Synthesis of 2,3-Dihydroxyhex-4-enoates by Palladium-Catalyzed Allylic Alkylations of Carbohydrate Derived Vinyl Lactones

Jamie Singleton, Krishna Sahteli, John O. Hoberg*

Department of Chemistry, University of Wyoming, 1000 East University Ave., Laramie, WY 82071, USA
Fax +1(307)7662807; E-mail: hoberg@uwyo.edu

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Abstract: D-Gulonic lactone or its L-isomer is easily converted to the vinyl lactone **1** via three convenient reactions in an overall 69% yield. Reaction of the D isomer of **1** with a variety of carbon, oxygen, sulfur, and nitrogen nucleophiles and a palladium catalyst produced carboxylic acids that were esterified with methyl iodide to give the esters **2**. Alternatively, reaction of L-lactone **1** with $Ph_3P{=}CHCO_2Et$ provided the Wittig product that underwent palladium-catalyzed rearrangement to give the cyclopentanone **3**.

Key words: gulonic lactone, rearrangement, π-allyl, allylic alkylation, palladium

A common motif found in a variety of natural products consists of an acid derivative with either a 2,3-dihydroxy, 2,3-diether, or hydoxyl ether moiety. Examples of this include peloruside A,[1] mycalamide A,[2] onnamide A,[3] theopederin,[4] pederin,[5] and the enterocins.[6] These natural products have displayed potent biological activity in a variety of cell lines and have therefore become targets for total synthesis. In view of their activity, the diverse stereochemical nature of this motif, and the interest by the synthetic community, a general synthetic route for the construction of this fragment would be desirable. We envisioned that such a route was available via functionalized vinyl lactones, such as **1**, and transition metal catalyzed allylic alkylations. Ample precedence exists for the conversion of **1** to **2** dating back to an initial report by Trost,[7] and more recently by others.[8–10] The required lactones, such as the gulonic lactone enantiomers used in this work, are obtainable from commercially available carbohydrate lactones as four isomers (Figure 1) or can easily be synthesized in one step when cost and/or availability becomes an issue. These gulono- and galactono-lactones are amenable to two- or three-step protection/deprotection strategies, making the total synthetic sequence presented herein highly efficient and practical.

Synthesis of diol **4**[11,12] and the required lactone **1**[13] have been described in various reports, however improved yields and more environmentally benign conditions can be obtained with slight modifications (Scheme 1). The yield of the initial diacetonation of the 2,3- and 5,6-diol groups of gulono lactone can be improved from 79 to 87% by simply stirring for 3 days versus overnight. Furthermore, extraction of the reaction mixture with dichloromethane can be omitted and replaced by precipitation with water to give the diacetonide as a white solid. The subsequent C5–C6 deprotection to give **4** has also been greatly enhanced from initial reports of 59–79%, with one such report using chloroform–methanol[12] mixtures as solvents for flash chromatography. Rather, the use of a 95% solution of acetic acid with several days of stirring followed by azeotropic removal of the acetic acid with toluene provides **4** as a highly pure solid. Finally, we were unable to reproduce the synthesis of **1** from **4** as reported by Chakravarthy.[13] Additionally, the authors report **1** as an oil, when in fact it exists as a solid. Thus, we have modified this reaction to produce **1** in good yield. However, this reaction is fraught with purification difficulties as the by-products are difficult to remove and hence greatly hinder acquiring pure solid **1**. Thus, Soxhlet extraction with hexanes was used on the crude mixture prior to flash chromatography to obtain pure material. In light of the ease and scalability of the first two steps and the removal of any column chromatography in their purification, improvements to the final step would be desirable and are being addressed. However, this overall sequence currently enables the construction of **1** on the multi-gram scale.

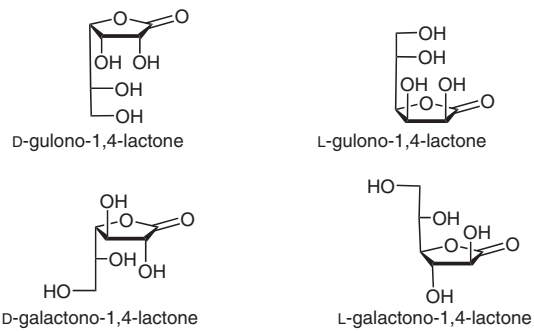
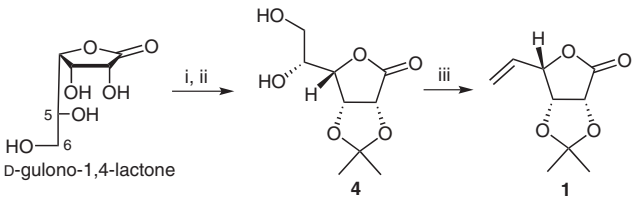


Figure 1 Commercially available carbohydrate lactones



Scheme 1 *Reagents and conditions*: (i) $(MeO)_2CMe_2$, acetone, *p*-TsOH, MeCN–DMF 10:1, r.t., 87%; (ii) 95% aq AcOH, r.t., 95%; (iii) Ph_3P, imidazole, I_2, toluene, MeCN, 83%.

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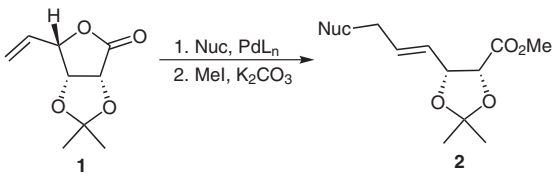
With vinyl lactone **1** in hand, the reaction with dimethyl malonate anion and various catalysts were studied. Of the catalysts used, $Pd(PPh_3)_4$, $Pd_2(dba)_3$, and $[C_3H_5PdCl]_2$ at 2 mol% loadings, only the allylpalladium dimer produced unacceptable results. Purification of the resulting acid was generally problematic and usually required highly polar solvents for chromatography that resulted in impure products. This issue was resolved by filtration of the acid product through silica gel and then esterification with MeI to give the methyl ester. Reactions with a variety of nucleophiles were next undertaken to test the generality of this sequence (Table 1). As expected, the reaction of vinyl lactone **1** with a range of carbon, oxygen, sulfur, and nitrogen nucleophiles is very general (entries 1, 5, 7, and 8 as examples). In all cases, mild conditions and good overall yields were observed. Reaction times of the initial alkylation reaction are especially convenient with entry 4 being the only outlier.

Given the propensity for this system towards palladium allylic alkylations, we suspected that other metal-catalyzed reactions leading to cyclopentyl systems could be used with it. In 1981, Trost reported on the rearrangement of 5-vinyl-2-alkylidenetetrahydrofurans (Scheme 2).[14,15] In this report, alkylidene **5** was constructed in nine steps and a series of rearrangements products were reported. These products included pentanone **6**, the decarboxylation product of **6** (loss of CO_2t-Bu), and a cycloheptene structure, in which the isolated yields and product distribution were modest to good. Furthermore, Gree[16] recently published the synthesis of cyclopentenones from vinylic furanoses using $Fe(CO)_5$ and light. In view of these, we felt that a more facile and synthetically shorter entry into the Trost system and an expansion of Gree's chemistry to multiple isomers would be readily available from vinyl lactone **1** and its isomers.

In the synthesis of **5**, it was reported that all attempts at its formation from a lactone using Wittig or Emmons–Wadsworth–Horner reagents failed. However, since then reports on the Wittig reaction of lactones have appeared.[17] Given that $Ph_3P{=}CHCO_2Et$[18] is a stable, easily formed Wittig reagent that has been used in the reaction with lactones, its use appeared to be ideal. Gratifyingly, reaction of **7**, the enantiomer of **1**, with $Ph_3P{=}CHCO_2Et$ in a sealed tube gave an excellent yield of **8** as a 1:1 mixture of *E*/*Z* isomers (Scheme 3). Additionally, reduction of **7** gave vinyl lactol **9** in again excellent yield. It should also be noted that the use of DIBAL-H in the reduction of **7** did not produce the desired lactol at temperatures ranging from –78 to 0 °C, rather, the starting material was recovered unchanged. We have not yet used **9** in the chemistry reported by Gree, although it is simply a diastereomer of that reported; however, heating of **8** at 90 °C in DMSO with a variety of palladium catalysts and ligands does result in the formation of cyclopentanone **3**. Although cyclopentanone formation was observed, low yields (40–50%) and a difficult purification plagued this reaction making it synthetically unusable in our opinion. Thus, further studies on this rearrangement are currently required and are being pursued.

Table 1 Reaction of Vinyl Lactone **1** with Nucleophiles

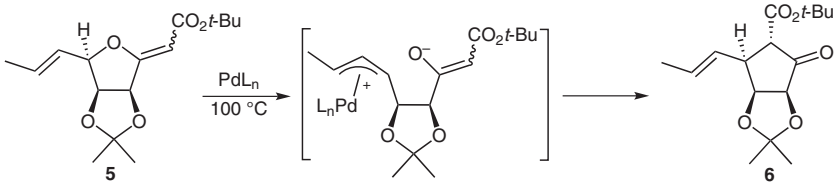


1 2

Entry[a]	Nucleophile	Time	Yield (%) of **2**[b]
1	$NaCH(CO_2Et)_2$	15 min	75 (**2a**)[c]
2	$NaCH(CO_2Me)_2$	15 min	67 (**2b**)
3	$NaCMe(CO_2Et)_2$	3 h	67 (**2c**)[d]
4	$NaCH(CO_2Me)SO_2Ph$	48 h	55 (**2d**)
5	$NaOCH_2C_6H_5$	4 h	76 (**2e**)
6	$NaOCH_2C_6H_4OMe$	2 h	57 (**2f**)
7	NaTs	4 h	66 (**2g**)
8	NaN_3	1 h	63 (**2h**)

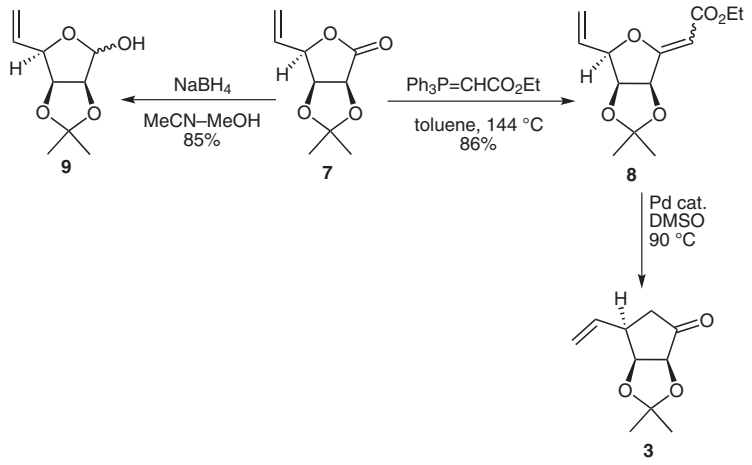
[a] Step 1 performed with 2 mol% $Pd(PPh_3)_4$ and 3 mol% PPh_3 in THF at r.t. for the time indicated in Table 1. Esterification reactions performed in acetone with MeI and K_2CO_3.
[b] Yields reported for combined two steps.
[c] A 25:1 ratio of *E*/*Z* isomers was obtained.
[d] A 2 h reflux period was required for completion of step 1.

In conclusion, D-gulonic lactone and its enantiomer[19] are easily converted to vinyl lactones **1** and **7**, respectively. These have been shown to be useful intermediates in palladium-catalyzed allylic alkylation reactions. Additionally, any of the four isomers of the esters **2** can be obtained by simply choosing the appropriate starting lactone shown in Figure 1. As the protection schemes of the galactono lactones are established, entry into a myriad of isomeric esters and cyclopentyl systems using the isomers of **8** and **9** are potentially available.



5 6

Scheme 2



Scheme 3

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in the indicated solvent. Chemical shifts are reported in δ units, parts per million (ppm) relative to $CDCl_3$ (7.27 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR). THF was distilled from NaK and acetone was distilled from anhyd $CaSO_4$. Toluene and MeCN were distilled from CaH_2. NaH was washed with hexane before use and dried. Flash chromatography was performed using Silicycle ultra pure silica gel 60 Å (230–400 mesh). All the TLC analyses were performed on Merck Silica gel 60 F precoated plates for TLC (layer thickness 250 μm). Standard syringe techniques were employed for handling air-sensitive reagents, glassware for experiments requiring anhydrous conditions were flame dried, and all reactions were carried out under argon.

2,3,5,6-Di-*O*-isopropylidenegulonolactone

MeCN–DMF (22.0 mL of a 10:1 ratio) was added to either D- or L-gulono-1,4-lactone (6.00 g, 33.7 mmol), followed by acetone (40.0 mL), 2,2-dimethoxypropane (25.0 mL), and PTSA (320 mg, 5 mol%). The mixture was stirred at r.t. for 3 days and then concentrated (40 °C rotovap bath temperature) to a thick, cloudy syrup. H_2O (40 mL) was added to the syrup producing a white solid that was stirred for 20 min at r.t. The mixture was cooled for 1 h by placing in a refrigerator (~5 °C), filtered, washed with cold H_2O (10 mL), and dried under vacuum to give 7.57 g (87%) of a white solid that needed no further purification; mp 150–152 °C.

^{1}H NMR ($CDCl_3$): δ = 4.85 (d, *J* = 5.6 Hz, 1 H), 4.75 (dd, *J* = 3.4, 5.6 Hz, 1 H), 4.45 (m, 2 H), 4.24 (m, 1 H), 3.82 (m, 1 H), 1.50 (s, 3 H), 1.48 (s, 3 H), 1.42 (s, 3 H), 1.39 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 173.3, 114.7, 110.5, 80.9, 76.0, 75.7, 75.2, 65.1, 26.5, 25.7, 25.0.

D or l-2,3-*O*-Isopropylidenegulonolactone (4)

2,3,5,6-Di-*O*-isopropylidenegulonolactone (3.30 g, 12.8 mmol) was added to 95% aq AcOH (40 mL) and stirred at r.t. for 3 d. Toluene (30 mL) was added to the mixture and the volume concentrated at a bath temperature of 46 °C. Additional toluene was added 2–3 times until the majority of the AcOH was removed from the crude material. The resulting solid was placed under vacuum (0.001 mmHg at 45 °C for 8 h) to yield 2.65 g (95%) of a white solid; mp 100–102 °C.

^{1}H NMR (D_2O): δ = 5.14 (d, *J* = 5.3 Hz, 1 H), 5.04 (dd, *J* = 5.3, 3.5 Hz, 1 H), 4.68 (dd, *J* = 8.4, 3.5 Hz, 1 H), 4.07 (m, 1 H), 3.79 (dd, *J* = 12.2, 3.3 Hz, 1 H), 3.71 (dd, *J* = 12.2, 5.4 Hz, 1 H), 1.34 (s, 3 H), 1.30 (s, 3 H).

^{13}C NMR: see reference 13.

D or l-2,3-*O*-Isopropylidene-5-vinylgulonolactone (1 or 7)

PPh_3 (2.00 g, 27.5 mmol) was added to a solution of I_2 (6.98 g, 27.5 mmol) in toluene (30 mL)–MeCN (15 mL) and the mixture stirred for 0.5 h at 60 °C. Imidazole (1.87 g, 27.5 mmol) was added in one portion and the mixture boiled for 0.5 h. The mixture was cooled to r.t. and solid 2,3-*O*-isopropylidenegulonolactone (2.00 g, 9.17 mmol) was added and stirred at 50 °C for 8 h. After cooling to r.t., the volume was reduced and the resulting solid was dissolved in CH_2Cl_2 (20 mL). The organic layer was washed with aq sat. $NaHCO_3$ (100 mL), dried (Na_2SO_4), filtered, and concentrated. The solid was loaded into a glass Soxhlet thimble and extracted, using a 500 mL Soxhlet extractor, with hexane (500 mL) until ca. 40–42 turns were achieved; usually about 10–12 h. Concentration and gradient flash chromatography with cyclohexane–EtOAc (10:1, 5:1, then elution with 2:1) gave 1.40 g (83%) of a white solid; mp 97–99 °C.

IR (neat): 2990, 2930, 1770, 1325 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.99 (ddd, *J* = 17.0, 10.4, 7.3 Hz, 1 H), 5.53 (dd, *J* = 16.9, 0.9 Hz, 1 H), 5.47 (dd, *J* = 10.5, 0.9 Hz, 1 H), 4.91 (ddd, *J* = 7.3, 2.3, 0.9 Hz, 1 H), 4.84 (d, *J* = 5.3 Hz, 1 H), 4.80 (dd, *J* = 5.2, 2.3 Hz, 1 H), 1.48 (s, 3 H), 1.40 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 173.9, 130.2, 121.2, 114.4, 80.2, 77.9, 76.3, 26.9, 26.0.

HRMS: *m*/*z* calcd for $C_9H_{12}O_4$: 184.0736; found: 184.0731.

Esters 2a–h; Diethyl 2-{(*E*)-3-[(4*R*,5*R*)-5-(Methoxycarbonyl)-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-enyl}malonate (2a); Typical Procedure

Lactone **1** (100.0 mg, 0.540 mmol), Ph_3P (4 mg, 0.01 mmol), and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) were stirred in THF (5 mL) at r.t. for 20 min. In a separate flask, a solution of diethyl malonate (206 μL, 1.36 mmol) in THF (1 mL) was slowly added to a slurry of hexane-washed NaH (32 mg, 1.33 mmol) in THF (4 mL) and stirred for 30 min (1 h stirring in the case of *p*-methoxybenzyl alcohol). The resulting clear solution was added in one portion to the former and the combined mixture was stirred at r.t. for 15 min. The mixture was cooled to 0 °C and acidified with 5% aq HCl. The yellow mixture was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), and the CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated in vacuo. Gradient flash chromatography/filtration using a plug of silica gel with cyclohexane–EtOAc (3:1), then cyclohexane–EtOAc–AcOH (2:1:0.1) gave the carboxylic acid (150 mg) as an oil. Indicative resonances in the in the IR included, (neat): 3510 1725, 1710 cm^{-1} and in ^{1}H NMR ($CDCl_3$): δ = 10.30 (br s, 1 H). To a solution of the acid

(150 mg) in acetone (6 mL) at r.t. was added anhyd Na_2CO_3 (120 mg, 0.84 mmol) and MeI (390 μL, 6.3 mmol). The mixture was stirred at r.t. for 4 h, then cooled to 0 °C and acidified with dilute HCl. The mixture was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL), the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), and the CH_2Cl_2 extracts were dried (Na_2SO_4), and concentrated in vacuo. Gradient flash chromatography with cyclohexane–EtOAc (5:1 to 2:1) gave **2a** (144.3 mg, 75% overall yield) as an oil.

IR (neat): 2990, 2940, 1725 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.81 (dtd, *J* = 14.0, 6.9, 0.7 Hz, 1 H), 5.43 (ddt, *J* = 14.6, 7.6, 1.3 Hz, 1 H), 4.74 (dd, *J* = 7.5, 2.2 Hz, 1 H), 4.62 (d, *J* = 7.1 Hz, 1 H), 4.19 (q, *J* = 7.1 Hz, 4 H) 3.35 (t, *J* = 7.5 Hz, 1 H), 2.64 (ddd, *J* = 7.4, 7.2, 1.3 Hz, 2 H), 1.6 (s, 3 H), 1.35 (s, 3 H), 1.25 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR ($CDCl_3$): δ = 169.7, 168.9, 131.5, 127.1, 111.0, 78.1, 77.5, 52.6, 52.5, 51.8, 51.0, 31.0, 26.9, 25.5.

HRMS: *m*/*z* calcd for $C_{17}H_{26}O_8$: 358.1627; found: 358.1638.

2b

Gradient flash chromatography with cyclohexane–EtOAc (5:1 to 2:1) gave **2b** as an oil.

IR (neat): 2995, 2950, 1740 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.79 (ddt, *J* = 15.4, 7.0, 0.8 Hz, 1 H), 5.42 (dd, *J* = 15.4, 7.5 Hz, 1 H), 4.72 (dd, *J* = 7.3 Hz, 1 H), 4.61 (d, *J* = 7.1 Hz, 1 H), 3.75 (s, 3 H), 3.70 (s, 6 H), 3.40 (t, *J* = 7.5 Hz, 1 H), 2.64 (ddd, *J* = 7.5, 7.5 0.8 Hz, 2 H), 1.6 (s, 3 H), 1.35 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 169.7, 168.9, 131.5, 127.1, 111.0, 78.1, 77.5, 52.6, 52.5, 51.8, 51.0, 31.0, 26.9, 25.5.

HRMS: *m*/*z* calcd for $C_{15}H_{22}O_8$: 330.1315; found: 330.1314.

2c

Gradient flash chromatography with cyclohexane–EtOAc (5:1 to 2:1) gave **2c** as an oil.

IR (neat): 2990, 2940, 1725 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.71 (dt, *J* = 15.0, 7.0 Hz, 1 H), 5.44 (dd, *J* = 15.0, 7.2 Hz, 1 H), 4.72 (dd, *J* = 7.2 Hz, 1 H), 4.60 (d, *J* = 7.0 Hz, 1 H), 4.15 (q, *J* = 7.1 Hz, 4 H) 3.68 (s, 1 H), 2.57 (m, 2 H), 1.57 (s, 3 H), 1.34 (s, 3 H), 1.32 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR ($CDCl_3$): δ = 171.6, 171.5, 169.8, 130.6, 128.4, 110.9, 78.3, 77.3, 61.3, 53.1, 51.7, 38.4, 29.6, 26.9, 25.5, 19.6, 13.9.

HRMS: *m*/*z* calcd for $C_{18}H_{28}O_8$: 372.1784; found: 372.1780.

2d

Gradient flash chromatography with cyclohexane–EtOAc (5:1 to 2:1) gave **2d** as an oil.

IR (neat): 2990, 2950, 1740 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.88–7.60 (m, 5 H), 5.72 (dt, *J* = 15.8, 6.8 Hz, 1 H), 5.46 (dd, *J* = 15.4, 7.8 Hz, 1 H), 4.64 (dd, *J* = 7.4, 7.2 Hz, 1 H), 4.00 (d, *J* = 7.3 Hz, 1 H), 3.70 (s, 3 H), 3.63 (s, 3 H), 2.8 (m, 2 H), 1.6 (s, 3 H), 1.40 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 169.7, 164.4, 136.5, 133.8, 129.2, 128.9, 128.3, 111.1, 78.8, 77.5, 69.7, 63.0, 53.1, 51.8, 29.3, 26.9, 25.5.

HRMS: *m*/*z* calcd for $C_{19}H_{24}O_8S$: 412.1192; found: 412.1200.

2e

Gradient flash chromatography with cyclohexane–EtOAc (5:1 to 2:1) gave **2e** as an oil.

IR (neat): 2995, 2940, 2850, 1750 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.35 (m, 5 H), 5.98 (dtd, *J* = 15.2, 5.4, 1.0 Hz, 1 H), 5.66 (ddt, *J* = 15.5, 7.3, 1.5 Hz, 1 H), 4.86 (t, *J* = 7.2 Hz, 1 H), 4.69 (d, *J* = 7.1 Hz, 1 H), 4.5 (s, 2 H), 4.03 (d, *J* = 5.3, 2 H), 3.70 (s, 3 H), 1.6 (s, 3 H), 1.40 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 169.9, 138.1, 132.0, 128.3, 127.7, 127.5, 126.1, 111.1, 77.9, 77.7, 72.0, 69.4, 51.8, 26.9, 25.5.

HRMS: *m*/*z* calcd for $C_{17}H_{22}O_5$: 306.1467; found: 306.1461.

2f

Gradient flash chromatography with cyclohexane–EtOAc (5:1 to 2:1) gave **2f** as an oil.

IR (neat):2995, 2940, 2850, 1750 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.17 (m, 2 H), 7.68 (m, 2 H), 5.89 (dt, *J* = 15.5, 5.7 Hz, 1 H), 5.56 (ddt, *J* = 15.5, 7.3, 1.5 Hz, 1 H), 4.77 (dd, *J* = 7.2, 7.2 Hz, 1 H), 4.61 (d, *J* = 7.1 Hz, 1 H), 4.34 (s, 2 H), 3.92 (d, *J* = 5.4 Hz, 2 H), 3.72 (s, 3 H), 3.6 (s, 3 H), 1.6 (s, 3 H), 1.35 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 169.9, 159.1, 132.1, 130.1, 129.4, 126.1, 113.7, 111.1, 77.9, 77.7, 71.6, 69.1, 55.2, 51.8, 26.9, 25.5.

HRMS: *m*/*z* calcd for $C_{18}H_{24}O_6$: 336.1573; found: 336.1581.

2g

A solution of *p*-toluenesulfinic acid sodium salt hydrate (1.5 equiv) in MeOH (1.5 mL, 0.54 mmol of **1**) was added to a mixture of **1** and the palladium catalyst. The mixture was stirred at r.t. for 4 h prior to treatment as described above. Gradient flash chromatography of crude **2g** with cyclohexane–EtOAc (5:1 to 2:1) gave **2g** as an oil.

IR (neat): 2995, 2950, 2940, 1750 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.75 (m, 2 H), 7.35 (m, 2 H), 5.78 (dt, *J* = 15.4, 7.3 Hz, 1 H), 5.63 (dd, *J* = 15.4, 6.4 Hz, 1 H), 4.80 (dd, *J* = 7.0, 6.7 Hz, 1 H), 4.70 (d, *J* = 7.2 Hz, 1 H), 3.76 (dd, *J* = 3.8, 3.9 Hz, 2 H), 3.72 (s, 3 H), 2.45 (s, 3 H), 1.58 (s, 3 H), 1.37 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 169.4, 144.8, 141.0, 135.7, 134.1, 129.9, 128.4, 127.8, 120.9, 111.4, 77.9, 77.6, 59.4, 52.2, 27.0, 25.5, 21.6.

HRMS: *m*/*z* calcd for $C_{17}H_{12}O_6S$: 344.0355; found: 344.0354.

2h

A solution of NaN_3 (2.5 equiv) in H_2O (1.5 mL, 0.65 mmol **1**) was added to a mixture of **1** and the palladium catalyst and the mixture was stirred at r.t. for 1 h prior to treatment as described above. Gradient flash chromatography of crude **2h** with cyclohexane–EtOAc (5:1 to 1:1) gave **2h** as a white solid; mp 84–86 °C.

IR (neat): 3200, 2990, 2940, 2050, 1750 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.95 (dtd, *J* = 15.4, 6.0, 1.0 Hz, 1 H), 5.76 (ddt, *J* = 15.4, 6.8, 1.3 Hz, 1 H), 4.85 (dd, *J* = 7.0, 7.1 Hz, 1 H), 4.71 (d, *J* = 7.3 Hz, 1 H), 3.8 (d, *J* = 6.0 Hz, 2 H), 1.64 (s, 3 H), 1.47 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 173.9, 128.5, 128.2, 111.5, 77.3, 77.2, 51.7, 26.8, 25.3.

HRMS: *m*/*z* calcd for $C_9H_{13}O_4N_3$: 227.0901; found: 227.0901.

2,3-*O*-Isopropylidene-5-vinyl-l-gulose (9)

$NaBH_4$ (20.5 mg, 0.543 mmol) was added to a 1:1 MeCN–MeOH (2 mL) solution of **7** (100.0 mg, 0.543 mmol) at 0 °C and stirred for 5 min. The ice bath was removed and the mixture was stirred at r.t. until TLC indicated the disappearance of the starting material (~1 h). Aq sat. NH_4Cl (5 mL) was added and stirred for 10 min, then the mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), filtered, and concentrated. Flash chromatography with cyclohexane–EtOAc (2:1) gave **9** as a colorless oil (86.0 mg, 85%).

IR (neat): 3316, 2982 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.0 (ddd, *J* = 16.4, 10.3, 6.9 Hz, 1 H), 5.4 (m, 3 H), 4.8 (dd, *J* = 6.0, 4.5 Hz, 1 H), 4.61 (d, *J* = 6 Hz, 1 H), 4.6 (m, 1 H), 3.4 (br s, 1 H), 1.5 (s, 3 H), 1.3 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 132.0, 119.3, 112.6, 101.0, 85.7, 81.5, 81.4, 26.8, 24.8.

HRMS: *m*/*z* calcd for $C_9H_{14}O_4$: 186.0892; found: 186.0888.

Vinylalkylidene 8

$Ph_3P{=}CHCO_2Et$ (1.80 g, 5.10 mmol) was added to a solution of **7** (375 mg, 2.04 mmol) in toluene (10 mL) and heated to 144 °C in a sealed flask for 24 h. The mixture was cooled, the volume reduced to a thick syrup and subjected to gradient flash chromatography with cyclohexane–EtOAc (4:1 then 2:1) to give a 1:1 *E*/*Z* mixture of **8**, which separated on the column (combined 86% yield).

First Isomer

IR (neat): 2987, 1711, 1657, 1117 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.0 (ddd, *J* = 17.8, 7.4, 3.0 Hz, 1 H), 5.75 (dd, *J* = 6.0, 1.3 Hz, 1 HH), 5.40 (m, 3 H), 4.75 (dd, *J* = 6.0, 4.3 Hz, 1 H), 4.59 (dd, *J* = 8.2, 4.2 Hz, 1 H), 4.19 (m, 2 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 171.8, 166.9, 131.0, 120.6, 113.2, 94.6, 85.0, 80.0, 79.1, 59.8, 26.6, 25.7, 14.3.

Second Isomer

^{1}H NMR ($CDCl_3$): δ = 6.05 (ddd, *J* = 17.3, 7.4, 3.0 Hz, 1 H), 5.5 (ddd, *J* = 17.2, 10.4, 1.2 Hz, 2 H), 5.15 (dd, *J* = 5.5, 1 Hz, 1 H), 5.1 (d, *J* = 1.1 Hz, 1 H), 5.5 Hz), 4.89 (m, 1 H), 4.69 (dd, *J* = 5.9 Hz, 1 H), 4.19 (m, 2 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 HH).

^{13}C NMR ($CDCl_3$): 169.1, 165.4, 130.7, 120.8, 114.0, 92.0, 86.4, 81.8, 78.5, 59.5, 27.1, 26.1, 14.3.

HRMS: *m*/*z* calcd for $C_{13}H_{18}O_5$, 254.1154; found: 254.1139.

Attempts at Cyclopentanone 3

Vinyl alkylidene **8** was heated at 60–100 °C in a combination of the following solvents, catalysts, and ligands: Solvents: DMSO, DMF, THF, or dioxane; Catalyst: $Pd_2(dba)_3{\cdot}CHCl_3$, $[Pd(allyl)Cl]_2$, $(PPh_3)_2NiCl_2$, $Mo(CO)_6$, $(COD)_2IrCl_2$; Ligands: DIPHOS, Trost's, PPh_3, DPPF, and 1,3-bis[2,6-(*i*-Pr)$_2$phenyl]imidazolium chloride. $Pd_2(dba)_3{\cdot}CHCl_3$ was the only catalyst to produce any of the cyclopentanone, with either DIPHOS or Trost's ligand with DMSO as solvent. The use of Trost ligand gave only 10% conversion and DIPHOS a complex mixture of products that after multiple flash chromatography with cyclohexane–EtOAc gave 40–50% yields of **3**. Comparison of the ^{1}H NMR to a literature[1] diastereomer confirmed the structure and stereochemistry.

^{1}H NMR ($CDCl_3$): δ = 6.0 (ddd, *J* = 18.2, 7.4, 4.9, 1 H), 5.24 (m, 2 H), 4.77 [dd, *J* = 4.5 Hz (identical coupling), 1 H], 4.25 [dd, *J* = 4.9 ($J_{3,4}$), 1.4 Hz, 1 H], 2.91 (m, 1 H), 2.58 (ddd, *J* = 18.2, 12.3, 1.2 Hz, 1 H), 2.37 (dddd, *J* = 18.2, 8.0, 1.7, 0.6 Hz, 1 H), 1.45 (s, 3 H), 1.38 (s, 3 H).

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