Formal Synthesis of Aspergillide A from Tri-*O*-acetyl-D-glucal

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Received 27 June 2011; revised 26 July 2011

Abstract: We describe an efficient synthesis of a key intermediate in the synthesis of aspergillide A from a commercially available, chiral starting material.

Key words: Claisen rearrangement, allylic alcohol, stereoselective synthesis, tri-*O*-acetyl-D-glucal, aspergillide A

Aspergillides A (**1**), B (**2**) and C (**3**) are novel 14-membered macrolides recently isolated by Kusumi and coworkers[1] from a culture of *Aspergillus ostianus* strain 01F313 in bromine-modified 1/2PD medium. These compounds show significant cytotoxic activity against the murine leukemia cell line L1210, with IC50 values ranging from 2.0–71 μg/mL. The structure originally proposed for aspergillide C (**3**) has been confirmed by synthesis,[2] while the structures of aspergillides A (**1**) and B (**2**) have been revised in the light of X-ray crystallography results.[3] The corrected structures are shown in Figure 1.

Because of their unique pharmaceutical profiles and intriguing structural features, these macrolides have attracted much interest in the synthetic chemistry community. To date, however, only a relatively small number of actual or formal total syntheses have been reported: nine for **1**,[4] nine for **2**[4b,c,e,i,5] and three for **3**.[2,6]

Here, we describe a formal total synthesis of aspergillide A (**1**) from the relatively inexpensive, commercially available product tri-*O*-acetyl-D-glucal. The retrosynthetic basis is outlined in Scheme 1. Since the conversion of **4** and **5** into **1** has already been reported in the literature,[4a] we describe only the preparation of compound **4**.

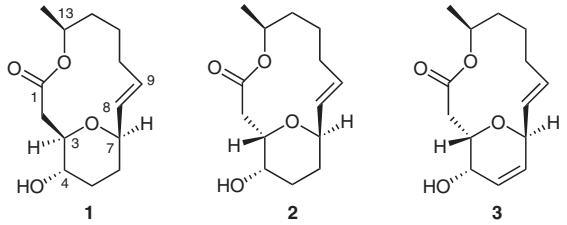
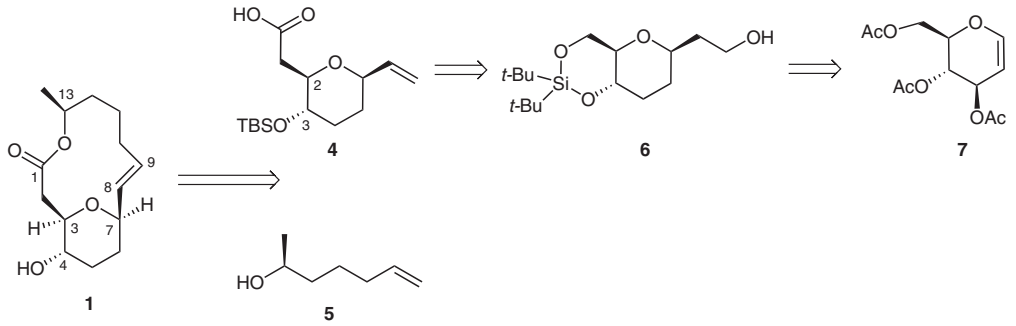


Figure 1 Structures of aspergillides A (**1**), B (**2**) and C (**3**)

The starting compound, tri-*O*-acetyl-D-glucal (**7**), was chosen because it already contains stereocenters 2 and 3 of compound **4**, and because it was envisaged as giving access to compound **6** through the very efficient Claisen rearrangement previously employed in our synthesis of (+)-isolaurepan.[7]

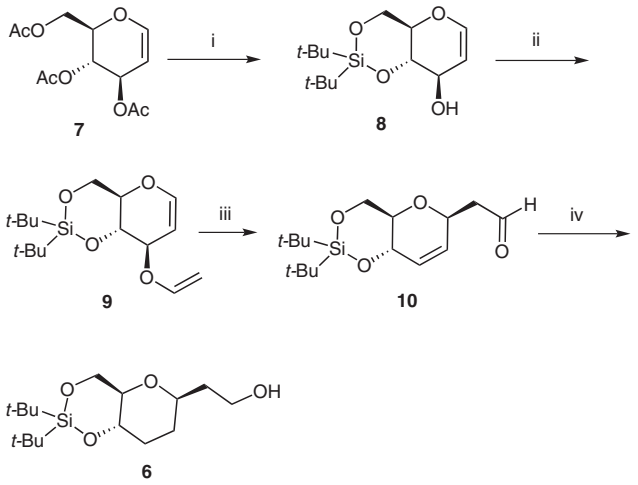
As hoped, compound **6** was readily obtained from known aldehyde **10**,[7] as shown in Scheme 2. Compound **8**[7] was prepared from triacetate **7** as per Mori and Hayashi[8a] and Hoberg[8b] in two steps and 91% yield. The mercury(II) acetate catalyzed reaction of allylic alcohol **8** with ethyl vinyl ether then afforded enol ether **9**[7] (80%), and Claisen rearrangement[9] of the latter in toluene at 185 °C gave a 95% yield of aldehyde **10**. Finally, hydrogenation of **10**, followed by sodium borohydride reduction, afforded a 90% yield of alcohol **6**, which possesses the stereocenters corresponding to C3, C4 and C7 of the target molecule.

The transformation of compound **6** into compound **4** was carried out as shown in Scheme 3. First, alcohol **6** was easily converted into iodide **11** in 80% yield.[10] Reaction of **11** with potassium *tert*-butoxide followed by tetrabutyl-



Scheme 1 Retrosynthetic analysis of aspergillide A (**1**)

SYNTHESIS 2011, No. 20, pp 3301–3306
Advanced online publication: 02.09.2011
DOI: 10.1055/s-0030-1260203; Art ID: Z64511SS



Scheme 2 *Reagents and conditions*: (i) (a) K_2CO_3, MeOH; (b) *t*-$Bu_2Si(OTf)_2$, DMF, pyridine, –30 °C, 91% (two steps);[8] (ii) ethyl vinyl ether, $Hg(OAc)_2$, 65 °C, 80%;[7] (iii) toluene, 185 °C, 5 h, 95%; (iv) (a) H_2, Pd/C, MeOH; (b) $NaBH_4$, MeOH, 90% (two steps).

ammonium fluoride afforded diol **12** in 79% overall yield (two steps). Unfortunately, the interesting one-step silyl-deprotection procedure described by Pagenkopf and co-workers[11] could not be used in this case because reaction of **11** with potassium *tert*-butoxide afforded a mixture of alkenes with di- and monoprotected hydroxy groups, which was then treated with tetrabutylammonium fluoride to yield **12**. Protection of the hydroxy groups of diol **12**, followed by selective deprotection of the primary hydroxy, gave alcohol **14**, which was uneventfully converted into nitrile **16** in 63% yield by tosylation followed by displacement of tosylate with sodium cyanide. Finally, reduction of nitrile **16** with diisobutylaluminum hydride, followed by TEMPO/BAIB oxidation in aqueous acetonitrile, afforded the target acid **4** in 61% yield (two steps).

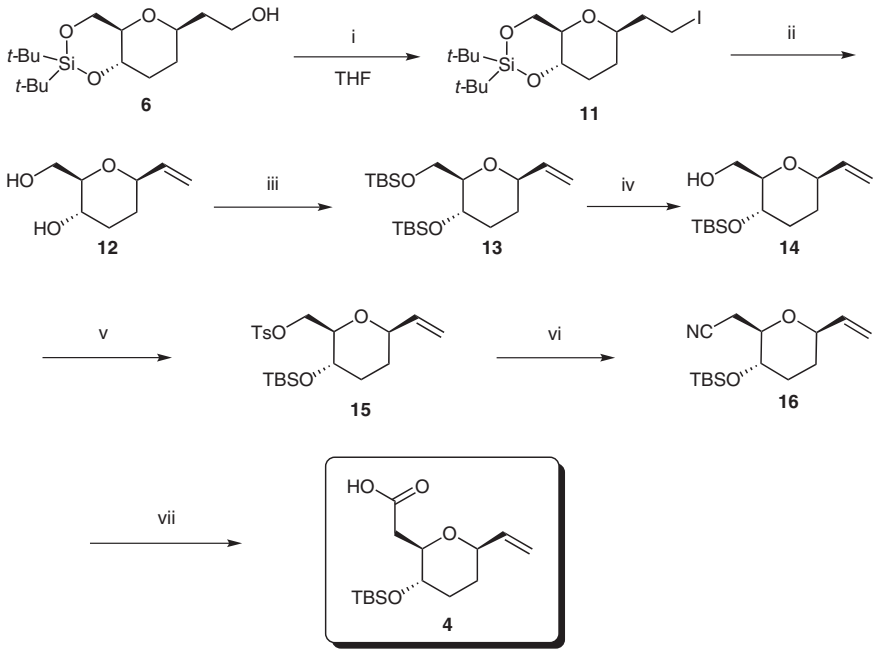
Sabitha and co-workers[4a] have published syntheses of acid **4** from chiral epoxides prepared by Sharpless epoxidation or by hydrolytic kinetic resolution of terminal epoxides catalyzed by a chiral (salen)Co(III) complex. Our synthesis of **4** compares favorably with those described so far in that it starts from a chiral compound that is commercially available and relatively inexpensive, and involves high-yielding reactions that can be carried out on a multigram scale.

In conclusion, we have developed a practical, efficient synthesis of acid **4**, an intermediate in a known synthesis of aspergillide A, and have hence achieved a new formal total synthesis of aspergillide A. Work is now in progress on the synthesis of new aspergillide A analogues with a view to their biological evaluation.

Solvents were purified and dried by standard procedures before use. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX-400 spectrometer (400 MHz, ^1H; 100.61 MHz, ^{13}C) using TMS as internal standard (chemical shifts in δ values, *J* in Hz). Mass spectrometry was carried out with a Hewlett Packard 5988A spectrometer. Specific rotations were recorded on a Jasco P-1020 polarimeter. Flash chromatography was performed on silica gel (Merck 60, 230–400 mesh); analytical TLC was performed on plates precoated with silica gel (Merck 60 F_{254}, 0.25 mm).

(4a*R*,8*R*,8a*S*)-2,2-Di-*tert*-butyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-8-ol (8)

To a soln of tri-*O*-acetyl-D-glucal (**7**; 14 g, 51.4 mmol) in MeOH (50 mL) was added K_2CO_3 (100 mg), and the mixture was stirred at r.t. for 12 h. The MeOH was removed, the crude material was diluted with $CHCl_3$ and the solvent was evaporated to eliminate all traces of MeOH. The resulting solid was dissolved in DMF (40 mL), py-



Scheme 3 *Reagents and conditions*: (i) I_2, Ph_3P, imidazole, THF, 80%; (ii) (a) *t*-BuOK, THF; (b) TBAF, THF, 79% (two steps); (iii) TBSCl, imidazole, DMAP, THF, 92%; (iv) PPTS, MeOH, 84%; (v) *p*-TsCl, pyridine, CH_2Cl_2, 95%; (vi) NaCN, DMSO, 66%; (vii) (a) DIBAL-H, CH_2Cl_2; (b) TEMPO, BAIB, MeCN, H_2O, 61% (two steps).

ridine (20 mL, 257.1 mmol) was added and the mixture was cooled to –30 °C. Then, *t*-$Bu_2Si(OTf)_2$ (18.3 mL, 56.6 mmol) was slowly added and the resulting mixture was allowed to warm to r.t. over 1.5 h. EtOAc (30 mL) was added to the mixture, and the organic phase was washed with 10% aq $CuSO_4$ (2 × 30 mL), H_2O (3 × 30 mL) and brine (3 × 30 mL). The organic phase was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc–hexane, 1:19) to afford **8**; yield: 13.4 g (91%).

White solid; mp 84–85 °C; $[\alpha]_D^{23}$ –16.3 (*c* 1.46, $CHCl_3$); R_f = 0.71 (EtOAc).

IR (NaCl): 3440, 3074, 2939, 2889, 2862, 1647 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.25 (dd, *J* = 6.1, 1.8 Hz, 1 H, H-6), 4.74 (dd, *J* = 6.1, 1.9 Hz, 1 H, H-7), 4.31–4.26 (m, 1 H, H-8), 4.16 (dd, *J* = 10.2, 4.9 Hz, 1 H, H-4), 3.98–3.88 (m, 2 H, H-4, H-8a), 3.85–3.78 (m, 1 H, H-4a), 2.66 (s, 1 H, OH), 1.05 [s, 9 H, $C(CH_3)_3$], 0.98 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 143.49 (CH-6), 103.07 (CH-7), 77.27 (CH-8a), 72.20 (CH-4a), 70.01 (CH-8), 65.63 (CH_2-4), 27.36 [$C(CH_3)_3$], 26.84 [$C(CH_3)_3$], 22.65 [$C(CH_3)_3$], 19.75 [$C(CH_3)_3$].

MS (FAB$^+$): *m*/*z* (%) = 287 (7) [M + H]$^+$, 286 (12) [M$^+$], 285 (18) [M – H]$^+$, 269 (100) [M – OH]$^+$, 229 (43) [M – *t*-Bu]$^+$.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{14}H_{26}O_4Si$: 286.1632; found: 286.1647.

(4a*R*,8*R*,8a*S*)-2,2-Di-*tert*-butyl-8-(vinyloxy)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (9)

A soln of alcohol **8** (5.2 g, 18.2 mmol) and $Hg(OAc)_2$ (1.74 g, 5.46 mmol) in ethyl vinyl ether (40 mL) was heated to 65 °C in a sealed tube for 4 d, during which time $Hg(OAc)_2$ (5.46 mmol) was added every 24 h. Then, the organic solution was washed with H_2O (3 × 35 mL) and brine (3 × 35 mL). The volatiles were removed under reduced pressure and the resulting residue was chromatographed on silica gel (EtOAc–hexane, 2:98), which afforded recovered starting material (0.51 g, 10%) and **9**; yield: 4.55 g (80%).

Colorless liquid; $[\alpha]_D^{23}$ –77.3 (*c* 0.042, MeOH); R_f = 0.63 (EtOAc–hexane, 3:7).

IR (NaCl): 2893, 1639 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.53 (dd, *J* = 14.00, 6.44 Hz, 1 H, H-1′), 6.32 (dd, *J* = 6.03, 1.24 Hz, 1 H, H-6), 4.78 (dd, *J* = 6.03, 1.88 Hz, 1 H, H-7), 4.43–4.36 (m, 2 H, H-8, H-2′), 4.18 (dd, *J* = 10.30, 4.94 Hz, 1 H, H-4), 4.13 (dd, *J* = 10.30, 7.08 Hz, 1 H, H-8a), 4.03 (dd, *J* = 6.44, 1.35 Hz, 1 H, H-2′), 3.98 (t, *J* = 10.30 Hz, 1 H, H-4), 3.90–3.81 (m, 1 H, H-4a), 1.06 [s, 9 H, $C(CH_3)_3$], 1.00 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 151.22 (C-1′), 144.67 (C-6), 100.58 (C-7), 88.90 (C-2′), 77.39 (C-8), 75.16 (C-8a), 72.49 (C-4a), 65.86 (C-4), 27.34 [$C(CH_3)_3$], 26.90 [$C(CH_3)_3$], 22.67 [$C(CH_3)_3$], 19.81 [$C(CH_3)_3$].

MS (FAB$^+$): *m*/*z* (%) = 313 (4) [M + H]$^+$, 312 (3) [M$^+$], 311 (9) [M – H]$^+$, 270 (23), 269 (100) [M – $OCHCH_2$]$^+$, 268 (8), 255 (7) [M – *t*-Bu]$^+$, 213 (8), 201 (5).

HRMS (FAB$^+$): *m*/*z* calcd for $C_{16}H_{29}O_4Si$: 313.1757; found: 313.1790.

2-{(4a*R*,6*S*,8a*S*)-2,2-Di-*tert*-butyl-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-6-yl}acetaldehyde (10)

A soln of **9** (4.2 g, 13.46 mmol) in toluene (40 mL) was heated to 185 °C in a sealed tube for 5 h. Then, the solvent was evaporated and the residue was chromatographed on silica gel (EtOAc–hexane, 2:98) to furnish the aldehyde **10**; yield: 4 g (95%).

White solid; mp 68 °C; $[\alpha]_D^{20}$ +31.4 (*c* 0.026, MeOH); R_f = 0.6 (EtOAc–hexane, 3:7).

IR (NaCl): 1728 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 9.75 (t, *J* = 2.06 Hz, 1 H, CHO), 5.93 (d, *J* = 10.34 Hz, 1 H, H-8′), 5.68–5.61 (m, 1 H, H-7′), 4.77–4.67 (m, 1 H, H-6′), 4.43–4.36 (m, 1 H, H-8a′), 4.16 (dd, *J* = 9.97, 5.05 Hz, 1 H, H-4′), 3.84 (t, *J* = 10.24 Hz, 1 H, H-4′), 3.54 (ddd, *J* = 10.34, 8.52, 5.08 Hz, 1 H, H-4a′), 2.57 (dd, *J* = 6.05, 2.06 Hz, 2 H, CH_2CHO), 1.05 [s, 9 H, $C(CH_3)_3$], 0.99 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 200.40 (C=O), 131.22 (C-8′), 127.80 (C-7′), 74.67 (C-4a′), 70.94 (C-6′), 69.96 (C-8a′), 66.99 (C-4′), 48.26 (CH_2CHO), 27.45 [$C(CH_3)_3$], 27.04 [$C(CH_3)_3$], 22.67 [$C(CH_3)_3$], 20.04 [$C(CH_3)_3$].

MS (FAB$^+$): *m*/*z* (%) = 313 (6) [M + H]$^+$, 312 (7) [M$^+$], 311 (21) [M – H]$^+$, 283 (11) [M – CHO]$^+$, 270 (23), 269 (100) [M – CH_2CHO]$^+$, 268 (13), 267 (15), 255 (17) [M – *t*-Bu]$^+$, 239 (20), 213 (21), 211 (19), 201 (27).

HRMS (FAB$^+$): *m*/*z* calcd for $C_{16}H_{29}O_4Si$: 313.1757; found: 313.1790.

2-[(4a*R*,6*R*,8a*S*)-2,2-Di-*tert*-butylhexahydropyrano[3,2-*d*][1,3,2]dioxasilin-6-yl]ethanol (6)

To a soln of aldehyde **10** (10.2 g, 32.69 mmol) in MeOH (60 mL) was carefully added 10% Pd/C (0.35 g, 0.33 mmol), and the mixture was stirred under H_2 atmosphere overnight. The solution was filtered over Celite®, which was then washed with CH_2Cl_2, and the resulting solution was concentrated under reduced pressure. The resulting residue (10.56 g, 33.63 mmol) was dissolved in MeOH (20 mL) and cooled to 0 °C. $NaBH_4$ (1.9 g, 50.44 mmol) was added in 8 portions, then the mixture was allowed to reach r.t. over 3 h. The solvent was evaporated, the residue was dissolved in EtOAc (20 mL), and the organic layer was washed with H_2O (2 × 15 mL) and brine (2 × 15 mL). The organic phase was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc–hexane, 1:9) to give the desired alcohol **6**; yield: 9.64 g (90%).

White solid; mp 89 °C; $[\alpha]_D^{23}$ –17.20 (*c* 2.09, $CHCl_3$); R_f = 0.35 (EtOAc–hexane, 3:7).

IR (NaCl): 3384, 2960, 2935, 2859 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.07 (dd, *J* = 10.12, 4.78 Hz, 1 H, H-4′), 3.81 (t, *J* = 10.40 Hz, 1 H, H-4′), 3.78–3.70 (m, 3 H, H-1, H-8a′), 3.67–3.60 (m, 1 H, H-6′), 3.35 (td, *J* = 9.70, 4.90 Hz, 1 H, H-4a′), 2.35 (s, 1 H, OH), 2.17–2.10 (m, 1 H, H-8′), 1.75–1.68 (m, 3 H, H-2, H-7′), 1.55–1.47 (m, 2 H, H-7′, H-8′), 1.05 [s, 9 H, $C(CH_3)_3$], 1.00 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 77.70 (CH-6′), 77.59 (CH-4a′), 73.66 (CH-8a′), 67.05 (CH_2-4′), 60.98 (CH_2-1), 37.63 (CH_2-2), 32.41 (CH_2-8′), 31.08 (CH_2-7′), 27.47 [$C(CH_3)_3$], 27.09 [$C(CH_3)_3$], 22.64 [$C(CH_3)_3$], 19.93 [$C(CH_3)_3$].

MS (FAB$^+$): *m*/*z* (%) = 339 (12) [M + Na]$^+$, 317 (100) [M + H]$^+$.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{16}H_{33}O_4Si$: 317.2143; found: 317.2143.

(4a*R*,6*R*,8a*S*)-2,2-Di-*tert*-butyl-6-(2-iodoethyl)hexahydropyrano[3,2-*d*][1,3,2]dioxasiline (11)

To a soln of **6** (9.64 g, 30.49 mmol) in THF (40 mL) were added Ph_3P (9.6 g, 36.59 mmol) and imidazole (6.23 g, 91.47 mmol). Once the mixture became homogeneous, I_2 (8.50 g, 33.54 mmol) was added at 0 °C. The solution was stirred at r.t. for 3 h and then sat. aq $NaHCO_3$ (15 mL) was added. The resulting mixture was extracted with EtOAc (2 × 15 mL), and the combined organic phases were washed with 10% aq $Na_2S_2O_4$ (2 × 20 mL) and brine (2 × 20 mL), then dried (Na_2SO_4). The solvents were removed under reduced pressure. The residue was chromatographed on silica gel (EtOAc–hexane, 2:98) to afford **11**; yield: 10.39 g (80%).

Brown oil; $[\alpha]_D^{22}$ +0.40 (*c* 6.36, $CHCl_3$); R_f = 0.68 (EtOAc–hexane, 3:7).

IR (NaCl): 2962, 2934, 2859, 2360, 2342 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.08 (dd, *J* = 10.40, 5.06 Hz, 1 H, H-4), 3.79 (t, *J* = 10.12 Hz, 1 H, H-4), 3.71 (td, *J* = 9.42, 4.07 Hz, 1 H, H-8a), 3.50–3.43 (m, 1 H, H-6), 3.31 (td, *J* = 9.42, 4.92 Hz, 1 H, H-4a), 3.24 (t, *J* = 7.03 Hz, 2 H, H-2′), 2.18–2.08 (m, 1 H, H-8), 2.00–1.89 (m, 2 H, H-1′), 1.75–1.69 (m, 1 H, H-7), 1.59–1.36 (m, 2 H, H-7, H-8), 1.05 [s, 9 H, $C(CH_3)_3$], 1.00 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 77.46 (CH-4a), 77.05 (CH-6), 73.84 (CH-8a), 67.09 (CH_2-4), 39.47 (CH_2-1′), 32.40 (CH_2-8), 30.51 (CH_2-7), 27.52 [$C(CH_3)_3$], 27.15 [$C(CH_3)_3$], 22.67 [$C(CH_3)_3$], 19.94 [$C(CH_3)_3$], 2.36 (CH_2-2′).

MS (FAB$^+$): *m*/*z* (%) = 445 (19), 427 (100) $[M + H]^+$, 391 (5), 301 (3).

HRMS (FAB$^+$): *m*/*z* calcd for $C_{16}H_{32}IO_3Si$: 427.1160; found: 427.1163.

(4aR,6R,8aS)-2,2-Di-*tert*-butyl-6-vinylhexahydropyrano[3,2-d][1,3,2]dioxasiline (A)

To a soln of iodide 11 (10.39 g, 24.39 mmol) in THF (30 mL) cooled to 0 °C was added *t*-BuOK (2.74 g, 24.39 mmol), and the mixture was stirred at r.t. for 14 h. Then, *t*-BuOK (1.37 g, 12.2 mmol) was added at 0 °C and the mixture was stirred for a further 6 h at r.t. The reaction was quenched with sat. aq NH_4Cl (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were dried (Na_2SO_4) and filtered, and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2) to afford A [yield: 2.4 g (33%)] and a mixture of alcohols B and C [yield: 4.09 g (56%)].

Compound **A**: White solid; mp 82 °C; $[\alpha]_D^{23}$ –2.79 (*c* 4.71, $CHCl_3$); R_f = 0.53 (EtOAc–hexane, 1:9).

IR (NaCl): 2962, 2935, 2860, 2360, 2341 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.85–5.75 (m, 1 H, H-1′), 5.23 (d, J_{trans} = 17.43 Hz, 1 H, H-2′), 5.11 (d, J_{cis} = 10.54 Hz, 1 H, H-2′), 4.12 (dd, *J* = 10.40, 4.92 Hz, 1 H, H-4), 3.92–3.82 (m, 2 H, H-4, H-6), 3.79–3.72 (m, 1 H, H-8a), 3.37 (td, *J* = 9.42, 5.06 Hz, 1 H, H-4a), 2.19–2.13 (m, 1 H, H-8), 1.82–1.76 (m, 1 H, H-7), 1.58–1.48 (m, 2 H, H-7, H-8), 1.05 [s, 9 H, $C(CH_3)_3$], 1.00 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 138.04 (CH-1′), 115.54 (CH_2-2′), 78.14 (CH-4a), 77.44 (CH-6), 73.60 (CH-8a), 67.13 (CH_2-4), 32.45 (CH_2-8), 30.95 (CH_2-7), 27.51 [$C(CH_3)_3$], 27.14 [$C(CH_3)_3$], 22.65 [$C(CH_3)_3$], 19.95 [$C(CH_3)_3$].

MS (FAB$^+$): *m*/*z* (%) = 299 (100) $[M + H]^+$, 282 (6).

HRMS (FAB$^+$): *m*/*z* calcd for $C_{16}H_{31}O_3Si$: 299.2037; found: 299.2035.

(2*R*,3*S*,6*R*)-2-(Hydroxymethyl)-6-vinyltetrahydro-2*H*-pyran-3-ol (12)

To a soln of compound **A** (1.65 g, 5.53 mmol) in THF (10 mL) was added 1.0 M TBAF in THF (6.64 mL, 6.64 mmol) at r.t., and the mixture was stirred at r.t. for 48 h. Then, the solvent was evaporated and the residue was chromatographed on silica gel (20% EtOAc–hexane → 50% EtOAc–hexane → 100% EtOAc) to provide the diol **12**; yield: 0.726 mg (83%).

To a soln of the mixture of alcohols **B** and **C** (4.09 g, 13.7 mmol) in THF (40 mL) was added 1.0 M TBAF in THF (16.44 mL, 16.44 mmol) at r.t., and the mixture was stirred at r.t for 48 h. Then, the solvent was evaporated and the residue was chromatographed on silica gel (20% EtOAc–hexane → 50% EtOAc–hexane → 100% EtOAc) to afford diol **12**; yield: 1.92 g (88%).

Colorless oil; $[\alpha]_D^{22}$ +25.32 (*c* 3.18, $CHCl_3$); R_f = 0.09 (EtOAc).

IR (NaCl): 3377, 2938, 2862, 2360, 2340 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.87–5.77 (m, 1 H, H-1′), 5.23 (d, J_{trans} = 17.29 Hz, 1 H, H-2′), 5.11 (d, J_{cis} = 10.40 Hz, 1 H, H-2′), 3.88–3.70 (m, 4 H, OH, H-1″, H-6), 3.58–3.49 (m, 1 H, H-3), 3.33–3.20 (m, 2 H, OH, H-2), 2.14–2.07 (m, 1 H, H-4), 1.79–1.73 (m, 1 H, H-5), 1.57–1.40 (m, 2 H, H-4, H-5).

^{13}C NMR ($CDCl_3$): δ = 138.20 (CH-1′), 115.60 (CH_2-2′), 81.36 (CH-2), 77.98 (CH-6), 66.76 (CH-3), 63.05 (CH_2-1″), 32.14 (CH_2-4), 30.81 (CH_2-5).

MS (FAB$^+$): *m*/*z* (%) = 182 (8) $[M + H + Na]^+$, 181 (100) $[M + Na]^+$, 180 (4), 159 (3) $[M + H]^+$.

HRMS (FAB$^+$): *m*/*z* calcd for $C_8H_{14}NaO_3$: 181.0835; found: 181.0837.

***tert*-Butyl{[(2*R*,3*S*,6*R*)-3-(*tert*-butyldimethylsilyloxy)-6-vinyltetrahydro-2*H*-pyran-2-yl]methoxy}dimethylsilane (13)**

To a soln of diol **12** (1.32 g, 8.35 mmol) in THF (20 mL) were added imidazole (3.4 g, 50.1 mmol), a catalytic amount of DMAP and TBSCl (3.0 g, 20.04 mmol), and the mixture was stirred at r.t. for 15 h. The volatiles were evaporated, H_2O (15 mL) was added and the product was extracted with CH_2Cl_2 (4 × 20 mL). The organic phase was dried (Na_2SO_4) and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc–hexane, 2:98) to afford **13**; yield: 2.97 g (92%).

Colorless oil; $[\alpha]_D^{22}$ +35.62 (*c* 11.10, $CHCl_3$); R_f = 0.71 (EtOAc–hexane, 3:7).

IR (NaCl): 2953, 2931, 2885, 2857, 2360, 2341 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.91–5.81 (m, 1 H, H-1′), 5.26 (d, J_{trans} = 17.15 Hz, 1 H, H-2′), 5.07 (d, J_{cis} = 10.68 Hz, 1 H, H-2′), 3.89–3.76 (m, 3 H, H-1″, H-6), 3.58 (td, *J* = 9.70, 4.78 Hz, 1 H, H-3), 3.20–3.15 (m, 1 H, H-2), 2.06–1.99 (m, 1 H, H-4), 1.76–1.70 (m, 1 H, H-5), 1.56–1.39 (m, 2 H, H-4, H-5), 0.91 [s, 9 H, $SiC(CH_3)_3$], 0.90 [s, 9 H, $SiC(CH_3)_3$], 0.09 [s, 6 H, $Si(CH_3)_2$], 0.08 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR ($CDCl_3$): δ = 139.02 (CH-1′), 114.22 (CH_2-2′), 83.00 (CH-2), 77.46 (CH-6), 66.42 (CH-3), 63.21 (CH_2-1″), 33.28 (CH_2-4), 31.20 (CH_2-5), 25.99 [$SiC(CH_3)_3$], 25.79 [$SiC(CH_3)_3$], 18.49 [$SiC(CH_3)_3$], 17.95 [$SiC(CH_3)_3$], –4.25, –4.91, –5.16 [2 × $Si(CH_3)_2$].

MS (FAB$^+$): *m*/*z* (%) = 410 (18) $[M + H + Na]^+$, 409 (100) $[M + Na]^+$, 387 (92) $[M + H]^+$, 255 (9).

HRMS (FAB$^+$): *m*/*z* calcd for $C_{20}H_{43}O_3Si_2$: 387.2745; found: 387.2742.

[(2*R*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-vinyltetrahydro-2*H*-pyran-2-yl]methanol (14)

To a soln of **13** (2.3 g, 5.95 mmol) in MeOH (15 mL) was added a catalytic amount of PPTS at 0 °C, and the mixture was stirred at 0 °C for 15 h. Then, a catalytic amount of PPTS was again added and stirring was continued for an additional 7 h at r.t. The reaction was quenched with Et_3N (1 mL), the volatiles were evaporated and the residue was chromatographed on silica gel (2% EtOAc–hexane → 10% EtOAc–hexane) to provide the alcohol **14**; yield: 1.36 g (84%).

Colorless oil; $[\alpha]_D^{22}$ +51.58 (*c* 12.36, $CHCl_3$); R_f = 0.5 (EtOAc–hexane, 3:7).

IR (NaCl): 3482, 2952, 2931, 2857, 2360, 2341 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.89–5.79 (m, 1 H, H-1′), 5.25 (dd, J_{trans} = 17.15 Hz, J_{gem} = 1.12 Hz, 1 H, H-2′), 5.12 (dd, J_{cis} = 10.68 Hz, J_{gem} = 1.12 Hz, 1 H, H-2′), 3.91–3.81 (m, 2 H, H-1″), 3.68–3.61 (m, 1 H, H-6), 3.55–3.47 (m, 1 H, H-3), 3.30–3.24 (m, 1 H, H-2),

2.18 (s, 1 H, OH), 2.07–2.00 (m, 1 H, H-4), 1.77 (d, J = 12.79 Hz, 1 H, H-5), 1.59–1.42 (m, 2 H, H-4, H-5), 0.89 [s, 9 H, $SiC(CH_3)_3$], 0.08 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR ($CDCl_3$): δ = 138.37 (CH-1′), 115.18 (CH_2-2′), 81.95 (CH-2), 77.74 (CH-6), 67.53 (CH-3), 63.00 (CH_2-1″), 33.04 (CH_2-4), 30.92 (CH_2-5), 25.73 [$SiC(CH_3)_3$], 17.89 [$SiC(CH_3)_3$], –4.16, –4.94 [$Si(CH_3)_2$].

MS (FAB$^+$): m/z (%) = 311 (28), 295 (100) [M + Na]$^+$, 273 (43) [M + H]$^+$, 271 (38) [M – H]$^+$.

HRMS (FAB$^+$): m/z calcd for $C_{14}H_{29}O_3Si$: 273.1880; found: 273.1881.

[(2*R*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-vinyltetrahydro-2*H*-pyran-2-yl]methyl 4-Methylbenzenesulfonate (15)

To a soln of alcohol **14** (1.11 g, 4.1 mmol) in CH_2Cl_2 (8 mL) at 0 °C were added dropwise pyridine (2 mL) and *p*-TsCl (1.56 g, 8.2 mmol). The mixture was stirred at r.t. for 20 h and then H_2O (5 mL) was added. The aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with 10% aq Cu_2SO_4 (2 × 10 mL), H_2O (10 mL) and brine (10 mL), then dried (Na_2SO_4). The solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc–hexane, 1:99) to afford **15**; yield: 1.65 g (95%).

Colorless oil; $[\alpha]_D^{21}$ +43.94 (*c* 1.98, $CHCl_3$); R_f = 0.49 (CH_2Cl_2).

IR (NaCl): 2953, 2930, 2857, 2360, 2341 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.76 (d, J = 8.04 Hz, 2 H, *o*-H_{Ts}), 7.28 (d, J = 8.15 Hz, 2 H, *m*-H_{Ts}), 5.76–5.66 (m, 1 H, H-1′), 5.12 (dd, J_{trans} = 17.29 Hz, J_{gem} = 1.12 Hz, 1 H, H-2′), 5.01 (dd, J_{cis} = 10.82 Hz, J_{gem} = 1.12 Hz, 1 H, H-2′), 4.22 (d, J = 10.26 Hz, 1 H, H-1″), 4.14–4.08 (m, 1 H, H-1″), 3.77–3.70 (m, 1 H, H-6), 3.43 (td, J = 9.56, 4.64 Hz, 1 H, H-3), 3.33–3.28 (m, 1 H, H-2), 2.40 (s, 3 H, $ArCH_3$), 2.03–1.96 (m, 1 H, H-4), 1.69 (dd, J = 12.93, 2.67 Hz, 1 H, H-5), 1.52–1.30 (m, 2 H, H-4, H-5), 0.81 [s, 9 H, $SiC(CH_3)_3$], 0.03, 0.01 [2 × s, 2 × 3 H, $Si(CH_3)_2$].

^{13}C NMR ($CDCl_3$): δ = 144.50 (C_{Ts}), 138.01 (CH-1′), 133.17 (C_{Ts}), 129.69 (*m*-CH_{Ts}), 127.98 (*o*-CH_{Ts}), 114.65 (CH_2-2′), 79.69 (CH-2), 77.44 (CH-6), 70.06 (CH_2-1″), 66.65 (CH-3), 33.05 (CH_2-4), 30.61 (CH_2-5), 25.68 [$SiC(CH_3)_3$], 21.53 ($ArCH_3$), 17.75 [$SiC(CH_3)_3$], –4.03, –5.03 [$Si(CH_3)_2$].

MS (FAB$^+$): m/z (%) = 450 (18) [M + H + Na]$^+$, 449 (92) [M + Na]$^+$, 444 (25), 428 (19) [M + 2 H]$^+$, 427 (100) [M + H]$^+$.

HRMS (FAB$^+$): m/z calcd for $C_{21}H_{35}O_5SSi$: 427.1969; found: 427.1972.

2-[(2*R*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-vinyltetrahydro-2*H*-pyran-2-yl]acetonitrile (16)

To a soln of tosylate **15** (0.405 g, 0.95 mmol) in DMSO (8 mL) was added NaCN (0.145 g, 2.85 mmol), and the mixture was stirred at 50 °C for 7 h. The reaction was quenched with H_2O (8 mL) and the mixture was extracted with EtOAc (2 × 10 mL). The organic layers were washed with H_2O (2 × 10 mL) and brine (2 × 10 mL), then dried (Na_2SO_4). The solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel (100% hexane → 2% EtOAc–hexane) to furnish the nitrile **16**; yield: 0.176 g (66%).

Colorless oil; $[\alpha]_D^{21}$ +42.26 (*c* 1.62, $CHCl_3$); R_f = 0.54 (EtOAc–hexane, 3:7).

IR (NaCl): 2942, 2858, 2360, 2251 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.88–5.78 (m, 1 H, H-1′), 5.30–5.24 (m, 1 H, H-2′), 5.14–5.09 (m, 1 H, H-2′), 3.91–3.85 (m, 1 H, H-6), 3.50–3.42 (m, 1 H, H-3), 3.41–3.35 (m, 1 H, H-2), 2.74 (dd, J = 16.87, 3.65 Hz, 1 H, H-1″), 2.62 (dd, J = 16.73, 5.76 Hz, 1 H, H-1″), 2.10–2.03 (m, 1 H, H-4), 1.81–1.75 (m, 1 H, H-5), 1.59–1.45 (m, 2 H, H-4, H-5), 0.89 [s, 9 H, $SiC(CH_3)_3$], 0.11, 0.10 [2 × s, 2 × 3 H, $Si(CH_3)_2$].

^{13}C NMR ($CDCl_3$): δ = 137.67 (CH-1′), 117.48 (CN), 115.37 (CH_2-2′), 78.06 (CH-6), 77.41 (CH-2), 69.83 (CH-3), 32.79 (CH_2-4), 30.70 (CH_2-5), 25.70 [$SiC(CH_3)_3$], 21.46 (CH_2-1″), 17.82 [$SiC(CH_3)_3$], –3.97, –4.87 [$Si(CH_3)_2$].

MS (FAB$^+$): m/z (%) = 305 (15) [M + H + Na]$^+$, 304 (100) [M + Na]$^+$, 299 (11), 282 (51) [M + H]$^+$.

HRMS (FAB$^+$): m/z calcd for $C_{15}H_{28}NO_2Si$: 282.1884; found: 282.1885.

2-[(2*R*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-vinyltetrahydro-2*H*-pyran-2-yl]acetic Acid (4)

To a soln of nitrile **16** (0.103 g, 0.366 mmol) in CH_2Cl_2 (4 mL), cooled to –78 °C, was added dropwise 1.0 M DIBAL-H in hexane (0.55 mL, 0.55 mmol), and the mixture was stirred for 1 h. Then, the temperature was allowed to warm to –40 °C and stirring was continued for 4 h. The reaction was quenched with sat. aq NH_4Cl (5 mL) and the mixture was extracted with CH_2Cl_2 (5 × 4 mL). The organic phases were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue (0.11 mg, 0.38 mmol) was dissolved in a mixture of MeCN–H_2O (1:1, 6 mL), and TEMPO (0.012 g, 0.075 mmol) and BAIB (0.266 g, 0.827 mmol) were added; the mixture was stirred at r.t. for 7 h. The reaction was quenched with 1.0 M aq $Na_2S_2O_3$ (1 mL), then the mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite®. The solvents were evaporated and the resulting solid was chromatographed on silica gel (2% EtOAc–hexane → 20% EtOAc–hexane) to afford the desired acid **4**; yield: 0.067 g (61%, two steps).

Colorless oil; $[\alpha]_D^{21}$ +20.84 (*c* 3.32, $CHCl_3$); R_f = 0.52 (EtOAc–hexane, 3:7).

IR (NaCl): 2930, 2858, 1715 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.87–5.77 (m, 1 H, H-1′), 5.24 (dd, J_{trans} = 17.43 Hz, J_{gem} = 1.41 Hz, 1 H, H-2′), 5.11 (dd, J_{cis} = 10.96 Hz, J_{gem} = 1.41 Hz, 1 H, H-2′), 3.93–3.85 (m, 1 H, H-6), 3.65 (td, J = 9.14, 3.09 Hz, 1 H, H-2), 3.41–3.32 (m, 1 H, H-3), 2.87 (dd, J = 15.74, 3.23 Hz, 1 H, H-1″), 2.45 (dd, J = 15.60, 8.85 Hz, 1 H, H-1″), 2.08–2.00 (m, 1 H, H-4), 1.82–1.75 (m, 1 H, H-5), 1.63–1.43 (m, 2 H, H-4, H-5), 0.89 [s, 9 H, $SiC(CH_3)_3$], 0.08 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR ($CDCl_3$): δ = 176.84 (CO_2H), 137.95 (CH-1′), 115.25 (CH_2-2′), 78.80 (CH-2), 77.85 (CH-6), 70.57 (CH-3), 37.91 (CH_2-1″), 33.09 (CH_2-4), 30.88 (CH_2-5), 25.73 [$SiC(CH_3)_3$], 17.88 [$SiC(CH_3)_3$], –4.01, –4.79 [$Si(CH_3)_2$].

MS (FAB$^+$): m/z (%) = 339 (4), 324 (15) [M + H + Na]$^+$, 323 (100) [M + Na]$^+$, 301 (4) [M + H]$^+$, 199 (5).

HRMS (FAB$^+$): m/z calcd for $C_{15}H_{28}NaO_4Si$: 323.1649; found: 323.1648.

Acknowledgment

This work was supported financially by the Spanish Ministry of Foreign Affairs and Cooperation (PCI A/030052/10) and the Xunta de Galicia (INCITE845B-2010/020, INCITE08PXIB314255PR). The work of the NMR and MS divisions of the research support services of the University of Vigo (CACTI) is also gratefully acknowledged. M.P. thanks the Xunta de Galicia for an Angeles Alvariño contract.

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