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Synthesis of (−)-Noviose from 2,3-*O*-Isopropylidene-D-erythronolactol

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Abstract: Noviose is a key synthon for the construction of novobiocin, a clinically useful antitumor agent that has been shown to inhibit both type II topoisomerases and Hsp90. The synthesis of D-noviose from 2,3-*O*-isopropylidene-D-erythronolactol is described.

Novobiocin is an antitumor agent that has been used clinically for the treatment of cancer for more than a decade.[1] Although originally identified as an inhibitor of type II topoisomerases,[2] novobiocin was recently shown to be an inhibitor of the 90 kDa heat shock proteins, Hsp90.[3] Hsp90 is a molecular chaperone responsible for the refolding of denatured proteins following cellular stress as well as for the conformational maturation of nascent polypeptides into biologically active three-dimensional structures.[4] In fact, proteins represented in all six hallmarks of cancer are Hsp90 dependent.[5] Consequently, Hsp90 has emerged as a promising target for the development of cancer chemotherapeutics because multiple oncogenic proteins can be simultaneously disrupted by inhibition of the Hsp90 protein folding machinery.[6]

Unlike well-investigated inhibitors of the *N*-terminal ATP binding site of Hsp90, novobiocin binds to and inhibits a previously unrecognized *C*-terminal ATP binding pocket.[3] Recently, cis-platinum was also shown to bind to this region;[7] however, the exact location of the *C*-terminal nucleotide-binding pocket remains unknown. New derivatives of novobiocin that have an increased affinity for the *C*-terminal ATP binding site may prove valuable toward the development of new Hsp90 inhibitors and elucidation of the *C*-terminal nucleotide binding domain.

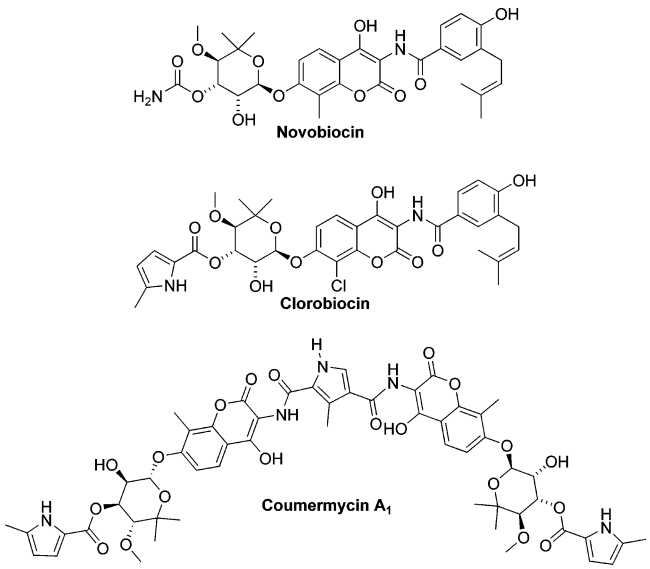

FIGURE 1. Coumarin antibiotics.

Novobiocin is a coumarin antibiotic isolated from *Streptomyces* species, which are also responsible for the biosyntheses of related compounds, clorobiocin and coumermycin A_1 (Figure 1).[8] All of these compounds contain not only the coumarin ring system, but also a carbamate-containing noviose moiety. Noviose is a unique C_8 sugar that has received considerable synthetic attention[9] due to novobiocin's role in the inhibition of type II topoisomerases and more recently Hsp90.

Although noviose has been prepared by a variety of methods, no single procedure capable of the synthesis of both enantiomers has been reported. It was envisioned that both L- and D-noviose could be synthesized from readily available reagents to provide both enantiomers in a minimal number of steps (Scheme 1). Commercially available 2,3-*O*-isopropylidene-D-erythronolactol is a suitable reagent for the synthesis of D-noviose; however, 2,3-*O*-isopropylidene-L-erythronolactol is also readily obtainable[10,11] and provides an appropriate reagent for the

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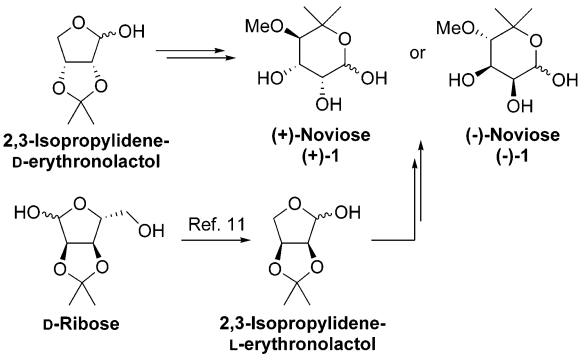
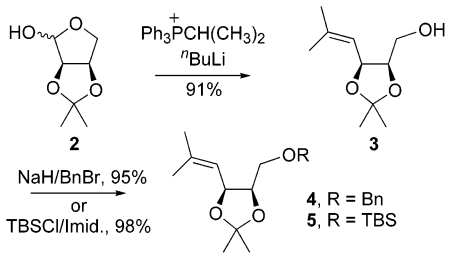
preparation of L-noviose following the procedure described herein.

SCHEME 1



With this vision in mind, we set out to prepare D-noviose from 2,3-*O*-isopropylidene-D-erythronolactol, **2**. Treatment of this hemiacetal with the ylide of isopropyl triphenylphosphonium bromide[12] provided the trisubstituted olefinic product **3** in good yield (Scheme 2). Protection of the primary alcohol was necessary to prevent alkylation in subsequent steps. Therefore, the primary alcohol was converted to benzyl ether **4** and the *tert*-butyldimethylsilyl ether **5**.

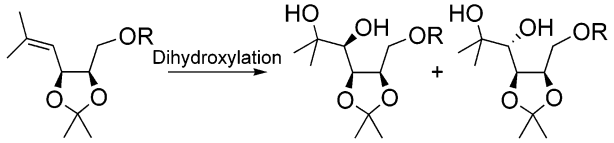
SCHEME 2



Dihydroxylation[13] of alkenes **4** and **5** proved to be troublesome (Table 1). Initial attempts to oxidize this double bond in the presence of the *tert*-butyldimethylsilyl ether resulted in poor diastereoselectivity (entries 1−3). Surprisingly, both AD-Mix α and *β*[14] furnished primarily the undesired products, **B**. When the silyl ether was replaced with a benzyl ether, a higher yield of the desired isomer was obtained; however, the major product remained the undesired compound under asymmetric conditions. Finally, the benzyl ether containing olefin was treated with osmium tetraoxide and stoichiometric 4-methylmorpholine *N*-oxide[13] to provide a 2:1 mixture of diastereomeric products (entry 6), which could be easily separated by silica chromatography.

Treatment of the desired diol (**6A**) with potassium *tert*-butoxide, followed by addition of methyl iodide provided the secondary methyl ether **8** in good yield (Scheme 3). The benzyl-protecting group was removed and the corresponding alcohol oxidized to provide lactone **10**. Treatment of **10** with diisobutylaluminum hydride, followed by aqueous sulfuric acid gave (−)-noviose as a 3:1 mixture of anomers. The ^{1}H and ^{13}C NMR spectra were identical with those obtained by literature procedures;[9e] however, the optical rotation was opposite to the reported value and indicative of the successful completion of (−)-noviose.

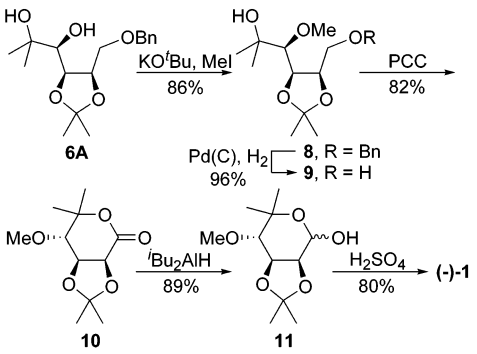
TABLE 1. Dihydroxylation of 4 and 5



entry	compd	oxidation	ratio (**A**:**B**)	yield (%)[a]
1	**5**	AD-Mix α	1:2	95
2	**5**	AD-Mix *β*	1:3	92
3	**5**	OsO_4,NMO	1.2:1	78
4	**4**	AD-Mix α	1:1	87
5	**4**	AD-Mix *β*	1:2	84
6	**4**	OsO_4,NMO	2:1	84

[a] Isolated yields.

SCHEME 3



In conclusion, we have prepared (−)-noviose from 2,3-*O*-isopropylidene-D-erythronolactol. The synthetic route described in this note proceeds in 8 steps. To date, this represents the shortest method for the preparation of (−)-noviose from commercially available reagents. In addition to the preparation of D-noviose, the L-enantiomer of 2,3-*O*-isopropylidene erythronolactol is readily available and provides a useful method for the synthesis of (+)-noviose. Using the procedure described above, studies are now underway to prepare new analogues of novobiocin for identification of Hsp90 structure−activity relationships and elucidation of the *C*-terminal ATP binding pocket.

Experimental Section

((4*R*,5*S*)-2,2-Dimethyl-5-(2-methylprop-1-enyl)-1,3-dioxolan-4-yl)methanol (3). A solution of *n*-butyllithium in hexane (1.6 M, 16 mL, 25.6 mmol) was added dropwise to a suspension of isopropyltriphenylphosphonium bromide (10.0 g, 25 mmol) in THF (120 mL) at −42 °C under argon. The mixture was stirred at −42 °C until a red solution appeared (30 min). A solution of **2** (1.60 g, 10 mmol) in THF (20 mL) was added dropwise at −42 °C before the mixture was gradually warmed to 25 °C and stirred for 20 h. Solid NH_4Cl (5 g) was added, and the resulting suspension filtered. The insoluble material was washed with EtOAc (3 × 50 mL), the eluent concentrated, and the residue

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purified by chromatography (SiO_2, 1:4, EtOAc in hexanes) to afford **3** (1.69 g, 91%) as a colorless oil; $[\alpha]^{25}_D$ +46.3 (*c* 2.01, $CHCl_3$) {lit.[12] $[\alpha]^{20}_D$ +43.1 (*c* 1.65, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 5.25 (d, J = 8.9 Hz, 1H), 4.95 (dd, J = 6.7, 8.8 Hz, 1H), 4.22 (dd, J = 6.7, 12.1 Hz, 1H), 3.57 (m, 2H), 1.78 (s, 3H), 1.73 (s, 3H), 1.51 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$ 100 MHZ) δ 139.5, 119.5, 108.6, 78.5, 74.2, 62.7, 28.4, 26.4, 25.7, 18.8.

(4*R*,5*S*)-4-(Benzyloxymethyl)-2,2-dimethyl-5-(2-methylprop-1-enyl)-1,3-dioxolane (4). Sodium hydride (60% in mineral oil, 80 mg, 2.0 mmol) was added to a solution of **3** (186 mg, 1.0 mmol) in THF (10 mL) at 25 °C. The suspension was stirred at 25 °C for 20 min before benzyl bromide (300 mg, 1.75 mmol) was added. The resulting mixture was stirred for 12 h before the addition of water (20 mL). The heterogeneous solution was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 1:20, EtOAc in hexanes) to afford **4** (263 mg, 95%) as a colorless oil; $[\alpha]^{25}_D$ +34.5 (*c* 3.30, CH_2Cl_2); ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.33 (m, 5H), 5.20 (d, J = 9.2 Hz, 1H), 4.92 (dd, J = 5.5, 9.2 Hz, 1H), 4.61 (d, J = 12.4 Hz, 1H), 4.53 (d, J = 12.4 Hz, 1H), 4.35 (dd, J = 6.1, 9.1 Hz, 1H), 3.50 (m, 2H), 1.76 (s, 3H), 1.70 (s, 3H), 1.50 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$ 100 MHZ) δ 138.6, 138.5, 128.7 (2C), 128.1 (2C), 128.0, 120.2, 108.7, 77.3, 74.4, 73.8, 70.1, 28.5, 26.5, 25.9, 18.6; IR (film) ν_{max} 2980, 2929, 2909, 2852, 1454, 1372, 1244, 1214, 1070, 1050, 1024, 737 cm^{-1}; HRMS (ESI$^+$) *m*/*z* 294.2067 (M + NH_4^+, $C_{17}H_{28}NO_3$ requires 294.2069).

(*S*)-1-((4*S*,5*R*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropane-1,2-diol (6A) and (*R*)-1-((4*S*,-5*R*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropane-1,2-diol (6B). Osmium tetraoxide (10 mg/mL in toluene, 0.1 mL) was added to a solution of olefin **4** (62 mg, 0.22 mmol) in acetone (1 mL) and H_2O (1 mL). The mixture was stirred at 25 °C for 15 min before addition of 4-methylmorpholine *N*-oxide (59 mg, 0.9 mmol). The resulting solution was stirred at 25 °C until TLC showed the consumption of **4** (~8 h). Water (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 1:8 to 1:3, EtOAc in hexanes) to afford **6B** (20 mg) as a higher R_f compound and **6A** (38 mg) as a lower R_f compound (84% total yield). **6B**: $[\alpha]^{25}_D$ −0.1 (*c* 0.97, CH_2Cl_2); ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.36 (m, 5H), 4.59 (s, 2H), 4.40 (ddd, J = 3.5, 5.3, 9.3 Hz, 1H), 4.25 (dd, J = 5.4, 9.6 Hz, 1H), 3.83 (d, J = 4.0 Hz, 1H), 3.72 (app t, J = 9.6 Hz, 1H), 3.51 (m, 2H), 3.16 (s, 1H), 1.39 (s, 3H), 1.36 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 136.9, 129.1 (2C), 128.8, 128.5 (2C), 109.7, 78.1, 76.3, 74.4, 73.9, 72.8, 69.0, 28.4, 26.0, 25.7, 25.5; IR (film) ν_{max} 3462, 2980, 2929, 2868, 1455, 1373, 1219, 1163, 1075, 958, 850, 732, 691 cm^{-1}; HRMS (ESI$^+$) *m*/*z* 328.2097 (M + NH_4^+, $C_{17}H_{30}NO_5$ requires 328.2124).

6A: $[\alpha]^{25}_D$ −38.5 (*c* 0.28, CH_2Cl_2); ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.33 (m, 5H), 4.63 (d, J = 9.0 Hz, 1H), 4.57 (d, J = 9.0 Hz, 1H), 4.42 (m, 2H), 3.80 (d, J = 5.5 Hz, 2H), 3.40 (dd, J = 1.3, 8.4 Hz, 1H), 2.83 (d, J = 8.4 Hz, 1H), 2.71 (s, 1H), 1.51 (s, 3H), 1.39 (s, 3H), 1.24 (s, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 138.0, 128.9 (2C), 128.4 (2C), 128.3, 109.0, 76.8, 76.0, 74.1, 74.0, 73.4, 69.5, 27.4, 27.3, 26.0, 25.1; IR (film) ν_{max} 3482, 2986, 2934, 2868, 1454, 1373, 1219, 1091, 743, 697 cm^{-1}; HRMS (ESI$^+$) *m*/*z* 328.2100 (M + NH_4^+, $C_{17}H_{30}NO_5$ requires 328.2124).

Oxidation of 4 with AD-mix-α. 4 (676 mg, 2.45 mmol) in *t*-BuOH (24 mL) was added to a mixture of AD-mix α (4.2 g) and methanesulfonamide (285 mg, 3 mmol) in H_2O (24 mL) at 0 °C. The resulting slurry was stirred at 0 °C for 48 h, before Na_2SO_3 (10 g) was added. The mixture was stirred for 15 min, and then extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 1:8 to 1:3, EtOAc in hexanes) to afford **6A** (353 mg, 46%) and **6B** (312 mg, 41%).

Oxidation of 4 with AD-mix-β. 4 (90 mg, 0.32 mmol) in *t*-BuOH (3 mL) was added to a mixture of AD-mix β (500 mg) and methanesulfonamide (30 mg, 0.31 mmol) in H_2O (3 mL) at 0 °C. The resulting slurry was stirred at 0 °C for 36 h, before Na_2SO_3 (1 g) was added. The mixture was stirred for 30 min, and then extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 1:8 to 1:3, EtOAc in hexanes) to afford **6A** (26 mg, 26%) and **6B** (58 mg, 58%).

(*S*)-1-((4*R*,5*R*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-methoxy-2-methylpropan-2-ol (8). Potassium *tert*-butoxide (28 mg, 0.25 mmol) was added to a solution of **6A** (68 mg, 0.21 mmol) in anhydrous THF (4 mL) at 25 °C under argon. The mixture was stirred for 20 min before addition of iodomethane (15 μL, 35 mg, 0.25 mmol). The resulting mixture was stirred for 10 h at 25 °C before water (10 mL) was added. The heterogeneous solution was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 1:4, EtOAc in hexanes) to afford **6A** (9 mg) and **8** (51 mg, 86%); $[\alpha]^{25}_D$ +15.1 (*c* 1.03, CH_2Cl_2); ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.35 (m, 5H), 4.61 (d, J = 7.6 Hz, 1H), 4.53 (d, J = 7.6 Hz, 1H), 4.37 (m, 2H), 3.66 (app t, J = 8.5 Hz, 1H), 3.51 (s, 3H), 3.45 (dd, J = 3.5, 9.3 Hz, 1H), 3.19 (m, 2H), 1.42 (s, 3H), 1.38 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 137.1, 129.0 (2C), 128.7, 128.6 (2C), 107.6, 85.0, 78.0, 76.2, 74.2, 72.3, 69.4, 61.8, 29.3, 28.6, 25.9, 23.3; IR (film) ν_{max} 3472, 2970, 2929, 2873, 2822, 1454, 1383, 1250, 1214, 1147, 1127, 1091, 1060, 737, 702 cm^{-1}; HRMS (ESI$^+$) *m*/*z* 342.2282 (M + NH_4^+, $C_{18}H_{32}NO_5$ requires 342.2280).

(*S*)-1-((4*R*,5*R*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-methoxy-2-methylpropan-2-ol (9). Palladium on charcoal (10%, 20 mg) was added to a solution of **8** (173 mg, 0.53 mmol) in EtOAc (2 mL). The mixture was stirred under hydrogen (1 atm) at 25 °C for 12 h, diluted with EtOAc (10 mL), and filtered through a plug of Celite. The filtrate was concentrated and the residue purified by chromatography (SiO_2, 1:1, EtOAc in hexanes) to afford **9** (120 mg, 96%) as a colorless oil; $[\alpha]^{25}_D$ +51.5 (*c* 2.12, CH_2Cl_2); ^{1}H NMR ($CDCl_3$ 400 MHz) δ 4.36 (dd, J = 5.3, 8.1 Hz, 1H), 4.21 (ap. q, J = 5.2 Hz, 1H), 3.75 (dt, J = 4.8, 10.8 Hz, 1H), 3.62 (m, 1H), 3.59 (t, 3H), 3.24 (d, J = 8.0 Hz, 1H), 3.20 (br t, J = 5.0 Hz, 1H), 3.06 (s, 1H), 1.47 (s, 3H), 1.39 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 107.8, 84.5, 78.1, 77.6, 73.1, 62.1, 62.0, 28.9, 28.5, 25.9, 24.7; IR (film) ν_{max} 3390, 2980, 2924, 1460, 1372, 1244, 1214, 1157, 1122, 1091, 1045, 927, 876 cm^{-1}; HRMS (ESI$^+$) *m*/*z* 252.1811 (M + NH_4^+, $C_{11}H_{26}NO_5$ requires 252.1811).

(3a*S*,7*S*,7a*S*)-7-Methoxy-2,2,6,6-tetramethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-4(6*H*)-one (10). Pyridinium chlorochromate (151 mg, 0.7 mmol) was added to a solution of **9** (53 mg, 0.23 mmol) in CH_2Cl_2 (2 mL) at 25 °C. The mixture was stirred at 25 °C for 8 h and filtered through a plug of silica gel (3 × 0.5 cm) and eluted with CH_2Cl_2. The eluent was concentrated to afford **10** (43 mg, 82%) as white solid; $[\alpha]^{25}_D$ +40.3 (*c* 0.6, CH_2Cl_2); ^{1}H NMR ($CDCl_3$ 400 MHz) δ 4.75 (d, J = 8.4 Hz, 1H), 4.49 (dd, J = 6.0, 8.4 Hz, 1H), 3.57 (s, 3H), 3.26 (d, J = 6.0 Hz, 1H), 1.52 (s, 3H), 1.47 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 169.3, 111.7, 84.9, 82.5, 77.8, 72.0, 59.4, 27.8, 27.0, 25.3, 22.5; IR (film) ν_{max} 2991, 2939, 2914, 2873, 1741, 1465, 1383, 1352, 1260, 1214, 1137, 1065, 1060, 1024, 973, 876 cm^{-1}; HRMS (ESI$^+$) *m*/*z* 248.1497 (M + NH_4^+, $C_{11}H_{22}NO_5$ requires 248.1498).

(3a*S*,7*S*,7a*S*)-7-Methoxy-2,2,6,6-tetramethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-4-ol (11). A solution of diisobutylaluminum hydride (1 M in hexane, 180 μL, 0.18 mmol) was added dropwise to a solution of **10** (35 mg, 0.15 mmol) in anhydrous CH_2Cl_2 (2 mL) at −78 °C. The mixture was stirred for 30 min at −78 °C before addition of saturated potassium sodium tartrate aqueous solution (3 mL). The mixture was warmed to 25 °C and stirred until layers separated (~1 h). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 1:1, EtOAc in hexane) to give **11** (31 mg, 89%) as a 3:1 mixture of anomers; $[\alpha]^{25}_D$ −1.6 (*c* 0.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$ 400 MHz) δ 5.12 (d, J = 4.0 Hz, major 1H), 5.11 (d, J = 2.7 Hz,

minor 1H), 4.37 (app t, J = 6.8 Hz, major 1H), 4.30 (app t, J = 6.5 Hz, minor 1H), 4.23 (dd, J = 2.7, 6.6 Hz, minor 1H), 4.16 (dd, J = 4.0, 7.0 Hz, major 1H), 3.56 (s, major 3H), 3.53 (s, minor 3H), 3.28 (d, J = 6.4 Hz, minor 1H), 3.20 (d, J = 6.6 Hz, major 1H), 1.57 (s, minor 3H), 1.54 (s, major 3H), 1.39 (s, minor 3H), 1.37 (s, major 3H), 1.35 (s, minor 3H), 1.35 (s, major 3H), 1.27 (s, major 3H), 1.16 (s, minor 3H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 110.2, 109.7, 92.9, 89.4, 89.3, 83.8, 83.7, 77.6, 75.9, 75.8, 74.7, 60.6, 60.5, 30.1, 29.0, 27.9, 27.7, 27.6, 26.2, 25.4, 25.0, 21.0; IR (film) ν_{max} 3436, 2975, 2929, 1460, 1378, 1239, 1209, 1157, 1106, 1065, 871, 804 cm^{-1}; HRMS (ESI$^+$) m/z 250.1654 (M + NH_4^+, $C_{11}H_{24}NO_5$ requires 250.1654).

(−)-Noviose, (−)-1. 11 (17 mg, 0.077 mmol) was dissolved in aqueous sulfuric acid (0.1 N, 0.2 mL) and warmed to 75 °C for 2 h. After the solution was cooled to 25 °C, solid Na_2CO_3 was added until pH 8. The mixture was evaporated to dryness and washed with ethanol (3 × 2 mL). The extracts were combined and concentrated to give a residue, which was purified by chromatography (SiO_2, 1:9, ethanol in CH_2Cl_2) to afford (−)-**1** (12 mg, 80%) as a white solid representing a 3:1 ratio of anomers; $[\alpha]^{25}_D$ −21.3 (*c* 0.1, EtOH/H_2O 1:1) {lit.[9e] $[\alpha]^{20}_D$ −29.2 (*c* 1.0, EtOH/H_2O 1:1)}; ^{1}H NMR (CD_3OD 400 MHz) δ 5.01 (d, J = 3.4 Hz, minor 1H), 4.88 (d, J = 1.3 Hz, major 1H), 4.00 (dd, J = 3.4, 8.2 Hz, minor 1H), 3.78 (dd, J = 1.3, 3.3 Hz, major 1H), 3.72 (app t, J = 3.4 Hz, minor 1H), 3.68 (dd, J = 3.3, 9.9 Hz, major 1H), 3.58 (s, major 3H), 3.54 (s, minor 3H), 3.22 (d, J = 8.2 Hz, minor 1H), 3.18 (d, J = 9.9 Hz, major 1H), 1.33 (s, minor 3H), 1.30 (s, major 3H), 1.28 (s, minor 3H), 1.15 (s, major 3H); ^{13}C NMR (CD_3OD 100 MHz) 94.6, 89.9, 84.8, 84.2, 77.1, 74.7, 72.8, 72.2, 71.5, 68.7, 61.2, 60.5, 27.9, 27.5, 24.0, 17.6.

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Supporting Information Available: ^{1}H and ^{13}C spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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