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Synthesis of 2-deoxy-α-DAH based on diazo chemistry by insertion reactions of 2-diazo-3-deoxy-D-*arabino*-heptulosonate derivatives mediated by rhodium(II)

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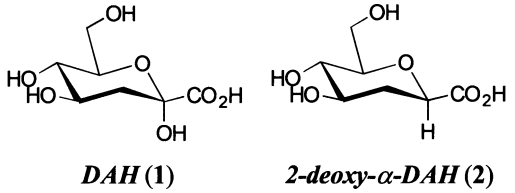
Abstract—The synthesis of 2-deoxy-α-DAH (**2**) is described based on the use of diazo chemistry as previously reported by us during the synthesis of the corresponding 2-deoxy-KDO. Initially, the D-arabino-aldehydo sugar derivative **3** was reacted with ethyl diazoacetate, using diethyl zinc as promoter. The corresponding β-hydroxy-α-diazo ester **4**, obtained in very good yield, was transformed into the corresponding 2-diazo-3-deoxy-heptulosonate derivative **10**, which was subjected to the action of rhodium(II). However, the major compound obtained in this reaction was the C-glycofuranoside **12** by the interaction of the benzyl protecting group employed at the OH of C-4 with the carbenoid generated at C-2. To avoid this undesired insertion reaction, aldehyde **13** was selected as a suitable starting material and, following the same chemistry than for **3**, diazo **19** was efficiently synthesized. Finally, the intramolecular OH insertion mediated by rhodium(II) of **19** provided the targeted 2-deoxy-DAH derivative **21** in a reasonable good yield, which was finally transformed into the potassium salt of 2-deoxy-α-DAH **2**.

1. Introduction

During the last few years, natural 3-deoxy-2-ulosonic acids† have elicited an intense interest by synthetic organic chemists due to their important biological functions, especially KDN and KDO.[1] These studies have culminated in the total synthesis of natural 3-deoxy-2-ulosonic acids and a large number of analogues, as potential inhibitors of the enzymes involved in these biological processes, essential for the development and growth of microorganisms.[2] In particular, specific KDN analogues have been used against the influenza virus[3] and some KDO analogues have shown potent inhibition against CMP-KDO and KDO-8-phosphate synthetases, two potential antibacterial targets.[4] On the other hand, 3-Deoxy-D-*arabino*-2-heptulosonic acid (DAH, **1**)[5] represents a key intermediate in the biosynthesis of aromatic amino acids in plants and bacteria by the shikimate pathway.[6] The disruption of the shikimate biosynthetic pathway by inhibition of any of the enzymes involved is considered to be an attractive target for biochemists and clinicians as it represents an interesting and alternative strategy for the development of antimicrobials.[7] In fact, a wide variety of analogues of shikimic acid have been synthesized[8] and have been shown to be biologically active. In contrast, DAH analogues, as potential inhibitors of 3-deoxy-D-*arabino*-heptulosonate-7-phosphate synthase, have received much less attention by the scientific community.[9] Recently, Shumilin et al.[10] have reported the crystal structure of DAH-7-P synthase, which should provide new opportunities for the structure based design and synthesis of novel and efficient inhibitors. In this paper, we wish to report a synthesis of 2-deoxy-α-DAH (**2**) (Fig. 1) based on the diazo chemistry,[11] which was previously employed for the synthesis of 2-deoxy-KDO.[12]

2. Results and discussion

The synthesis of 2-deoxy-α-DAH (**2**) was envisioned to proceed along the path previously charted in our



***DAH* (1)** ***2-deoxy-α-DAH* (2)**

Figure 1. Structures of DAH (**1**) and 2-deoxy-α-DAH (**2**).

Keywords: DAH analogues; 2-deoxy-DAH; shikimate pathway inhibitors; diazo; carbenoids; monosaccharides.

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† The acronyms used for the natural 3-deoxy-2-ulosonic acids (DAH, KDO and KDN) are internationally accepted by the scientific community. The full names corresponding to them are the following: 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH), 3-deoxy-D-*manno*-2-octulosonic acid (KDO) and 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN).

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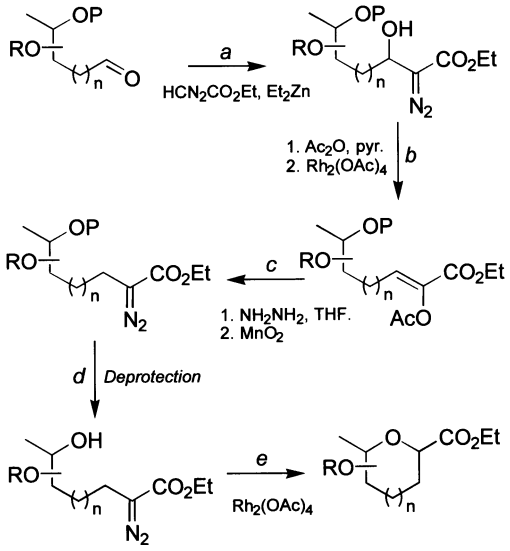
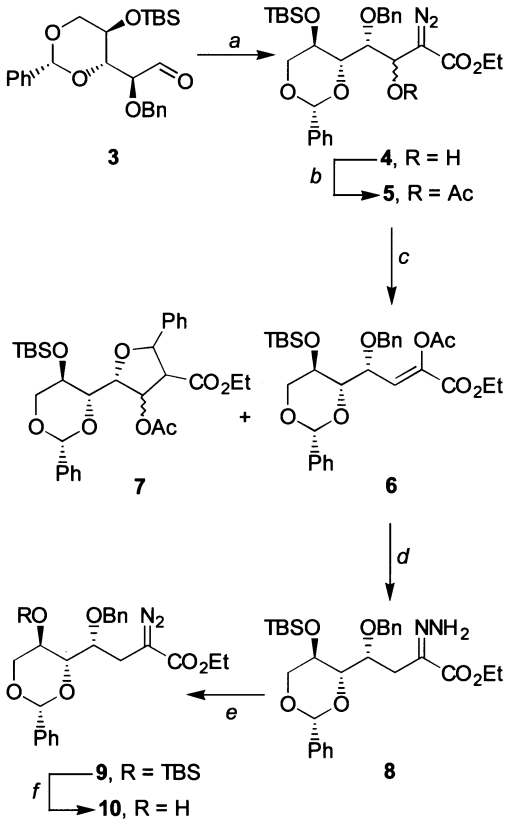
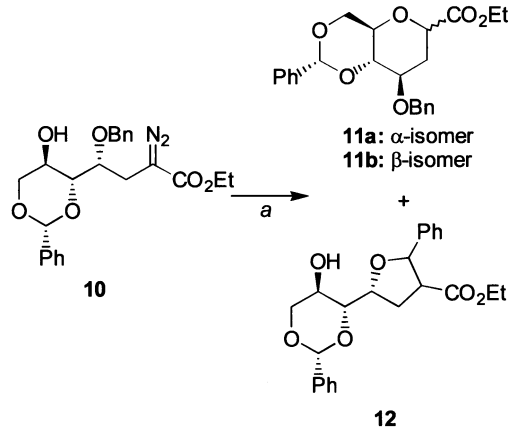


Scheme 1. General approach to the synthesis of 2,3-dideoxy-ulosonic acids based on diazo chemistry.

laboratories for 2-deoxy-KDO[12] that involve: (a) reaction with ethyl diazoacetate, (b) acetylation and conversion to the enol ester by the catalytic action of rhodium(II), (c) transformation of the enol ester to the corresponding



Scheme 2. Synthesis of the diazo (**10**) from the aldehyde **3**. *Reagents and conditions*: (a) 1.5 equiv. HCN_2CO_2Et, 1.5 equiv. Et_2Zn, CH_2Cl_2, $-78°C \rightarrow -50°C \rightarrow 0°C$, 8 h, 84%. (b) 5.0 equiv. Ac_2O, pyr., 25°C, 1 h, 85%. (c) 0.02 equiv. $Rh_2(OAc)_4$, CH_2Cl_2, 25°C, 2 h, 73% for **6**, 25% for **7**. (d) 4.0 equiv. NH_2NH_2, 8.0 equiv. AcOH, THF, 0°C, 2 h, 93%. (e) 2.0 equiv. MnO_2, CH_2Cl_2, 25°C, 0.5 h, 99.5%. (f) 1.2 equiv. TBAF, THF, 25°C, 0.5 h, 95%.



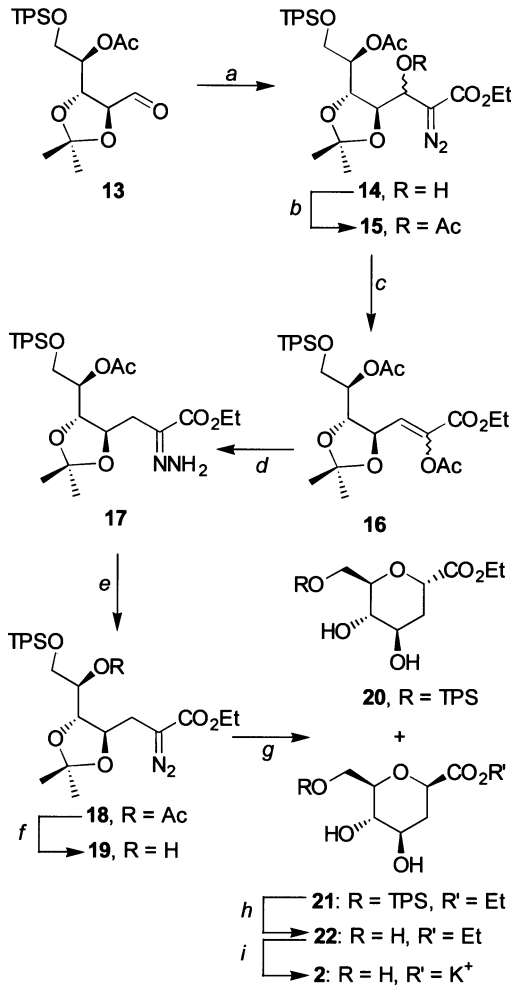
Scheme 3. Reaction of the diazo **10** with Rh(II). Synthesis of the 2-deoxy-DAH derivative **12**. *Reagents and conditions*: (a) 0.1 equiv. $Rh_2(OAc)_4$, C_6H_6 (0.01 M), 80°C, 6 h, 18% for **11a**, 4.4% for **11b**, 72% for **12**.

2-hydrazone derivative, and subsequent oxidation to the diazo compound, followed by (d) OH insertion into the carbenoid species generated by rhodium(II) (Scheme 1).

Initially, aldehyde **3** was chosen as a suitable starting material. Thus, **3** was reacted with ethyl diazoacetate following a new, efficient and high-yielding procedure mediated by Et_2Zn,[13] as previously reported.[14] The reaction provided the corresponding β-hydroxy-α-diazo ester **4** in 84% yield and good stereoselectivity at C-3 (4:1). When this reaction was performed using conventional conditions by mixing ethyl diazoacetate and the aldehyde in the absence of solvent and catalyst, which proved successful in previous cases,[12b,15] gave a poor yield of **4** (30%) after a long reaction time (7 days). The establishment of the absolute stereochemistry of the new chiral center generated at C-3 of **4** was not necessary because the chirality at this center is lost in subsequent steps. Then, diazo **4** was transformed into the diazo **10** with no problems, through compounds **5**, **6**, **8** and **9**, following the synthetic path developed previously (Scheme 2).[12] It is noteworthy to mention that during the conversion of diazo **5** to enol ester **6**, obtained in a 73% yield, a 25% yield of the tetrahydro furane derivative **7** was obtained as a result of a C–H insertion of the emerging rhodiumcarbenoid into the benzylic position.

With the hydroxy diazo **10** in hand, we proceeded with the intramolecular OH insertion reaction mediated by the rhodium(II) dimer.[16] Thus, when a hot diluted solution of diazo **10** in benzene (0.01 M) was subjected to the action of a catalytic amount of rhodium(II) acetate dimer, the result was the clean formation of compounds **11** and **12** in 22 and 72% yields, respectively (Scheme 3).

Similar to the conversion of diazo **5** to enol ester **7**, the benzyl protecting group interfered with the insertion reaction rendering the desired compound **11** as the minor product in a 4:1 mixture of stereoisomers at C-2, and **12** as the major product as only one stereoisomer, whose absolute stereochemistry was not determined. Modification of reaction conditions or catalysts did not improve the ratio of compounds **11**/**12** in favor of the OH insertion compound.



Scheme 4. Synthesis of 2-deoxy-α-DAH (**2**) from aldehyde **13**. *Reagents and conditions*: (a) 1.5 equiv. HCN_2CO_2Et, 1.5 equiv. Et_2Zn, CH_2Cl_2, −78°C→−50°C→0°C, 8 h, 80%. (b) 5.0 equiv. Ac_2O, pyr., 25°C, 1 h, 98%. (c) 0.02 equiv. $Rh_2(OAc)_4$, CH_2Cl_2, 25°C, 1 h, 98%. (d) 4.0 equiv. NH_2NH_2, 8.0 equiv. AcOH, THF, 0°C, 2 h, 77%. (e) 2.0 equiv. MnO_2, CH_2Cl_2, 25°C, 0.5 h, 86%. (f) 1.0 equiv. NaEtO, EtOH, 0°C, 0.5 h, 90%. (g) 0.1 equiv. $Rh_2(OAc)_4$, CH_2Cl_2 (0.01 M), 0°C, 1 h, 17% for **20**, 48% for **21**. (h) 1.2 equiv. TBAF, THF, 25°C, 0.5 h, 92%. (i) 1.0 equiv. KOH, EtOH/H_2O (1:1), 0°C, 0.5 h, 97%.

In order to avoid undesired insertion reactions, a modification of the protecting group employed at C-2 of the starting aldehyde was required. Then, we considered aldehydo-sugar **13**[17] as a suitable alternative for the efficient construction of the target molecule. In a similar synthetic sequence than for **3**, **13** was reacted with ethyl diazoacetate to yield the corresponding β-hydroxy-α-diazo ester **14**, as a 1:1 mixture of diastereoisomers, in good yield (80%). In this case, the reaction carried out without solvent or catalyst, afforded a better yield of product **14** (52%) compared with the reaction of **3** with ethyl diazoacetate under similar conditions. Then, the implementation of the strategy based on diazo chemistry towards compound **19** proceeded along a similar path to that developed for the corresponding diazo **10**, described above. Thus, diazo **19** was successfully synthesized via intermediates **15** (98%), **16** (98%), **17** (77%) and **18** (86%). Finally, hydroxy diazo **19** was reacted with a catalytic amount of rhodium(II) acetate dimer in CH_2Cl_2 at 0°C, to afford a mixture of **20** (17%) and **21** (48%). This insertion reaction was accompanied with the cleavage of the isopropylidene acetal that occurred during the formation of the pyranoside ring. This cleavage reaction is explained by the high strain of the emerging cyclic *trans* acetal system and the Lewis acidity of the Rh(II), which promotes hydrolysis. Both isomers, **20** and **21**, were separated by flash column chromatography, and their respective stereochemistry at C-2 were established according to their ^{1}H NMR spectra. In fact, spectra of **20** showed a doublet-doublet at 4.44 ppm corresponding to H-2 with a coupling constant J_{H2-H3a}=6.5 Hz, whereas the corresponding H-2 of compound **21** appeared as doublet–doublet at 4.02 ppm with J_{H2-H3a}=12.0 Hz. These values reveal a *trans* diaxial relationship between H-2 and H-3a for the major compound **21**. Furthermore, compound **21** was transformed into the triol **22** by treatment with TBAF, which has been described in the literature,[9c] prepared by a stereoselective hetero Diels–Alder reaction for the construction of the pyranoside ring, followed by an asymmetric dihydroxylation. In a final step, compound **22** was transformed into the potassium salt of **2** by reaction with potassium hydroxide. This compound has been similarly described in the literature,[18] obtained as a minor product during the basic treatment of 7-bromo-3,7-dideoxy-D-*gluco*-heptono-1,4-lactone. Thus, comparison of its spectrocopic data (NMR spectra) confirmed the identity of **2** (Scheme 4).

3. Conclusions

The use of diazo compounds in the carbohydrate field[19] represents an efficient and versatile methodology for the elongation of monosaccharides and especially for the preparation of natural 2-ulosonic acids and analogues thereof. The present paper describes an extension of this methodology for the synthesis of a 2-deoxy-DAH analogue and provides access to a family of more complex analogues of the natural partner via key intermediates. By combining the structural information of the enzymes involved in the shikimate pathway for the biosynthesis of 7-phosphate DAH, with molecular modeling tools and a suitable synthetic technology, one can envision the rational design and synthesis of novel structures with potential inhibitory effects. We are currently devoting efforts in pursuit of these goals.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and ethyl ether (ether) were distilled from sodium benzophenone, and methylene chloride (CH_2Cl_2), benzene (PhH), and toluene from calcium hydride. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. All solutions used in workup procedures were saturated unless otherwise noted. All reagents were purchased at highest commercial quality and used without further purification unless otherwise stated.

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25, 0.50 or 1 mm E. Merck silica gel plates (60F-254).

NMR spectra were recorded on a Bruker Advanced-400 instrument and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; b, broad. IR spectra were recorded on a Beckman Aculab IV spectrometer. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on a Kratos MS 80 RFA mass spectrometer under fast atom bombardment (FAB) conditions.

4.1.1. Aldehyde 3. A solution of 3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-D-*gluco*furanose (17.2 g, 49.08 mmol, 1.0 equiv.) in 1,4-dioxane (35 mL) was treated with 1N H_2SO_4 (15 mL, 0.3 equiv.) and heated at 70°C overnight. Then, the reaction was allowed to reach room temperature and neutralized to pH 7 by slow addition of a 40% NaOH solution. The resulting mixture was extracted with CH_2Cl_2 (3×50 mL), and the combined organic solution was washed with water. The resulting combined aqueous solution was then concentrated under vacuum to dryness, and the crude so obtained was extracted with EtOH (3×75 mL). The alcoholic suspension was filtered and the filtrate concentrated to a solid, corresponding to 3-*O*-benzyl-D-*gluco*pyranose (9.8 g, 74%) practically pure. This compound (9.8 g, 36.26 mmol, 1.0 equiv.) was subjected to the action of benzaldehyde dimethylacetal (6.8 mL, 45.32 mmol, 1.25 equiv.) and CSA (1.68 g, 7.25 mmol, 0.2 equiv.) in DMF (30 mL) at 25°C for 8 h. Triethylamine (1.29 mL, 9.25 mmol, 0.25 equiv.) was added at this temperature and the crude mixture was poured into an ice-water mixture. After vigorous stirring for 1 h, a white solid was formed, then it was filtered, washed with hexanes and dried. The solid, corresponding to 3-*O*-benzyl-4,6-*O*-benzylidene-D-*gluco*pyranose (11.0 g, 85%), did not require further purification. To a solution of 3-*O*-benzyl-4,6-*O*-benzylidene-D-*gluco*pyranose (10.0 g, 27.90 mmol, 1.0 equiv.) in EtOAc (300 mL) was added portionwise $Pb(OAc)_4$ (15.6 g, 33.48 mmol, 1.2 equiv.) at 0°C and the mixture was vigorously stirred for 0.5 h at 0°C. After completion of the reaction, the mixture was filtered through silicagel and washed with 50% EtOAc in hexanes. The solvents were removed under reduced pressure providing the corresponding pure aldehyde (10.6 g, 98%) as a colorless oil. The resulting aldehyde (10.6 g, 29.74 mmol, 1.0 equiv.) was subjected to the action of sodium borohydride (1.69 g, 44.62 mmol, 1.5 equiv.) in MeOH (150 mL) at 0°C. After stirring at 0°C for 0.5 h, the reaction was complete, and EtOAc (200 mL) and saturated aqueous NH_4Cl solution (150 mL) were sequentially added and the organic layer was separated. The aqueous phase was extracted with EtOAc (2×100 mL), and the combined organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 50% EtOAc in hexanes) provided pure diol (5.5 g, 56%) as a colorless oil. This diol (5.5 g, 16.64 mmol, 1.0 equiv.) was selectively benzylated by treatment with benzoyl chloride (1.93 mL, 16.64 mmol, 1.0 equiv.) in pyridine (20 mL) at 0°C. After 1 h at 0°C, the reaction mixture was allowed to reach room temperature and stirred for additional 2 h. Then, CH_2Cl_2 (80 mL) was added and the organic solution washed with 10% HCl solution (50 mL), saturated aqueous $NaHCO_3$ solution (100 mL) and brine (100 mL). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 25% EtOAc in hexanes) provided the corresponding monobenzoyl derivative (5.5 g, 76%) as a white solid. The resulting alcohol monobenzoylated (5.5 g, 12.66 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (50 mL), the solution was cooled at 0°C, and 2,6-lutidine (2.2 mL, 19.00 mmol, 1.5 equiv.) was added. After being stirred for 5 min at that temperature, *tert*-butyldimethylsilyltriflate (3.5 mL, 15.19 mmol, 1.2 equiv.) was added dropwise and the reaction mixture was allowed to stir at 0°C for 30 min, after which time no starting material was detected by TLC. Saturated aqueous NH_4Cl solution (30 mL) was added, and the reaction mixture was allowed to warm to room temperature. The organic phase was separated, and the aqueous layer was extracted with ether (3×30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvents were removed under reduced pressure. The obtained crude was then dissolved in MeOH (50 mL) and treated with MeONa (14.0 mL, 1.0 M solution in MeOH, 14.0 mmol, 1.1 equiv.) at 0°C for 30 min. The resulting mixture was neutralized with 10% HCl and diluted with CH_2Cl_2 (50 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic solution was washed with brine (150 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification by flash column chromatography (silica gel, 10% EtOAc in hexanes) furnished pure alcohol (4.5 g, 80% overall yield) as a slightly yellow oil. Finally, to a solution of oxalyl chloride (0.71 mL, 8.10 mmol, 1.8 equiv.) in CH_2Cl_2 (30 mL) was added dropwise DMSO (0.70 mL, 9.90 mmol, 2.2 equiv.) at −78°C. After the mixture was stirred for 15 min, a solution of alcohol (2.0 g, 4.50 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) was added dropwise at −78°C. The solution was stirred for 30 min at −78°C, and Et_3N (3.13 mL, 22.5 mmol, 5.0 equiv.) was added at the same temperature. The reaction mixture was allowed to warm to 0°C over 30 min, and then ether (100 mL) was added, followed by saturated aqueous NH_4Cl solution (50 mL). The organic phase was separated, and the aqueous phase was extracted with ether (2×50 mL). The combined organic solution was washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 25% EtOAc in hexanes) provided aldehyde **3** (1.72 g, 86%) as a colorless oil: R_f=0.58 (silica gel, 25% EtOAc in hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.76 (d, J=1.8 Hz, 1H, CHO), 7.56–7.30 (m, 10H, 2×Ph), 5.48 (s, 1H, CHPh), 4.75 (s, 2H, PhCH_2O), 4.37–4.15 (m, 3H, C*H*(OR)), 4.05 (dd, J=7.2, 3.0 Hz, 1H, C*H*(OR)), 3.62 (dd, J=7.5 Hz, 1H,

C*H*(OR)), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.05, 0.04 (2s, $Si(CH_3)_2$).

4.1.2. β-Hydroxy-α-diazo ester 4: reaction of aldehyde 3 with ethyl diazoacetate. To a solution of ethyl diazoacetate (0.61 mL, 5.84 mmol, 1.5 equiv.) in CH_2Cl_2 (20 mL) was added dropwise Et_2Zn (5.84 mL, 1 M solution in hexanes, 5.84 mmol, 1.5 equiv.) at −78°C. After being stirred for 30 min, the solution was allowed to warm to −50°C. Then, a solution of aldehyde **3** (1.72 g, 3.89 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) was added dropwise, and the resulting mixture was stirred for 2 h at −50°C, and overnight at room temperature. After this time, the reaction mixture was cooled to 0°C and then quenched by slow addition of 15% NH_4OH solution (30 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic solution was dried over $MgSO_4$ and concentrated under vacuum. The crude mixture was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to provide β-hydroxy-α-diazo ester **4** (1.81 g, 83.5%) as a 4:1 inseparable mixture of stereoisomers at C-3: R_f=0.32 (silica gel, 25% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 3462, 3043, 2936, 2864, 2103, 1735, 1685, 1653, 1383, 1256; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.64 (m, 2H, Ph), 7.56–7.30 (m, 8H, Ph), 5.48 (s, 1H, CHPh, major isomer), 5.47 (s, 1H, CHPh, minor isomer), 5.02 (dd, *J*=6.7, 4.9 Hz, 1H, C*H*(OR), major isomer), 4.93 (dd, *J*=6.0, 4.7 Hz, 1H, C*H*(OR), minor isomer), 4.85 (d, *J*=11.5 Hz, 1H, PhCH_2O, major isomer), 4.82 (d, *J*=11.4 Hz, 1H, PhCH_2O, minor isomer), 4.78 (d, *J*=11.4 Hz, 1H, PhCH_2O, minor isomer), 4.62 (d, *J*=11.5 Hz, 1H, PhCH_2O, major isomer), 4.29–4.04 (m, both isomers), 3.95 (dd, *J*=9.0, 1.5 Hz, 1H, C*H*(OR), major isomer), 3.84 (dd, *J*=9.2, 2.7 Hz, 1H, C*H*(OR), minor isomer), 3.61 (dd, *J*=10.3 Hz, 1H, C*H*(OR), major isomer), 3.39 (d, *J*=6.8 Hz, 1H, major isomer), 1.25 (t, *J*=7.3 Hz, 3H, $CO_2CH_2CH_3$, minor isomer), 1.23 (t, *J*=7.0 Hz, 3H, $CO_2CH_2CH_3$, major isomer), 0.89 (s, 9H, $SiC(CH_3)_3$, minor isomer), 0.87 (s, 9H, $SiC(CH_3)_3$, major isomer), 0.09, 0.05, 0.04 (3s, $Si(CH_3)_2$, both isomers); ^{13}C NMR (50.3 MHz, $CDCl_3$) (major isomer) δ 166.3, 138.1, 137.3, 128.9, 128.4, 128.2, 127.9, 127.7, 126.1, 101.3, 82.3, 76.5, 74.2, 72.3, 71.9, 66.9, 61.9, 25.7, 17.9, 14.4, −3.8, −4.8; FAB HRMS (NBA) *m/e* 557.2931, M+1 calcd for $C_{29}H_{40}N_2O_7Si$: 557.2934.

4.1.3. β-Acetoxy-α-diazo ester 5: acetylation of 4. β-Hydroxy-α-diazo ester **4** (1.80 g, 3.25 mmol, 1.0 equiv., 4:1 mixture of stereoisomers at C-3) was dissolved in pyridine (15 mL) and acetic anhydride (1.7 mL, 16.25 mmol, 5.0 equiv.) was added at 0°C. The reaction mixture was stirred at 25°C for 1 h. After this time, CH_2Cl_2 (30 mL) and saturated aqueous NH_4Cl solution (30 mL) were sequentially added and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2×10 mL), and the combined organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% EtOAc in hexanes) provided β-acetoxy-α-diazo ester **5** (1.64 g, 85%) as a yellow oil: (4:1 inseparable mixture of stereoisomers at C-3) R_f=0.35 (silica gel, 25% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 3042, 2936, 2112, 1752, 1735, 1685, 1671, 1460, 1382, 1216; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72–7.66 (m, 2H, Ph), 7.55–7.30 (m, 8H, Ph), 5.92 (d, *J*=5.7 Hz, 1H, C*H*(OAc), major isomer), 5.85 (d, *J*=8.9 Hz, 1H, C*H*(OAc), minor isomer), 5.49 (s, 1H, CHPh, minor isomer), 5.47 (s, 1H, CHPh, major isomer), 4.95 (d, *J*=11.8 Hz, 1H, PhCH_2O, minor isomer), 4.86 (d, *J*=11.6 Hz, 1H, PhCH_2O, major isomer), 4.81 (d, *J*=11.8 Hz, 1H, PhCH_2O, minor isomer), 4.75 (d, *J*=11.6 Hz, 1H, PhCH_2O, major isomer), 4.54–4.52 (m, 1H, major isomer), 4.38–4.29 (m, both isomers), 4.27 (q, *J*=7.3 Hz, 2H, $CO_2CH_2CH_3$, major isomer), 4.22–4.09 (m, both isomers), 3.84 (dd, *J*=8.9, 0.9 Hz, 1H, C*H*(OR), major isomer), 3.80 (dd, *J*=9.2, 1.0 Hz, 1H, C*H*(OR), minor isomer), 3.66 (dd, *J*=10.3 Hz, 1H, C*H*(OR), major isomer), 2.13 (s, 3H, $OCOCH_3$, major isomer), 1.97 (s, 3H, $OCOCH_3$, minor isomer), 1.31 (t, *J*=7.3 Hz, 3H, $CO_2CH_2CH_3$, major isomer), 1.16 (t, *J*=7.0 Hz, 3H, $CO_2CH_2CH_3$, minor isomer), 0.96 (s, 9H, $SiC(CH_3)_3$, both isomers), 0.13 (s, $Si(CH_3)_2$, both isomers); ^{13}C NMR (50.3 MHz, $CDCl_3$) (major isomer) δ 169.5, 165.2, 137.9, 137.3, 137.2, 128.5, 128.1, 127.9, 127.3, 126.8, 125.8, 100.8, 81.6, 75.9, 74.1, 71.7, 70.4, 62.3, 60.5, 25.6, 20.7, 17.7, 14.1, −3.6, −4.9; (minor isomer) δ 170.5, 164.7, 138.5, 137.3, 137.2, 128.7, 128.1, 127.9, 127.1, 126.6, 125.9, 101.1, 81.6, 75.6, 73.9, 71.3, 70.4, 61.8, 60.8, 25.6, 20.6, 17.7, 14.2, −3.6, −4.9; FAB HRMS (NBA) *m/e* 571.2741, M+1−28 calcd for $C_{31}H_{42}N_2O_8Si$: 571.2727.

4.1.4. Products 6 and 7: treatment of β-acetoxy-α-diazo ester 5 with $Rh_2(OAc)_4$. To a solution of diazo **5** (1.5 g, 2.51 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) was added a catalytic amount of $Rh_2(OAc)_4$ (22 mg, 0.050 mmol, 0.02 equiv.) at 25°C. After stirring for 2 h, the mixture was filtered through Celite, and the resulting clear colorless solution was concentrated under reduced pressure. Flash column chromatography (silica gel, 10% EtOAc in hexanes) afforded enol ester **6** (1.05 g, 73%) and compound **7** (0.36 g, 25%) as colorless oils.

Compound **6** (1:1 mixture of *Z*/*E* isomers): R_f=0.42 (silica gel, 25% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 3074, 2939, 2865, 1773, 1735, 1663, 1496, 1472, 1116; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75–7.63 (m, 2H, Ph), 7.55–7.25 (m, 8H, Ph), 6.85 (d, *J*=9.5 Hz, 0.5H, C*H*=(OAc)), 6.26 (d, *J*=9.7 Hz, 0.5H, C*H*=(OAc)), 5.50 (s, 0.5H, CHPh), 5.49 (s, 0.5H, CHPh), 4.70 (d, *J*=11.7 Hz, 0.5H, PhCH_2O), 4.68 (dd, 0.5H, *J*=9.7, 8.0 Hz, 0.5H, C*H*(OR)), 4.66 (d, *J*=11.7 Hz, 0.5H, PhCH_2O), 4.53 (d, *J*=11.7 Hz, 0.5H, PhCH_2O), 4.42 (d, *J*=11.7 Hz, 0.5H, PhCH_2O), 4.34–4.17 (m, 5H), 3.80 (dd, *J*=8.5, 1.8 Hz, 0.5H, CH_2(OR)), 3.67–3.60 (m, 1H), 2.29 (s, 1.5H, $OCOCH_3$), 2.22 (s, 1.5H, $OCOCH_3$), 1.36 (t, *J*=7.2 Hz, 1.5H, $CO_2CH_2CH_3$), 1.34 (t, *J*=7.0 Hz, 1.5H, $CO_2CH_2CH_3$), 0.96 (s, 4.5H, $SiC(CH_3)_3$), 0.93 (s, 4.5H, $SiC(CH_3)_3$), 0.17, 0.14, 0.11, 0.08 (4s, 6H, $Si(CH_3)_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$) (both isomers) δ 170.9, 170.3, 169.2, 168.5, 161.3, 161.0, 139.8, 139.1, 138.2, 137.8, 137.7, 137.5, 128.2, 128.1, 127.4, 127.3, 126.3, 101.2, 101.1, 84.2, 83.7, 76.2, 75.3, 71.7, 71.6, 71.0, 70.9, 70.7, 70.4, 61.7, 61.6, 61.4, 61.3, 25.6, 20.3, 20.1, 17.8, 17.7, 14.0, 13.9, −3.9, −4.3, −5.0, −5.2; FAB HRMS (NBA) *m/e* 571.2737, M+1 calcd for $C_{31}H_{42}O_8Si$: 571.2727.

Compound **7**: R_f=0.45 (silica gel, 25% EtOAc in hexanes);

IR (thin film) ν_{max} (cm^{-1}) 3074, 2939, 2865, 1773, 1735, 1663, 1496, 1472, 1116; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75–7.63 (m, 2H, Ph), 7.55–7.25 (m, 8H, Ph), 6.85 (d, J=9.5 Hz, 0.5H, C*H*=(OAc)), 6.26 (d, J=9.7 Hz, 0.5H, C*H*=(OAc)), 5.50 (s, 0.5H, CHPh), 5.49 (s, 0.5H, CHPh), 4.70 (d, J=11.7 Hz, 0.5H, PhCH_2O), 4.68 (dd, 0.5H, J=9.7, 8.0 Hz, 0.5H, C*H*(OR)), 4.66 (d, J=11.7 Hz, 0.5H, PhCH_2O), 4.53 (d, J=11.7 Hz, 0.5H, PhCH_2O), 4.42 (d, J=11.7 Hz, 0.5H, PhCH_2O), 4.34–4.17 (m, 5H), 3.80 (dd, J=8.5, 1.8 Hz, 0.5H, CH_2(OR)), 3.67–3.60 (m, 1H), 2.29 (s, 1.5H, $OCOCH_3$), 2.22 (s, 1.5H, $OCOCH_3$), 1.36 (t, J=7.2 Hz, 1.5H, $CO_2CH_2CH_3$), 1.34 (t, J=7.0 Hz, 1.5H, $CO_2CH_2CH_3$), 0.96 (s, 4.5H, $SiC(CH_3)_3$), 0.93 (s, 4.5H, $SiC(CH_3)_3$), 0.17, 0.14, 0.11, 0.08 (4s, 6H, $Si(CH_3)_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$) (both isomers) δ 170.9, 170.3, 169.2, 168.5, 161.3, 161.0, 139.8, 139.1, 138.2, 137.8, 137.7, 137.5, 128.2, 128.1, 127.4, 127.3, 126.3, 101.2, 101.1, 84.2, 83.7, 76.2, 75.3, 71.7, 71.6, 71.0, 70.9, 70.7, 70.4, 61.7, 61.6, 61.4, 61.3, 25.6, 20.3, 20.1, 17.8, 17.7, 14.0, 13.9, −3.9, −4.3, −5.0, −5.2; FAB HRMS (NBA) *m/e* 571.2715, M+1 calcd for $C_{31}H_{42}O_8Si$: 571.2727.

4.1.5. Hydrazone 8: reaction of enol ester 6 with hydrazine. Enol ester **6** (100 mg, 0.175 mmol, 1.0 equiv.) was dissolved in THF (2 mL), the solution was cooled to 0°C, and NH_2NH_2 (0.70 mL, 1 M solution in THF, 0.70 mmol, 4.0 equiv.) and glacial AcOH (80 μL, 1.40 mmol, 8.0 equiv.) were sequentially added. After stirring for 2 h at 25°C, the reaction mixture was diluted with Et_2O (5 mL), treated with an aqueous Na_2CO_3 solution (5 mL), and the organic layer was separated. The aqueous phase was extracted with Et_2O (2×5 mL), and the combined organic solution was washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 50% EtOAc in hexanes) furnished hydrazone **8** (89 mg, 93%) as a colorless oil: R_f=0.62 (silica gel, 50% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 3450, 3345, 3253, 2958, 2865, 1710, 1650, 1486, 1475, 1116; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73–7.65 (m, 2H, Ph), 7.57–7.25 (m, 8H, Ph), 6.44 (bs, 2H, =NNH_2), 5.45 (s, 1H, CHPh), 4.77 (d, 1H, J=11.6 Hz, PhCH_2O), 4.67 (d, 1H, J=11.6 Hz, PhCH_2O), 4.28 (dd, 1H, J=10.6, 5.3 Hz, CH_2(OCHPh)), 4.21–4.17 (m, 4H), 3.57 (dd, 1H, J=10.4, 10.1 Hz, CH_2(OCHPh)), 3.44 (dd, 1H, J=8.9, 1.8 Hz, C*H*(OCHPh)), 3.07 (dd, 1H, J=13.7, 6.4 Hz, CH_2CO_2Et), 2.82 (dd, 1H, J=13.7, 8.1 Hz, CH_2CO_2Et), 1.27 (t, 3H, J=7.1 Hz, $CO_2CH_2CH_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.09, 0.08 (2s, 6H, $Si(CH_3)_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 165.4, 138.2, 137.4, 136.0, 129.1, 128.4, 128.3, 128.0, 127.5, 127.3, 126.1, 101.5, 82.9, 74.9, 72.5, 71.8, 62.0, 52.2, 25.8, 25.7, 17.8, 14.1, −3.6, −4.8; FAB HRMS (NBA) *m/e* 543.2885, M+1 calcd for $C_{29}H_{42}N_2O_6Si$: 543.2890.

4.1.6. Diazo 9: oxidation of hydrazone 8. A solution of hydrazone **8** (89 mg, 0.163 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL) at 25°C was treated with activated MnO_2 (28.3 mg, 0.326 mmol, 2.0 equiv.). After 30 min, TLC revealed depletion of starting hydrazone and the crude mixture was filtered through silica gel. The filtrate was concentrated under reduced pressure to obtain diazo **9** (88 mg, 99.5%) as a yellow oil, which was used in the next step without further purification: R_f=0.57 (silica gel, 25% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 2960, 2872, 2110, 1735, 1680, 1476, 1457, 1118; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.65 (m, 2H, Ph), 7.57–7.27 (m, 8H, Ph), 5.47 (s, 1H, CHPh), 4.74 (d, 1H, J=11.6 Hz, PhCH_2O), 4.65 (d, 1H, J=11.6 Hz, PhCH_2O), 4.31 (dd, 1H, J=10.6, 4.3 Hz, CH_2(OCHPh)), 4.23 (q, 2H, J=7.0 Hz, $CO_2CH_2CH_3$), 4.17 (ddd, 1H, J=9.8, 9.0, 5.3 Hz, CH(OTBS)), 4.06 (ddd, 1H, J=7.2, 6.4, 2.2 Hz, C*H*(OCH_2Ph)), 3.64 (dd, 1H, J=9.0, 2.2 Hz, C*H*(OCHPh)), 3.62 (dd, 1H, J=10.4 Hz, CH_2(OCHPh)), 2.78 (dd, 1H, J=14.9, 6.3 Hz, CH_2CO_2Et), 2.69 (dd, 1H, J=14.9, 7.9 Hz, CH_2CO_2Et), 1.24 (t, 3H, J=7.0 Hz, $CO_2CH_2CH_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.09, 0.08 (2s, 6H, $Si(CH_3)_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 165.7, 138.3, 137.5, 128.9, 128.7, 128.3, 128.2, 128.1, 127.4, 127.3, 126.9, 126.1, 101.3, 82.8, 75.0, 71.9, 71.8, 62.2, 51.9, 25.7, 24.0, 17.8, 14.3, −3.8, −4.8.

4.1.7. Diazo alcohol 10: desilylation of 9. A solution of silyl diazo **9** (88 mg, 0.163 mmol, 1.0 equiv.) in THF (4 mL) at 25°C was treated with TBAF (0.20 mL, 1 M solution in THF, 0.195 mmol, 1.2 equiv.). After being stirred for 30 min, the reaction mixture was diluted with Et_2O (8 mL) and washed with water (10 mL). The aqueous phase was extracted with Et_2O (2×5 mL), and the combined organic phase was washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The crude mixture was purified by flash column chromatography (silica gel, 50% EtOAc in hexanes) to provide diazo alcohol **10** (66 mg, 95%) as a yellow oil: R_f=0.51 (silica gel, 50% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 3330, 2958, 2875, 2105, 1715, 1684, 1475, 1437, 1119; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.42 (m, 2H, Ph), 7.37–7.31 (m, 8H, Ph), 5.41 (s, 1H, CHPh), 4.71 (d, 1H, J=11.7 Hz, PhCH_2O), 4.60 (d, 1H, J=11.7 Hz, PhCH_2O), 4.25 (dd, 1H, J=10.7, 5.3 Hz, CH_2(OCHPh)), 4.21 (q, 2H, J=7.1 Hz, $CO_2CH_2CH_3$), 3.95–3.91 (m, 2H, C*H*(OH)), C*H*(OCH_2Ph)), 3.67 (dd, 1H, J=9.2, 3.8 Hz, C*H*(OCHPh)), 3.54 (dd, 1H, J=10.5 Hz, CH_2(OCHPh)), 2.71 (d, 2H, J=6.1 Hz, CH_2CO_2Et), 2.21 (bs, 1H, OH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 166.5, 137.4, 137.3, 128.9, 128.7, 128.4, 128.2, 126.2, 126.1, 101.9, 80.5, 75.7, 72.8, 70.7, 62.8, 52.0, 24.7, 14.1.

4.1.8. Treatment of diazo alcohol 10 with with $Rh_2(OAc)_4$. A solution of diazo alcohol **10** (60 mg, 0.140 mmol, 1.0 equiv.) in benzene (15 mL, 0.01 M) is heated at 80°C. At this temperature, a catalytic amount of $Rh_2(OAc)_4$ (6.2 mg, 0.014 mmol, 0.1 equiv.) was added and the reaction mixture was left at 80°C for 6 h. After this time, no starting diazo was detected by TLC, and then, the crude mixture was filtered and concentrated. Purification by preparative thin-layer chromatography (silica gel, 20% EtOAc in hexanes) provided compounds **11a** (9.6 mg, 18%), **11b** (2.4 mg, 4.4%) and **12** (40 mg, 72%) as colorless oils.

Compound **11a**: R_f=0.63 (silica gel, 50% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 2960, 2875, 1720, 1675, 1475, 1444, 1018; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.46 (m, 2H, Ph), 7.40–7.30 (m, 8H, Ph), 5.63 (s, 1H, CHPh), 4.86 (d, 1H, J=11.9 Hz, PhCH_2O), 4.71 (d, 1H, J=11.9 Hz, PhCH_2O), 4.59 (dd, 1H, J=7.0, 4.0 Hz), 4.41–4.34 (m, 1H), 4.17 (q, 2H, J=7.1 Hz, $CO_2CH_2CH_3$),

3.77–3.70 (m, 4H), 2.65 (ddd, 1H, J=13.5, 4.2, 2.3 Hz, CH_2CH(O)CO_2Et), 2.00 (ddd, 1H, J=13.5, 10.6, 6.6 Hz, CH_2CH(O)CO_2Et), 1.29 (t, 3H, J=7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.3, 128.9, 128.5, 128.4, 128.2, 127.7, 127.6, 126.0, 101.3, 83.3, 73.5, 73.1, 72.9, 68.8, 68.0, 52.5, 32.4, 13.8; FAB HRMS (NBA) *m/e* 399.1815, M+1 calcd for $C_{23}H_{26}O_6$: 399.1807.

Compound **11b**: R_f=0.61 (silica gel, 50% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 2959, 2875, 1718, 1680, 1487, 1453, 1018; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.46 (m, 2H, Ph), 7.40–7.30 (m, 8H, Ph), 5.61 (s, 1H, CHPh), 4.73 (d, 1H, J=11.7 Hz, PhCH_2O), 4.62 (dd, 1H, J=5.6, 2.9 Hz), 4.55 (d, 1H, J=11.7 Hz, PhCH_2O), 4.25 (q, 2H, J=7.0 Hz, $CO_2CH_2CH_3$), 3.91 (dd, 1H, J=10.5, 5.5 Hz), 3.75–3.69 (m, 2H), 3.60 (dd, 1H, J=9.0, 8.5 Hz), 2.63 (ddd, 1H, J=13.0, 4.2, 2.5 Hz, CH_2CH(O)CO_2Et), 1.86 (ddd, 1H, J=13.0, 9.0, 6.7 Hz, CH_2CH(O)CO_2Et), 1.31 (t, 3H, J=7.0 Hz, $CO_2CH_2CH_3$).

Compound **12**: R_f=0.41 (silica gel, 50% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 2987, 2881, 1735, 1678, 1487, 1212, 917; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.47 (m, 2H, Ph), 7.40–7.28 (m, 8H, Ph), 5.56 (s, 1H, CHPh), 5.09 (d, 1H, J=8.5 Hz, PhCH), 4.74 (ddd, 1H, J=8.5, 5.9, 2.8 Hz, C$H$$CO_2$Et), 4.34 (dd, 1H, J=10.6, 5.3 Hz, CH_2(OCHPh)), 4.26–4.19 (m, 1H, CH(OH)), 4.17 (q, 2H, J=7.5 Hz, $CO_2CH_2CH_3$), 3.74 (dd, 1H, J=9.0, 2.7 Hz, CH(OCHPh)), 3.67 (dd, 1H, J=10.4, 10.3 Hz, CH_2(OCHPh)), 3.07 (c, 1H, J=8.5 Hz, CH(O)CH_2), 2.54 (ddd, 1H, J=12.8, 8.9, 5.9 Hz, CH_2CHCO_2Et), 2.45 (ddd, 1H, J=12.8, 8.2 Hz, CH_2CHCO_2Et), 1.70 (bs, 1H, OH), 1.23 (t, 3H, J=7.5 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.9, 140.4, 137.7, 129.4, 129.0, 128.6, 128.4, 128.3, 128.1, 126.5, 126.2, 101.5, 84.2, 81.8, 76.8, 70.9, 61.8, 60.9, 31.5, 14.1; FAB HRMS (NBA) *m/e* 399.1797, M+1 calcd for $C_{23}H_{26}O_6$: 399.1807.

4.1.9. β-Hydroxy-α-diazo ester 14: reaction of aldehyde 13 with ethyl diazoacetate. The reaction of aldehyde **13**[17] (6.2 g, 13.2 mmol, 1.0 equiv.) with ethyl diazoacetate (2.1 g, 19.8 mmol, 1.5 equiv.) mediated by Et_2Zn (19.8 mL, 19.8 mmol, 1.5 equiv.), was carried out exactly as described for **4** above and yielded β-hydroxy-α-diazo ester **14** (6.17 g, 80%) as a 1:1 mixture of stereoisomers at C-3 which was separated by flash column chromatography on silica gel: (more polar isomer) R_f=0.75 (silica gel, 25% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 3430, 3050, 2957, 2865, 2109, 1737, 1653, 1390, 1256; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.50 (m, 4H, $SiPh_2$), 7.45–7.30 (m, 6H, $SiPh_2$), 4.66 (d, J=4.5 Hz, 1H, CH(OH)CN_2), 4.20–4.05 (m, 4H), 3.83–3.77 (m, 2H), 3.72 (dd, J=6.0, 3.5 Hz, 1H), 3.60 (bs, 1H, OH), 3.05 (bs, 1H, OH), 1.30 (s, 3H, C$(CH_3)_2$), 1.24 (s, 3H, C$(CH_3)_2$), 1.19 (t, J=7.5 Hz, 3H, $CO_2CH_2CH_3$), 0.99 (s, 9H, SiC$(CH_3)_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 167.3, 135.4, 129.8, 127.6, 109.8, 81.6, 78.2, 72.9, 67.9, 65.8, 64.8, 60.8, 29.7, 26.7, 25.4, 19.1, 14.3; (less polar isomer): 7.71–7.62 (m, 4H, $SiPh_2$), 7.38–7.28 (m, 6H, $SiPh_2$), 4.51 (d, J=6.3 Hz, 1H, CH(OH)CN_2), 4.25–4.14 (m, 2H), 4.12 (c, J=7.5 Hz, 2H, $CO_2CH_2CH_3$), 3.80–3.71 (m, 3H), 3.65 (bs, 1H, OH), 2.81 (d, J=3.8 Hz, 1H, OH), 1.32 (s, 3H, C$(CH_3)_2$), 1.28 (s, 3H, C$(CH_3)_2$), 1.18 (t, J=7.5 Hz, 3H, $CO_2CH_2CH_3$), 0.98 (s, 9H, SiC$(CH_3)_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 168.3, 135.9, 130.3, 128.2, 128.1, 109.7, 83.4, 76.9, 73.2, 64.9, 61.8, 46.3, 29.8, 26.9, 26.7, 26.1, 19.7, 14.6; FAB HRMS (NBA) *m/e* 585.2635, M+1 calcd for $C_{30}H_{40}N_2O_8Si$: 585.2632.

4.1.10. β-Acetoxy-α-diazo ester 15: acetylation of 14. β-Acetoxy-α-diazo ester **15** was prepared from hydroxy diazo **14** (3.0 g, 5.14 mmol) by treatment with acetic anhydride according to the same procedure described above for the preparation of **5**, to obtain pure diazo ester **15** (3.16 g, 98%) as a yellow oil (1:1 mixture of stereoisomers at C-3): R_f=0.82 (silica gel, 25% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 2986, 2116, 1754, 1735, 1685, 1667, 1458, 1376, 1216; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.54 (m, 4H, $SiPh_2$), 7.33–7.25 (m, 6H, $SiPh_2$), 5.78 (d, J=2.8 Hz, 0.5H, CH(OAc)CN_2), 5.66 (d, J=3.5 Hz, 0.5H, CH(OAc)CN_2), 4.96 (ddd, J=8.0, 5.0, 2.9 Hz, 0.5H, CH(OAc)), 4.89 (ddd, J=7.8, 4.3, 3.0 Hz, 0.5H, CH(OAc)), 4.19 (dd, J=6.9, 3.5 Hz, 0.5H, CH(OR)), 4.15–4.09 (m, 3H, both isomers), 3.94 (dd, J=8.2, 8.1 Hz, 0.5H, CH(OR)), 3.84–3.77 (m, 2H, both isomers), 2.07 (s, 1.5H, $OCOCH_3$), 2.02 (s, 1.5H, $OCOCH_3$), 2.00 (s, 3H, $OCOCH_3$, both isomers), 1.35 (s, 1.5H, C$(CH_3)_2$), 1.32 (s, 1.5H, C$(CH_3)_2$), 1.26 (s, 1.5H, C$(CH_3)_2$), 1.25 (s, 1.5H, C$(CH_3)_2$), 1.17 (t, J=7.5 Hz, 1.5H, $CO_2CH_2CH_3$), 1.15 (t, J=7.0 Hz, 1.5H, $CO_2CH_2CH_3$), 0.94 (s, 9H, SiC$(CH_3)_3$, both isomers); ^{13}C NMR (50.3 MHz, $CDCl_3$) (both isomers) δ 171.0, 169.9, 169.4, 135.6, 135.5, 133.2, 129.7, 127.6, 111.1, 110.7, 80.8, 80.1, 75.2, 74.5, 74.4, 73.8, 68.6, 66.6, 63.3, 62.6, 61.1, 27.4, 26.8, 26.6, 25.9, 20.9, 20.8, 20.6, 19.2, 19.1, 14.4, 14.3; FAB HRMS (NBA) *m/e* 627.2981, M+1 calcd for $C_{32}H_{42}N_2O_9Si$: 627.2989.

4.1.11. Enol ester 16: treatment of β-acetoxy-α-diazo ester 15 with $Rh_2(OAc)_4$. The conversion of **15** (1.10 g, 1.76 mmol) to the enol ester **16** (1.03 g, 98%) was carried out by treatment with a catalytic amount of $Rh_2(OAc)_4$ under similar conditions than for **5**: (1:1 mixture of *Z*/*E* isomers): R_f=0.78 (silica gel, 25% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 3072, 2956, 2864, 1775, 1738, 1665, 1450, 1378, 1016; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.57 (m, 4H, $SiPh_2$), 7.35–7.26 (m, 6H, $SiPh_2$), 6.34 (d, J=8.8 Hz, 0.5H, CH=(OAc)), 5.78 (d, J=9.9 Hz, 0.5H, CH=(OAc)), 5.24 (dd, 0.5H, J=9.9, 8.0 Hz, 0.5H, CH(OR)CH=(OAc)), 5.08–5.04 (m, 1H, CH(OAc), both isomers), 4.57 (dd, J=8.8, 7.6 Hz, 0.5H, CH(OR)CH=(OAc)), 4.21–4.12 (m, 2H), 4.04–3.99 (m, 1H), 3.83–3.74 (m, 2H), 2.13 (s, 1.5H, CH=(OCOCH_3)), 2.12 (s, 1.5H, CH=(OCOCH_3)), 1.97 (s, 1.5H, $OCOCH_3$), 1.95 (s, 1.5H, $OCOCH_3$), 1.34 (s, 1.5H, C$(CH_3)_2$), 1.33 (s, 1.5H, C$(CH_3)_2$), 1.30 (s, 3H, C$(CH_3)_2$), 1.22 (t, J=7.5 Hz, 1.5H, $CO_2CH_2CH_3$), 1.19 (t, J=7.0 Hz, 1.5H, $CO_2CH_2CH_3$), 0.96 (s, 9H, SiC$(CH_3)_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) (both isomers) δ 170.4, 170.2, 168.9, 168.2, 161.2, 160.9, 140.7, 135.5, 133.2, 129.6, 127.6, 126.2, 110.4, 109.9, 78.0, 77.8, 74.2, 73.9, 73.7, 73.5, 73.3, 27.3, 26.8, 25.9, 20.9, 20.7, 20.3, 20.1, 19.2, 19.1, 14.0, 13.9; FAB HRMS (NBA) *m/e* 599.2674, M+1 calcd for $C_{32}H_{42}O_9Si$: 599.2676.

4.1.12. Hydrazone 17: reaction of enol ester 16 with hydrazine. Enol ester **16** (402 mg, 0.67 mmol, 1.0 equiv.) was reacted with NH_2NH_2 according to the same procedure as described above for **6** to afford, after similar processing,

hydrazone **17** (295 mg, 77%) as a colorless oil: R_f=0.37 (silica gel, 20% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 3448, 3376, 3215, 2978, 2865, 1715, 1654, 1486, 1389, 1096; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.63 (m, 4H, $SiPh_2$), 7.38–7.30 (m, 6H, $SiPh_2$), 6.64 (bs, 2H, $=NNH_2$), 5.07 (ddd, 1H, *J*=7.8, 5.3, 3.6 Hz, C*H*(OAc)), 4.24 (c, 2H, *J*=7.0 Hz, $CO_2CH_2CH_3$), 4.13–4.06 (m, 1H, C*H*(OR)CH_2), 3.99 (dd, 1H, *J*=8.0, 7.7 Hz, C*H*(OR)), 3.92 (dd, 1H, *J*=11.3, 3.6 Hz, $CH_2(OSiPh_2)$), 3.85 (dd, 1H, *J*=11.3, 5.3 Hz, $CH_2(OSiPh_2)$), 3.08 (dd, 1H, *J*=14.4, 2.2 Hz, $CH_2CO_2CH_2CH_3$), 2.61 (dd, 1H, *J*=14.4, 8.7 Hz, $CH_2CO_2CH_2CH_3$), 2.13 (s, 3H, $OCOCH_3$), 1.38 (s, 3H, $C(CH_3)_2$), 1.30 (t, 3H, *J*=7.0 Hz, $CO_2CH_2CH_3$), 1.27 (s, 3H, $C(CH_3)_2$), 1.03 (s, 9H, $SiC(CH_3)_3$); FAB HRMS (NBA) *m/e* 571.2840, M+1 calcd for $C_{30}H_{42}N_2O_7Si$: 571.2839.

4.1.13. Diazo 18: oxidation of hydrazone 17. Hydrazone **17** (250 mg, 0.438 mmol) was oxidized to diazo **18** (215 mg, 86%) by the action of activated MnO_2 according to the procedure described above for **9**: R_f=0.82 (silica gel, 20% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 2958, 2875, 2109, 1745, 1678, 1489, 1390, 1056; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.61 (m, 4H, $SiPh_2$), 7.40–7.34 (m, 6H, $SiPh_2$), 4.89 (m, 1H, C*H*(OAc)), 4.02 (c, 2H, *J*=7.1 Hz, $CO_2CH_2CH_3$), 3.97 (ddd, 1H, *J*=7.3, 7.1, 3.2 Hz, C*H*(OR)CH_2), 3.80 (dd, 1H, *J*=7.6, 7.3 Hz, C*H*(OR)), 3.75 (dd, 1H, *J*=11.4, 3.3 Hz, $CH_2(OSiPh_2)$), 3.67 (dd, 1H, *J*=11.4, 5.3 Hz, $CH_2(OSiPh_2)$), 2.56 (dd, 1H, *J*=15.3, 3.2 Hz, $CH_2CO_2CH_2CH_3$), 2.29 (dd, 1H, *J*=15.3, 7.0 Hz, $CH_2CO_2CH_2CH_3$), 1.92 (s, 3H, $OCOCH_3$), 1.21 (s, 3H, $C(CH_3)_2$), 1.15 (s, 3H, $C(CH_3)_2$), 1.08 (t, 3H, *J*=7.1 Hz, $CO_2CH_2CH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.1, 167.1, 135.6, 135.4, 133.1, 129.6, 129.5, 127.6, 109.6, 78.2, 76.9, 74.3, 62.8, 60.7, 27.3, 26.8, 26.6, 20.8, 19.1, 14.4.

4.1.14. Hydroxy diazo 19: deacetylation of diazo 18. A solution of diazo **18** (200 mg, 0.352 mmol, 1.0 equiv.) in EtOH (5 mL) was treated at 0°C with EtONa (0.35 mL, 1 M solution in ethanol, 0.350 mmol, 1.0 equiv.). After 30 min, the reaction mixture was diluted with EtOAc (15 mL), and washed with water (20 mL). The aqueous phase was extracted with EtOAc (2×10 mL), and the combined organic phase was washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The crude mixture was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes) to provide diazo alcohol **19** (167 mg, 90%) as a yellow oil: R_f=0.54 (silica gel, 20% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 3345, 2960, 2875, 2116, 1715, 1675, 1486, 1398, 1089; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.52 (m, 4H, $SiPh_2$), 7.37–7.29 (m, 6H, $SiPh_2$), 4.28–4.19 (m, 3H), 4.17–4.07 (m, 2H), 3.91–3.77 (m, 2H), 3.63 (bs, 1H, OH), 2.87 (dd, 1H, *J*=15.5, 3.5 Hz, $CH_2CO_2CH_2CH_3$), 2.71 (dd, 1H, *J*=15.5, 4.3 Hz, $CH_2CO_2CH_2CH_3$), 1.42 (s, 3H, $C(CH_3)_2$), 1.34 (s, 3H, $C(CH_3)_2$), 1.26 (t, 3H, *J*=7.0 Hz, $CO_2CH_2CH_3$), 1.08 (s, 9H, $SiC(CH_3)_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 168.1, 136.3, 135.6, 135.5, 133.1, 132.9, 129.9, 127.6, 108.8, 79.4, 73.3, 65.1, 60.8, 26.8, 26.7, 19.2, 14.3; FAB HRMS (NBA) *m/e* 527.2584, M+1 calcd for $C_{28}H_{38}N_2O_6Si$: 527.2577.

4.1.15. Treatment of diazo alcohol 19 with $Rh_2(OAc)_4$. A solution of diazo alcohol **19** (120 mg, 0.228 mmol, 1.0 equiv.) in CH_2Cl_2 (22.8 mL, 0.01 M) was treated at 0°C with a catalytic amount of $Rh_2(OAc)_4$ (10.1 mg, 0.023 mmol, 0.1 equiv.). After 1 h, no starting diazo was detected by TLC, and the crude mixture was filtered through silica gel and concentrated. Purification by flash column chromatography (silica gel, 10% EtOAc in hexanes) provided compounds **20** (18 mg, 17%) and **21** (50.5 mg, 48%) as colorless oils.

Compound **20** (minor isomer): R_f=0.35 (silica gel, 50% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 2958, 2886, 1715, 1687, 1489, 1367, 1019; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.64 (m, 4H, $SiPh_2$), 7.41–7.38 (m, 6H, $SiPh_2$), 4.44 (dd, 1H, *J*=6.5, 1.2 Hz, $CH_2CH(CO_2Et)$), 4.19 (c, 2H, *J*=7.1, $CO_2CH_2CH_3$), 3.97–3.94 (m, 1H), 3.84–3.75 (m, 2H, $CH_2(OSiPh_2)$), 3.64 (ddd, 1H, *J*=11.9, 8.8, 4.7 Hz, C*H*(OH)CH_2), 3.51 (dd, 1H, *J*=8.7, 8.3 Hz, C*H*(OH)CH(OH)CH_2), 3.22 (bs, 1H, OH), 2.61 (bs, 1H, OH), 2.44 (ddd, 1H, *J*=13.1, 4.6, 1.2 Hz, $CH_2CH(O)CO_2Et$), 1.83 (ddd, 1H, *J*=13.1, 11.9, 6.5 Hz, $CH_2CH(O)CO_2Et$), 1.26 (t, 3H, *J*=7.1, $CO_2CH_2CH_3$), 1.06 (s, 9H, $SiC(CH_3)_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.2, 135.5, 132.5, 132.4, 130.0, 129.9, 127.8, 75.2, 74.0, 72.1, 69.7, 65.8, 61.2, 32.9, 26.8, 19.2, 14.2.

Compound **21** (major isomer): R_f=0.38 (silica gel, 50% EtOAc in hexanes); IR (thin film) ν_{max} (cm^{-1}) 2964, 2886, 1718, 1689, 1492, 1367, 1019; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.65 (m, 4H, $SiPh_2$), 7.44–7.40 (m, 6H, $SiPh_2$), 4.17 (c, 2H, *J*=7.1, $CO_2CH_2CH_3$), 4.02 (dd, 1H, *J*=12.0, 2.0 Hz, $CH_2CH(CO_2Et)$), 3.98 (dd, 1H, *J*=10.3, 4.5 Hz, $CH_2(OSiPh_2)$), 3.88 (dd, 1H, *J*=10.3, 7.2 Hz, $CH_2(OSiPh_2)$), 3.75 (ddd, 1H, *J*=11.5, 8.6, 5.0 Hz, C*H*(OH)CH_2), 3.69 (bs, 1H, OH), 3.55 (dd, 1H, *J*=8.9, 8.6 Hz, C*H*(OH)CH(OR)CH_2), 3.36 (ddd, 1H, *J*=9.2, 7.2, 4.6 Hz, C*H*(O)$CH_2(OSiPh_2)$), 2.75 (bs, 1H, OH), 2.30 (ddd, 1H, *J*=12.9, 5.0, 2.1 Hz, $CH_2CH(O)CO_2Et$), 1.67 (ddd, 1H, *J*=12.9, 12.0, 11.5 Hz, $CH_2CH(O)CO_2Et$), 1.24 (t, 3H, *J*=7.1, $CO_2CH_2CH_3$), 1.05 (s, 9H, $SiC(CH_3)_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 169.8, 135.6, 135.5, 132.3, 132.0, 130.0, 127.9, 76.7, 75.6, 74.2, 72.1, 66.1, 61.1, 34.9, 26.8, 19.1, 14.1; FAB HRMS (NBA) *m/e* 459.2212, M+1 calcd for $C_{25}H_{34}O_6Si$: 459.2203.

4.1.16. Ethyl 2,3-dideoxy-D-arabino-2-heptulosonate 22: desilylation of 21. A solution of silyl ether **21** (30 mg, 0.065 mmol, 1.0 equiv.) in THF (2 mL) at 25°C was treated with TBAF (78 μL, 1 M solution in THF, 0.078 mmol, 1.2 equiv.). After being stirred for 30 min, the reaction mixture was directly concentrated and subjected to flash column chromatography (silica gel, 5% MeOH in CH_2Cl_2), to yield **22** (13 mg, 92%) as white crystals whose physical and spectroscopic properties were identical to those reported in the literature.[9c]

4.1.17. Compound 2: basic treatment of 22. A solution of ethyl ester **22** (10 mg, 0.04 mmol, 1.0 equiv.) in 1:1 H_2O/EtOH (1 mL) was treated at 0°C with potasium hydroxide (2.55 mg, 0.04 mmol, 1.0 equiv.). After 30 min, the reaction mixture was subjected to reduced pressure to remove the solvents and the resulting crude was redissolved in water (2 mL) and then liophilized. The resulting solid, potassium salt of **2**, exhibited identical spectroscopic properties as

reported in the literature.[18] ^{1}H NMR (400 MHz, D_2O) δ 4.12 (dd, 1H, J=12.0, 2.5 Hz, $CH_2CH(CO_2K)$), 3.94–3.60 (m, 4H), 3.27 (t, 1H), 2.25 (ddd, 1H, J=12.0, 5.0, 2.5 Hz, $CH_2CH(O)CO_2K$), 1.90 (ddd, 1H, J=13.0, 12.0, 11.5 Hz, $CH_2CH(O)CO_2K$); ^{13}C NMR (50.3 MHz, D_2O) δ 181.7, 87.7, 78.6, 72.6, 71.9, 64.0, 40.3.

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