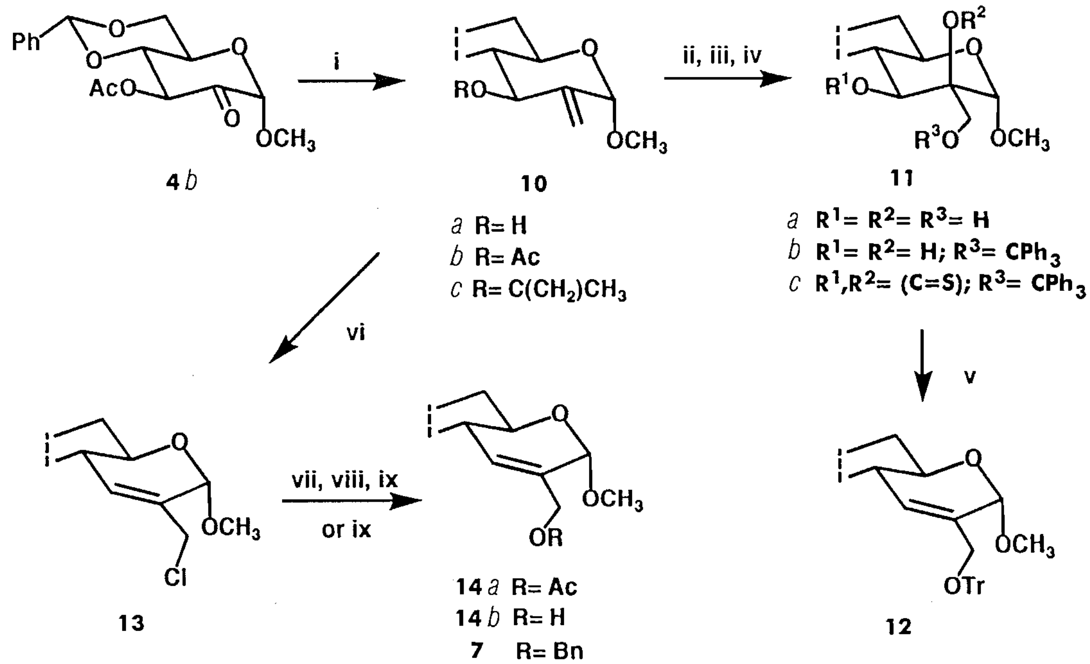
8

FIG. 1. ORTEP diagram (50% probability ellipsoids) showing the crystallographic atom numbering scheme and solid-state conformation of **8**. Small circles represent hydrogen atoms.



(i) Bu_3SnCH_2OBn, *n*BuLi, THF; (ii) TBAF,THF; (iii) $(im)_2C{=}S$, toluene; (iv) $P(OMe)_3$
(v) 1,3-dimethyl-2-phenyl-1,2-diazaphospholidene; (vi) Dess-Martin periodinane,CH_2Cl_2; (vii) $NaBH_4$, MeOH

SCHEME 1



(i) Cp_2TiCl_2 $AlMe_3$ gave **10***a* (75%), **10***b* (10%), **10***c* (5%); (ii) OsO_4, Et_4NOH, *t*-BuOOH, *t*-BuOH, THF, 30%; (iii) TrCl, DMAP, pyridine, 80%; (iv) NaH, CS_2, nBu_4NI CH_3I, 88%; (v) $P(OMe)_3$, 59%; (vi) $SOCl_2$, pyridine, THF; (vii) KOAc, HMPA, 51% from **10***b*; (viii) NaOMe, 64%; (ix) NaH, BnBr, THF, 81%; (x) NaOH, Bu_4NHSO_4, BnOH, CH_2Cl_2/water 19:1, ultrasound 4 days, 54% from **10***b*.

SCHEME 2

cessed to give **8** by prolonged treatment in toluene under reflux. The structure **8** was confirmed by the X-ray crystal structure shown in Fig. 1.[3]

By comparison with the corresponding C2-CH_3 analogue used earlier (2), the reaction of **8** was disappointing in that treatment with trimethylphosphite gave the desired alkene **10** in only 4% yield. Use of 1,3-dimethyl-2-phenyl-1,2-diazaphospholidene as recommended by Corey and Hopkins (8) was even more discouraging in that the only course of reaction with this reagent was regeneration of diol **5***b*.

There should be fewer problems with formation and reaction of this *cis*-fused thionocarbonate and hence the diol **5***b* was processed with this objective in mind. Oxidation to ketone **11***a* was best effected with the Dess–Martin reagent (9) and sodium borohydride reduction led to **11***b* without event. As expected, the thionocarbonate **12** was now obtained without complication, and reductive elimination to **10** proceeded in 60% yield. Thus although it involves one more step, the route via **12** was slightly higher yielding overall, and much easier operationally than that via **8**.

The results with **8** and **12** showed that the *cis*-fused thionocarbonate better underwent reductive elimination, in spite of the lack of preference that we had found in the earlier work (1). It was therefore of interest to see how the alternative *cis* analog (i.e., the *manno* counterpart) would fare. A C2-*exo* methylene derivative was seen as a plausible precursor since dihydroxylation should occur from the ß face.

Some deacetylation would be expected to accompany olefination of **4***b* with methylenetriphenylphosphorane, and hence an alternative route was examined. Tebbe's reagent (10) reacts with the carbonyl groups of ketones and esters, but the enol ether resulting from the latter would be readily hydrolysed. In the event, the best procedure turned out to be to treat **4***b* with 2.5 equivalents of Tebbe's reagent, which gave the allylic alcohol **10***a* as the major product and the corresponding acetate **10***b* as the minor. A third product, obtained in 4% yield, was assigned as the enol ether **10***c* since it decomposed to **10***a* on standing.

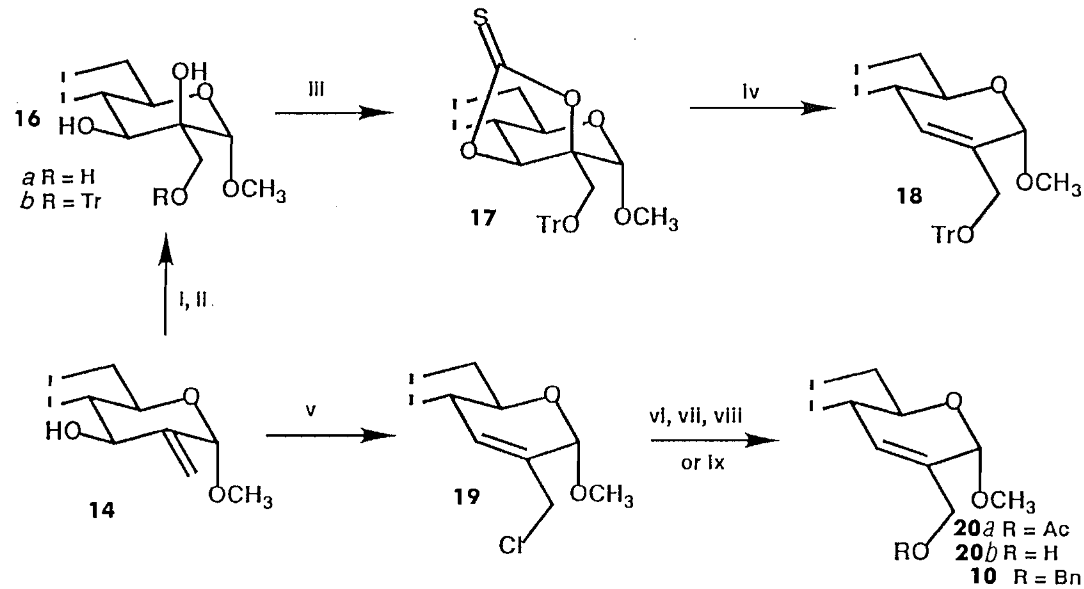
Dihydroxylation of **10***a* gave the triol **11***a*, which was processed to give the thionocarbonate **11***c*. Reductive elimination to **12** proceeded in virtually the same yield (59%) as had the diastereomer **9**.

The allylic alcohol **10***a* offered yet another alternative route to the desired alkene via S_N2' rearrangement. Indeed this was accomplished by treating **10***a* with thionyl chloride to give the 2-alkene **13**. Acetolysis then afforded **14***a* in 50% overall yield from **10***a*. Saponification to **14***b*, followed by benzylation, then gave the previously described alkene **7**. Alternatively, alkene **7** could be obtained directly from the chloride **13** in a yield of 54% by a process involving nucleophilic displacement with benzylate ion under phase transfer conditions (11).

In summary, four routes to the generalized hex-2-enopyranoside **3***b* have been examined: (*i*) **4***a* → **5** → **8** → **9** → **7**; (*ii*) **4***b* →

[3]Crystallographic data for **1** have been deposited and can be purchased from: The Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada.

The ORTEP diagram, crystallographic data, tables of H-atom coordinates and of bond lengths and angles for **1** have also been deposited with the Cambridge Crystallographic Data Centre, and can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, 12 Union Road, Cambridge, CB2 1EZ, U.K.



(i) OsO_4, Et_4NOH, *t*-BuOOH, *t*-BuOH, THF, 30%; (ii) TrCl, DMAP, pyridine, 80%; (iii) NaH, CS_2, *n*Bu_4NI CH_3I, 88%: (iv) $P(OMe)_3$, 59%; (v) $SOCl_2$, pyridine, THF; (vi) KOAc, HMPA, 51% from **13**; (vii) NaOMe, 64%; (viii) NaH, BnBr, THF, 81%; (ix) NaOH, Bu_4NHSO_4, BnOH, CH_2Cl_2/water 19:1, ultrasound 4 days, 54% from **13**.

SCHEME 3

10 → **11** → **12**; (*iii*) **4***b* → **13** → **14** → **7**; and (*iv*) **4***b* → **13** → **7**. The last is the most direct but, for large-scale preparations, the need for prolonged ultrasonication could present practical problems and, in such cases, route (*iii*) may be more attractive, particularly since the intermediates are crystalline. Routes (*i*) and (*ii*) are seen as second choices to (*iv*) and (*iii*), respectively.

Experimental

*Methyl 4,6-*O*-benzylidene-2-*C*-benzyloxymethyl-α,*D*-glucopyranoside* 5b, *and its 3-*O*-tert-butyldimethysilymethyl derivative* 5a

To (benzyloxymethyl)tributylstannane (7) (1.30 g, 3.16 mmol) and two crystals of 2,2-dipyridyl in dry THF (10 mL), cooled to −78°C under a stream of argon, was added *n*BuLi (1.35 mL, 2.06 M in hexane, 2.79 mmol) dropwise with stirring. The appearance of a red color indicated an excess of *n*BuLi; a few drops of the stannane were then added to dissipate the color. After stirring for 20 min, a cooled solution (−78°C) of ketone **4***a* (5) (714 mg, 1.81 mmol) in dry THF (10 mL) was added by cannula and stirring was continued for 1 h. The reaction was quenched by the addition of brine and diluted with ether, warmed to room temperature, and separated. The aqueous layer was extracted with ether (×2) and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. Flash chromatography (2–15% EtOAc –petroleum ether) gave **5***a* (674 mg, 72%) and the product of silyl migration (12%) as oils. For **5***a*: R_f 0.40 (20% EtOAc –petroleum ether); $[\alpha]_D^{20}$ +9.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.03, 0.06 (s, 6H, $(CH_3)_2Si$), 0.82 (s, 9H, $(CH_3)_3CSi$), 2.69 (s, 1H, OH), 3.44 (s, 3H, OCH_3), 3.45 (d, 1H, J = 9.6 Hz, C*H*′HOBn), 3.65–3.85 (m, 4H, H4, H5, H6a, O*H*′HOBn), 4.01 (d, 1H, $J_{3,4}$ = 9.5 Hz, H3), 4.26 (dd, 1H, $J_{5,6e}$ = 4.2 Hz, $J_{6a,6e}$ = 9.5 Hz, H6e), 4.59, 4.63 (d, 2H, J = 12.4 Hz, PhCH_2O), 4.90 (s, 1H, H1), 5.46 (s, 1H, PhC*H*), 7.30–7.50 (m, 10 H, aromatic). ^{13}C NMR δ: 18.4, 25.9 (TBDMS), 55.6 (q, OCH_3), 62.5 (d, C5), 69.0 (t, PhCH_2), 69.1 (t, C6), 73.8 (t, CH_2OCH_2Ph), 76.0 (s, C2), 80.7 (d, C4), 100.7 (d, C1), 101.7 (d, Ph*C*H), 126.1–137.9 (aromatic). MS *m/z*: 516 (M^+). Anal. calcd. for $C_{28}H_{40}O_7Si$: C 65.07, H 7.82; found: C 64.88, H 7.81.

*Methyl 4,6-*O*-benzylidene-2-*C*-benzyloxymethyl-α,*D*-glucopyranoside* 5b

(*a*) Compound **5***a* (292 mg, 0.57 mmol) in dry THF (35 mL) was stirred with tetra-*n*-butylammonium fluoride (0.68 mL, 1.0 M in THF, 0.68 mmol) overnight. Evaporation of the solvent and flash chromatography (20–70% EtOAc –petroleum ether) gave **5***b* (200 mg, 88%) as an oil: R_f 0.48 (70% EtOAc – petroleum ether); $[\alpha]_D^{20}$ +27.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.82, 2.97 (s, 2H, OH), 3.44 (s, 3H, OCH_3), 3.51 (t, $J_{3,4}$ = $J_{4,5}$ = 9.9 Hz, H4), 3.71, 3.87 (d, 2H, J = 10.0 Hz, CH_2OBn), 3.71 (t, 1H, $J_{5,6a}$ = $J_{6a,6e}$ = 9.9 Hz, H6a), 3.83 (td, 1H, $J_{5,6e}$ = 4.4 Hz, H5), 4.09 (d, 1H, H3), 4.25 (dd, 1H, H6e), 4.59, 4.62 (d, 2H, J = 12.0 Hz, PhCH_2), 4.80 (s, 1H, H1), 5.47 (s, 1H, Ph C*H*), 7.30–7.50 (m, 10H, aromatic). ^{13}C NMR δ: 55.8 (q, OCH_3), 62.8 (d, C5), 69.0 (t, C6), 69.4 (t, PhCH_2), 72.9 (d, C3), 74.0 (t, CH_2OBn), 75.5 (s, C2), 79.7 (d, C4), 100.5 (d, C1), 102.1 (d, Ph*C*H), 126.4–137.5 (aromatic). MS *m/z*: 402 (M^+). Anal. calcd. for $C_{22}H_{26}O_7$: C 65.65, H 6.52; found: C 65.43, H 6.54.

(*b*) Compound **6** (13 mg, 0.03 mmol) in 1,3-dimethyl-2-phenyl-1,3-diazaphospholidine (18 mg, 0.09 mmol) was stirred under a stream of argon at 40°C for 12 h. Flash chromatography (30–50% EtOAc – petroleum ether) gave diol **5***b* (5 mg, 42%).

*Methyl 4,6-*O*-benzylidene-2-*C*-benzyloxymethyl-2,3-*O*-thionocarbonyl-α,*D*-glucopyranoside* **6**

Diol **5***b* (98 mg, 0.24 mmol) and 1,1′-thiocarbonyldiimidazole (90 mg, 0.51 mmol) in toluene (4 mL) were heated to reflux under a stream of argon for 12 h. Evaporation of the solvent and flash chromatography (10–70% EtOAc – petroleum ether) gave **6** (57 mg, 53%) as a white solid and the uncyclized, C-3 imidazoyl-*N*-thionocarbonyl derivative (44%) as an oil. For **6**: R_f 0.29 (30% EtOAc – petroleum ether); $[\alpha]_D^{20}$ −9.6 (*c* 1.00, $CHCl_3$); mp 158°C (recrystallized from methylene chloride – petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$)δ 3.51 (s, 3H, OCH_3), 3.68–3.72 (m, 4 H, H4, H6a, CH_2OBn), 4.02–4.10 (m, 1H, H5), 4.21–4.30 (m, 1H, H6e), 4.57, 4.64 (d, 2H, J = 12.2 Hz, PhCH_2O), 5.06 (d, 1H, $J_{3,4}$ = 11.0 Hz, H3), 5.07 (s, 1H, H1), 5.50 (s, 1H, PhC*H*), 7.30–7.50 (m, 10H, aromatic). ^{13}C NMR δ: 56.4 (q, OCH_3), 66.4 (d, C5), 68.3 (t, PhCH_2), 69.0 (t, C6), 74.2 (t, CH_2OBn), 77.5 (d, C3), 79.8 (d, C4), 87.4 (s, C2), 98.5 (d, C1), 101.4 (d, Ph*C*H), 126.0–136.9 (aromatic), 190.2 (s, C=S). Structure confirmed by X-ray crystallography.

*Methyl 4,6-*O*-benzylidene-2-*C*-benzyloxymethyl-α,*D*-*erythro*-hex-2-enopyranoside* **7**

(*a*) Thionocarbonate **6** (32 mg, 0.07 mmol) was dissolved in trimethylphosphite (3 mL) and heated to reflux under a stream of argon for 12 h. Evaporation of the solvent and flash chromatography (0–20% EtOAc – petroleum ether) gave **7** (1 mg, 4%) as a white solid: R_f 0.56 (20% EtOAc – petroleum ether); $[\alpha]_D^{20}$ +84.7 (*c* 0.71, $CHCl_3$); mp 110°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.43 (s, 3H, OCH_3), 3.77–3.96 (m, 3H, H5, H6a, CH_2OBn), 4.10–4.22 (m, 2H, H4, CH_2OBn), 4.30 (dd, 1H, $J_{5,6e}$ = 3.0 Hz, $J_{6a,6e}$ = 8.9 Hz, H6e), 4.46, 4.55 (d, 2H, *J* = 12.0 Hz, PhCH_2O), 4.92 (s, 1H, H1), 5.57 (s, 1H, Ph*CH*), 6.09 (br s, 1H, H3), 7.30–7.50 (m, 10H, aromatic). ^{13}C NMR δ: 56.3 (q, OCH_3), 64.3 (d, C5), 69.5 (t, C6), 70.0 (t, PhCH_2), 72.5 (t, CH_2OBn), 75.5 (d, C4), 96.8 (d, C1), 102.3 (d, Ph*C*H), 129.2 (d, C3), 136.0 (s, C2), 126.3–137.4 (aromatic). Anal. calcd. for $C_{22}H_{24}O_5$: C 71.71, H 6.58; found: C 71.72, H 6.66.

(*b*) Compound **9** (20 mg, 0.05 mmol) was dissolved in trimethylphosphite (2 mL) and heated to reflux under a stream of argon for 18 h. The solvent was partially evaporated. Flash chromatography (5–15% EtOAc – petroleum ether) gave **7** (10 mg, 60%).

(*c*) Compound **14*b*** (28 mg, 0.10 mmol) in dry THF (2 mL) was stirred with NaH (7 mg, 60% dispersion in oil, 0.17 mmol) under a stream of argon for 2 h. Tetra-*n*-butylammonium iodide (catalytic amount) and benzyl bromide (0.02 mL, 24 mg, 0.14 mmol) were added and the reaction stirred overnight. The mixture was diluted with brine, extracted with ether (×3), and the combined extracts washed with brine (×2) and dried over Na_2SO_4. Flash chromatography (5–15% EtOAc – petroleum ether) gave **7** (30 mg, 81%).

(*d*) To allylic chloride **13** (synthesized as below from allylic alcohol **10*b*** (68 mg, 0.24 mmol)) in methylene chloride (3 mL) was added water (2 mL), benzyl alcohol (0.03 mL, 31 mg, 0.29 mmol), NaOH (60 mg, 1.5 mmol), and tetrabutylammonium hydrogen sulfate (98 mg, 0.29 mmol). The mixture was placed under a stream of argon and subjected to ultrasonication for 4 days. The mixture was diluted with CH_2Cl_2 and water then separated. The aqueous layer was extracted with CH_2Cl_2 (×2), and the combined extracts were washed with brine and dried over Na_2SO_4. Flash chromatography (5–15% EtOAc – petroleum ether) gave **7** (49 mg, 54% from **10*b***).

Methyl 4,6-O-benzylidene-2-C-benzyloxymethyl-2,3-thionocarbonyl-α,D-allopyranoside 9

To diol **5*b*** (62 mg, 0.15 mmol) in dry methylene chloride (3 mL) was added Dess–Martin periodinane (9) (140 mg, 0.33 mmol) and the reaction mixture was stirred overnight at room temperature under a stream of argon. Methylene chloride, saturated $NaHCO_3$, and $Na_2S_2O_3$ solutions were added and stirring was continued for 30 min. The layers were separated and the organic layer dried over Na_2SO_4. Flash chromatography (10–50% EtOAc – petroleum ether) gave **8*a*** (44 mg, 71%) as an oily solid: R_f 0.60 (70% EtOAc – petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.39 (s, 3H, OCH_3), 3.74 (t, 1H, $J_{5,6a}$ = $J_{6a,6e}$ = H6a), 3.74 (br s, 1H, OH), 3.75, 3.99 (d, 2H, *J* = 10.6 Hz, CH_2OBn), 3.97 (td, 1H, $J_{4,5}$ = 10.0 Hz, $J_{5,6e}$ = 4.6 Hz, H5), 4.19 (d, 1H, H4), 4.32 (dd, 1H, $J_{6a,6e}$ = 10.0 Hz, H6e), 4.43, 4.70 (d, 2H, *J* = 12.2 Hz, PhCH_2O), 4.73 (s, 1H, H1), 5.38 (s, 1H, Ph*CH*), 7.30–7.50 (m, 10H, aromatic). ^{13}C NMR δ: 55.9 (q, OCH_3), 66.0 (d, C5), 69.5 (t, C6), 72.8 (t, PhCH_2), 73.7 (t, CH_2OCH_2Ph), 81.3 (d, C4), 82.6 (s, C2), 102.0 (d, Ph*C*H), 103.8 (d, C1), 126.4–137.2 (aromatic), 198.4 (s, C3). Ketone **8*a*** (44 mg, 0.11 mmol) in methanol (2 mL) was stirred with sodium borohydride (2 mg, 0.05 mmol) under a stream of argon for 1 h. The reaction was quenched with a few drops of acetic acid and the solvent evaporated. The mixture was dissolved in ethyl acetate, washed with saturated $NaHCO_3$ solution (×2) and brine (×2), and dried over Na_2SO_4. Flash chromatography (30–70% EtOAc – petroleum ether) gave **8*b*** (39 mg, 88%) as an oil: R_f 0.48 (70% EtOAc – petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.44 (s, 3H, OCH_3), 3.57 (br s, 2H, CH_2OBn), 3.64 (t, 1H, $J_{5,6a}$ = $J_{6a,6e}$ = 10.0 Hz, H6a), 4.10 (td, 1H, $J_{4,5}$ = 10.0 Hz, $J_{5,6e}$ = 5.1 Hz, H5), 4.24 (br s, 1H, H3), 4.31 (dd, 1H, H6e), 4.45 (s, 1H, H1), 4.53, 4.71 (d, 2H, *J* = 12.2 Hz, PhCH_2O), 5.44 (s, 1H, Ph*CH*), 7.30–7.50 (m, 10H, aromatic). ^{13}C NMR δ: 56.6 (q, OCH_3), 57.7 (d, C5), 69.3 (t, C6), 69.5 (d, C3), 71.6 (t, PhCH_2), 73.2 (s, C2), 73.7 (t, CH_2OBn), 77.1 (d, C4), 101.6 (d, C1), 102.0 (d, Ph*C*H), 126.1–137.7 (aromatic). Compound **8*b*** (39 mg, 0.10 mmol) and 1,1-thiocarbonyldiimidazole (36 mg, 0.20 mmol) in dry toluene (2 mL) was heated to reflux under a stream of argon overnight. Flash chromatography (10–50% EtOAc – petroleum ether) gave **9** (36 mg, 84%) as a white solid: R_f 0.47 (50%EtOAc – petroleum ether) $[\alpha]_D^{20}$ +131.3 (*c* 1.00, $CHCl_3$); mp 186°C. ^{1}H NMR (300 MHz, $CDCl_3$ δ: 3.42 (s, 3H, OCH_3), 3.63–3.75 (m, 3H, H4, H6a, CH_2OBn), 3.85 (d, 1H, *J* = 11.7 Hz, CH_2OBn), 4.21 (td, 1H, $J_{4,5}$ = $J_{5,6a}$ = 10.1 Hz, $J_{5,6e}$ = 5.2 Hz, H5), 4.34 (dd, 1H, $J_{6a,6e}$ = 10.1 Hz, H6e), 4.53 (s, 1H, H1), 4.58, 4.65 (d, 2H, *J* = 12.0 Hz, PhCH_2O), 5.15 (d, 1H, $J_{3,4}$ = 3.4 Hz, H3), 5.52 (s, 1H, Ph*CH*), 7.30–7.50 (m, 10H, aromatic). ^{13}C NMR δ: 56.2 (q, OCH_3), 57.1 (d, C5), 67.5 (t, PhCH_2), 68.8 (t, C6), 74.0 (t, CH_2OBn), 74.1 (d, C3), 78.7 (d, C4), 86.9 (s, C2), 98.2 (d, C1), 102.8 (d, Ph*C*H), 126.4–136.6 (aromatic), 191.4 (s, C═S). Anal. calcd. for $C_{23}H_{24}O_7S$: C 62.14, H 5.45, S 7.21; found: C 62.21, H 5.48, S, 7.12.

Methyl 4,6-O-benzylidene-2-C-methylene-α,D-arabino-hexopyranoside, 10a, and its 3-O-acetyl derivative 10b

The use of Tebbe's reagent was adapted from the published procedure 10*b*. In a dry box, titanocene dichloride (1.4, 5.62 mmol) was added to an oven-dried flask that was then closed with a septum. The flask was removed from the dry box and the septum wrapped with parafilm. Trimethyl aluminium (5.62 mL, 2 M in toluene, 11.24 mmol) was added and the methane gas generated was allowed to escape through the needle of a cannula that was then removed. The red solution was stirred for 4 days. Methane gas was vented once a day. Ketoacetate **4*b*** (820 mg, 2.54 mmol) in THF (5 mL) was added by syringe and the solution stirred for 1 h. The septum was removed and anhydrous ether (5 mL) was added. Sixteen drops of 1 M $NaOH_{(aq)}$ was added over a period of 1 h and the stirring continued overnight. Ether and anhydrous Na_2SO_4 were added and stirring continued for 1 h. The mixture was filtered through Celite (eluted with a copious quantity of ether) and the solvent evaporated. Flash chromatography (0–40% EtOAc – petroleum ether) gave **10*b*** (73 mg, 10%) and **10*a*** (530 mg, 75%). A high R_f material was also obtained and was assigned as **10*c*** since it rearranged on standing to give **10*a*** (29 mg; 4%).

10*a*: R_f 0.41 (30% EtOAc – petroleum ether); $[\alpha]_D^{20}$ +54.3 (*c* 1.05, $CHCl_3$); mp 178°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.62 (s, 1H, OH), 2.63 (d, 1H, J_{LR} = 3.0 Hz, OH), 3.40 (s, 3H, OCH_3), 3.45 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 10.0 Hz, H4), 3.74 (t, 1H, $J_{5,6}$ = $J_{6a,6e}$ = 10.0 Hz, H6a), 4.00 (td, 1H, $J_{5,6e}$ = 4.9 Hz, H5), 4.30 (dd, 1H, H6e), 4.62 (dd, 1H, J_{LR} = 2.0 Hz, H3), 5.03 (s, 1H, H1), 5.21, 5.43 (d, 2H, *J* = 1.5 Hz, ═CH_2), 5.54 (s, 1H, Ph*CH*), 7.32–7.52 (m, 5H, aromatic). ^{13}C NMR δ: 54.8 (q, OCH_3), 63.3 (d, C5), 69.1 (d, C3), 69.5 (t, C6), 84.2 (d, C4), 102.0 (d, Ph*C*H), 103.1 (d, C1), 112.2 (t, ═CH_2), 126.3–137.2 (aromatic), 142.9 (s, C2). MS *m/z*: 278 (M^+). Anal. calcd. for $C_{15}H_{18}O_5$: C 64.73, H 6.53; found: C 64.85, H 6.50.

10*b*: R_f 0.44 (30% EtOAc – petroleum ether); $[\alpha]_D^{20}$ +54.5 (*c* 1.10, $CHCl_3$); mp 100°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.16 (s, 3H, OAc), 3.41 (s, 3H, OCH_3), 3.62 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 10.0 Hz, H4), 3.76 (t, 1H, $J_{5,6a}$ = $J_{6a,6e}$ = 10.0 Hz, H6a), 4.11 (td, 1H, $J_{5,6e}$ = 4.8 Hz, H5), 4.31 (dd, 1H, H6e), 5.04 (s, 1H, H1), 5.07, 5.18 (d, 2H, *J* = 2.2 Hz, ═CH_2), 5.52 (s, 1H, Ph*CH*), 5.88 (dt, 1H, J_{LR} = 2.2 Hz, H3), 7.32–7.52 (m, 5H, aromatic). ^{13}C NMR δ: 20.8 (q, OAc), 54.7 (q, OCH_3)m 63.7 (d, C5), 69.0 (t, C6), 70.5 (d, C3), 81.3 (d, C4), 101.5 (d, C1), 102.9 (d, Ph*C*H), 111.9 (t, ═CH_2), 126.1–137.7 (aromatic). Anal. calcd. for $C_{17}H_{20}O_6$: C 63.73, H 6.31; found: C 63.56, H 6.34.

Methyl 4,6-O-benzylidene-2-C-hydroxymethyl-α,D-mannopyranoside, 11a

To **10*a*** (490 mg, 1.76 mmol) in THF (10 mL) and *t*-BuOH (10 mL) were added tetraethylammonium hydroxide (0.26 mL, 54 mg, 20 wt.% in water, 0.36 mmol), tertiary butyl hydroperoxide (0.76 mL, 504 mg, 70%, 5.6 mmol), and osmium tetroxide (0.08 mL, 2.5 wt.% in *t*-BuOH, 0.007 mmol) and the solution was stirred at room temperature overnight. More Et_4NOH (0.2 mL), *t*-BuOOH (0.7 mL), and OsO_4 (0.08 mL) were added and the reaction was stirred for 7 h, with periodic additions of Et_4NOH to maintain the basicity of the solution (monitored with pH paper). Aqueous sodium bisulfite solution (10 mL of 10%) was added and stirring was continued for 30 min. Most of the organic solvent was removed by rotary evaporatory (very mild heat), the mixture diluted with brine, extracted with methylene chloride (×3), and the combined extracts washed with brine and dried over Na_2SO_4. Flash chromatography (5:45:45 EtOH:EtOAc:petroleum ether) gave **11***a* (200 mg, 36%) as a solid: R_f 0.17 (70% EtOAc – petroleum ether); $[\alpha]_D^{20}$ +79.6 (*c* 1.00, $CHCl_3$); mp 102°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.37 (s, 1H, OCH_3), 3.57, 3.75 (d, 2H, J = 11.8 Hz, CH_2OH), 3.75–3.88 (m, 2H, H4, H5), 3.91 (t, 1H, $J_{5,6a} = J_{6a,6e}$ = 9.3 Hz, H6a), 4.07 (d, 1H, $J_{3,4}$ = 9.5 Hz, H3), 4.26 (dd, 1H, $J_{5,6e}$ = 3.4 Hz, H6e), 4.56 (s, 1H, H1), 5.54 (s, 1H, PhC*H*), 7.30–7.50 (m, 5H, aromatic). ^{13}C NMR δ: 55.3 (q, OCH_3), 63.0 (d, C5), 65.3 (t, CH_2OH), 68.8 (t, C6), 70.0 (d, C3), 74.4 (s, C2), 79.4 (d, C4), 102.2 (d, Ph*C*H), 103.1 (d, C1), 126.4–137.3 (aromatic). Anal. calcd. for $C_{15}H_{20}O_7$·0.4 H_2O: C 76.57, H 6.33; found: C 76.46, H 6.62.

*Methyl 4,6-*O*-benzylidene -2-*C*-triphenylmethoxymethyl-2,3-*O*-thionocarbonyl-α,*D*-mannopyranoside 11*b

Compound **11***a* (90 mg, 0.29 mmol) and triphenylmethyl chloride (125 mg, 0.43 mmol) in dry pyridine (3 mL) were stirred with a catalytic amount of DMAP at 100°C for 2 h. Evaporation of the solvent and flash chromatography (0–20% EtOAc – petroleum ether) gave **11***b* (148 mg, 80%) as an oil: R_f 0.23 (30% EtOAc – petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.32 (s, 1H, OCH_3), 3.44, 3.47 (d, 2H, J = 9.5 Hz, CH_2OTr), 3.76–3.95 (m, 4H, H3, H4, H5, H6a), 4.27 (m, 1H, H6e), 4.76 (s, 1H, H1), 5.55 (s, 1H, PhC*H*), 7.20–7.50 (m, 20 H, aromatic). ^{13}C NMR δ: 55.3 (q, OCH_3), 62.7 (d, C5), 66.1 (t, CH_2OTr), 69.0 (t, C6), 70.5 (d, C3), 75.4 (s, C2), 79.5 (d, C4), 87.2 (s, Ph_3C), 102.1 (d, C1), 102.2 (d, Ph*C*H), 126.3–143.4 (aromatic). To **11***b* (122 mg, 0.22 mmol) in dry THF (3 mL) under a stream of argon was added NaH (25 mg, 60% dispersion in oil, 0.62 mmol), followed by tetra-*n*-butylammonium iodide (catalytic amount) and carbon disulfide (0.04 mL, 0.68 mmol), and the reaction was stirred for 15 min. Methyl iodide (0.04 mL, 0.66 mmol) was added and the reaction stirred overnight. Saturated NH_4Cl (0.4 mL) was added and the mixture was diluted with ether, washed with brine (×2), and dried over Na_2SO_4. Flash chromatography (5–25% EtOAc – petroleum ether) gave **11***c* (116 mg, 88%) as an oil: R_f 0.48 (30% EtOAc – petroleum ether); $[\alpha]_D^{20}$ –5.1 (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.26 (s, 3H, OCH_3), 3.30, 3.39 (d, 2H, J = 11.0 Hz, CH_2OTr), 3.70 (td, 1H, $J_{4,5} = J_{5,6a}$ = 9.8 Hz, $J_{5,6e}$ = 4.4 Hz, H5), 3.78 (t, 1H, $J_{6a,6e}$ = 9.8 Hz, H6a), 3.84 (dd, 1H, $J_{3,4}$ = 7.1 Hz, H4), 4.31 (dd, 1H, H6e), 4.69 (d, 1H, H3), 4.98 (s, 1H, H1), 5.57 (s, 1H, PhC*H*), 7.20–7.50 (m, 20 H, aromatic). ^{13}C NMR δ: 55.9 (q, OCH_3), 58.8 (d, C5), 65.2 (t, CH_2OTr), 68.7 (t, C6), 79.1 (d, C4), 81.9 (d, C3), 87.6 (s, Ph_3C), 89.2 (s, C2), 98.1 (d, C1), 101.9 (d, Ph*C*H), 126.1–143.0 (aromatic), 189.8 (s, C=S). Anal. calcd. for $C_{35}H_{32}O_7S$·0.5 H_2O: C 69.39, H 5.50; found: C 69.64, H 5.63.

*Methyl 4,6-*O*-benzylidene-2-*C*-triphenylmethoxymethyl-α,*D*-*erythro*-hex-2-enopyranoside 12*

Compound **11***c* (92 mg, 0.15 mmol) in $P(OMe)_3$ (3 mL) was heated to reflux under a stream of argon for 18 h. Partial evaporation of the solvent and flash chromatography (0–10% EtOAc – petroleum ether) gave **12** (47 mg, 59%) as an oil: R_f 0.45 (15% EtOAc – petroleum ether); $[\alpha]_D^{20}$ +45.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.35 (s, 3H, OCH_3), 3.65 (br s, 1H, CH_2OTr), 3.81 (t, 1H, $J_{5,6} = J_{6a,6e}$ = 10.2 Hz, H6a), 3.87 (td, 1H, $J_{4,5}$ = 10.2 Hz, $J_{5,6e}$ = 3.8 Hz, H5), 4.16–4.23 (m, 1H, H4), 4.27–4.33 (m, 1H, H6e), 4.88 (s, 1H, H1), 5.59 (s, 1H, PhC*H*), 6.18 (br s, 1H, H3), 7.20–7.50 (m, 20H, aromatic). ^{13}C NMR δ: 56.0 (q, OCH_3), 63.6 (t, CH_2OTr), 64.3 (d, C5), 69.5 (t, C6), 75.7 (d, C4), 86.9 (s, Ph_3C), 97.1 (d, C1), 102.3 (d, Ph*C*H), 125.4 (d, C3), 126.4–136.4 (aromatic), 137.5 (s, C2). Anal. calcd. for $C_{34}H_{32}O_5$·0.7 H_2O: C 76.57, H 6.33; found: C 76.46, H 6.62.

*Methyl 4,6-*O*-benzylidene-2-*C*-hydroxymethyl-α,*D*-*erythro*-hex-2-enopyranoside 14*b

To **10***a* (510 mg, 1.83 mmol) in dry THF (150 mL) were added pyridine (1.3 mL, 16 mmol) and thionyl chloride (1 mL, 13.7 mmol), and the mixture was stirred overnight under a stream of argon. It was then diluted with ether, washed with brine (×2), saturated $NaHCO_3$ (×2), brine (×2), and dried over Na_2SO_4 to give crude **13** as a slightly brown solid: R_f 0.67 (20% EtOAc – petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.48 (s, 3H, OCH_3), 3.75–4.36 (m, 6H, H4, H5, H6a, H6e, CH_2Cl), 5.03 (s, 1H, H1), 5.56 (s, 1H, PhC*H*), 6.13 (s, 1H, H3), 7.30–7.50 (m, 5H, aromatic). ^{13}C NMR δ: 44.5 (t, CH_2Cl), 56.5 (q, OCH_3), 64.2 (d, C5), 69.3 (t, C6), 75.3 (d, C4), 96.2 (d, C1), 102.2 (d, Ph*C*H), 129.2 (d, C3), 135.2 (s, C2), 126.3–137.2 (aromatic). To crude **13** in HMPA (20 mL) was added potassium acetate (180 mg, 1.83 mmol) and the mixture was stirred overnight under argon. It was then diluted with brine, extracted with ether (×4), and the combined extracts were washed with saturated $NaHCO_3$ (×2), and dried over Na_2SO_4. Flash chromatography (2–10% EtOAc – petroleum ether) gave **14***a* (298 mg, 51% from **10***a*) as a white solid: R_f 0.41 (30% EtOAc – petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.06 (s, 3H, OAc), 3.45 (s, 3H, OCH_3), 3.80 (t, 1H, $J_{5,6a} = J_{6a,6e}$ = 10.5 Hz, H6a), 3.85 (td, 1H, $J_{4,5} = J_{5,6e}$ = 3.7 Hz, H5), 4.11–4.19 (m, 1H, H4), 4.26–4.34 (m, 1H, H6e), 4.55, 4.60 (d, 2H, J = 13.4 Hz, CH_2OAc), 4.86 (s, 1H, H1), 5.56 (s, 1H, PhC*H*), 6.09 (br s, 1H, H3), 7.30–7.50 (m, 5H, aromatic). ^{13}C NMR δ: 20.9 (q, OAc), 56.3 (q, OCH_3), 63.7 (t, CH_2OAc), 64.1 (d, C5), 69.4 (t, C6), 75.3 (d, C4), 96.7 (d, C1), 102.3 (d, PhCH), 126.3–137.3 (aromatic), 128.0 (d, C3), 133.9 (s, C2), 170.6 (s, C=O). Compound **14***a* (250 mg, 0.78 mmol) in MeOH (15 mL) was stirred with a catalytic amount of sodium methoxide (1 M in MeOH) for 2 h. Dowex 50X8-100 acidic ion exchange reagent (prewashed in MeOH) was added and the mixture stirred for 15 min. The mixture was filtered and the solvent removed. Flash chromatography (30–50% EtOAc – petroleum ether) gave **14***b* (139 mg, 64%) as a white solid: R_f 0.31 (50% EtOAc – petroleum ether); $[\alpha]_D^{20}$ +98.5 (*c* 1.00, $CHCl_3$); mp 146°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.47 (s, 1H, OCH_3), 3.80 (t, 1H, $J_{5,6a} = J_{6a,6e}$ = 10.4 Hz, H6a), 3.84 (td, 1H, $J_{5,6e}$ = 3.4 Hz, H5), 4.09–4.19 (m, 3H, H4, CH_2OH), 4.28–4.33 (m, 1H, H6e), 4.91 (s, 1H, H1), 4.57 (s, 1H, PhCH), 6.06 (br s, 1H, H3), 7.30–7.50 (m, 5H, aromatic). ^{13}C NMR δ: 56.2 (q, OCH_3), 63.2 (t, CH_2OAc), 64.3 (d, C5), 69.4 (t, C6), 75.4 (d, C5), 97.5 (d, C1), 102.3 (d, PhCH), 126.3–137.6 (aromatic), 126.8 (d, C3), 137.6 (s, C2). Anal. calcd. for $C_{15}H_{18}O_5$: C 64.73, H 6.53; found: C 64.65, H 6.57.

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