Asymmetric Formal Synthesis of (+)-Pyrenolide D

Martin Markovič,[a] Pavol Lopatka,[a] Peter Koóš,[b] Tibor Gracza*[a]

[a] Department of Organic Chemistry, Slovak University of Technology, Radlinského 9, 812 37 Bratislava, Slovakia
Fax +421(2)57294998; E-mail: tibor.gracza@stuba.sk

[b] Georganics Ltd., Koreničova 1, 811 03 Bratislava, Slovakia

Received: 13.11.2013; Accepted after revision: 19.12.2013

Abstract: A concise, asymmetric formal synthesis of (+)-pyrenolide D from (*E*)-crotonaldehyde is described. The key steps include an enantioselective Sharpless dihydroxylation of protected hex-4-en-1-yn-3-ol and a highly diastereoselective palladium-catalysed oxycarbonylation of (2*R*,3*S*,4*S*)-hex-5-ene-2,3,4-triol using iron pentacarbonyl as the carbon monoxide source.

Key words: natural products, pyrenolide D, oxycarbonylation, palladium catalysis, iron pentacarbonyl

(+)-Pyrenolide D (**1**, Figure 1) is a highly oxygenated tricyclic γ-spirolactone isolated from the phytogenic fungus *Pyrenophora teres* (Diedicke) Drechsler (IFO 7508).[1] In contrast to the pyrenolides A–C,[2] simple macrocyclic lactones that exhibit potent growth-inhibitory and morphogenic activities toward fungi, the structure of pyrenolide D is related to certain members **2** of the cephalosporolide class of natural products (Figure 1).[3] Moreover, pyrenolide D exhibits significant cytotoxic activity toward HL-60 cells (IC_{50} = 4 μg/mL).[1]

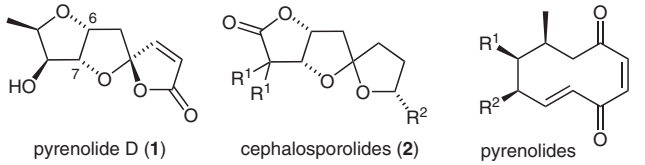


Figure 1 Structure of pyrenolide D, cephalosporolides E, H and I, and pyrenolides A–C

The noteworthy cytotoxic activity of **1** and unknown mode of its *in vitro* action has resulted in considerable attention from the synthetic community.[4–7]

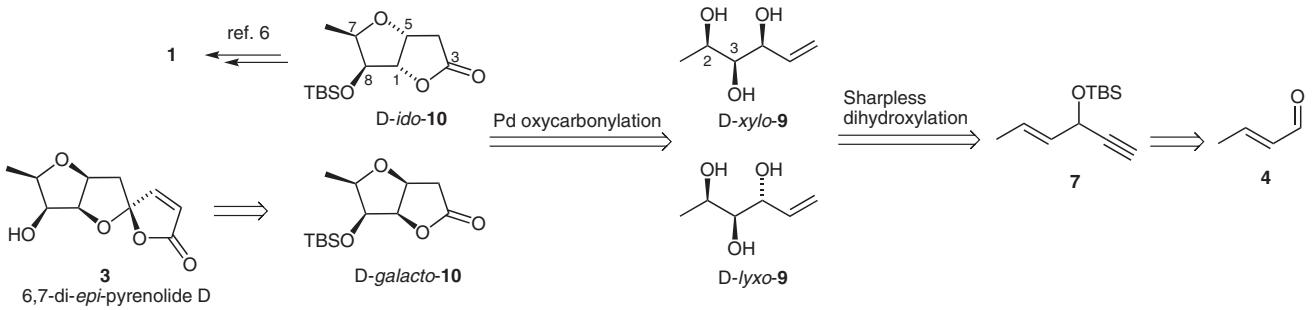
To date, only four syntheses of (+)-pyrenolide D (**1**) have been reported. In 2001, Gin and co-workers[4] unveiled the first total synthesis of pyrenolide D, starting from tri-*O*-acetyl-D-galactal. Their synthesis featured an efficient oxidative ring-contraction approach in the construction of the furanoside part of the tricyclic natural product. Another carbohydrate-based synthesis of **1** and its 4-epimer has been reported by Mohapatra's group.[5] Furthermore, in 2009, Vassilikogiannakis and co-workers[7] outlined a synthesis of crassalactone showing a feasible approach for the synthesis of γ-spirolactones. Applying this strategy based on a simple furan alkylation, followed by asymmetric Sharpless dihydroxylation of an exocyclic double bond and singlet oxygen furan oxidation, this group also managed to prepare three other diastereomers of pyrenolide D. Most recently, Du and co-workers[6] outlined a chiral pool approach involving a nucleophilic addition of the methyl propiolate anion to a key lactone, D-*ido*-**10**, followed by triple bond reduction and tandem one-pot desilylation–spirolactonisation that remarkably shortened the synthesis and provided the natural compound in good overall yield.

Despite these different approaches in the synthesis of pyrenolide D, none has revealed accessibility to different epimers at the C-6,7 centres. Thus, our group has focused on the development of a short asymmetric approach to the key D-*ido*-**10** intermediate, along with the possibility to access different stereoisomers (Scheme 1). Based on our previous experience in the total syntheses of biologically interesting natural compounds,[8] we herein propose and describe the first asymmetric formal synthesis of pyrenolide D (**1**) and its 6,7-diastereomer **3** employing regioselective and diastereoselective bicyclisation using palladium catalysis.[9]

Our retrosynthetic analysis, outlined in Scheme 1, takes advantage of a Sharpless asymmetric dihydroxylation of protected hex-4-en-1-yn-3-ol **7** to correctly install the chiral centres at C-2 and C-3. Then, highly diastereoselective palladium(II)-catalysed oxycarbonylation of the alkene-triols D-*xylo*-**9** and D-*lyxo*-**9** would easily provide the final lactones **10** with correct configuration at C-5.

Accordingly, the synthesis of the target lactone intermediates of pyrenolide D and its 6,7-diastereomer **3** started from the commercially available (*E*)-crotonaldehyde (**4**) (Scheme 2). Thus, enynol **5** was prepared in 70% yield by using a modified Grignard procedure[10] for the addition of ethynylmagnesium bromide to aldehyde **4**. Alternatively, alcohol **5** can be prepared in 86% yield by addition of in situ generated lithium (trimethylsilyl)acetylide to aldehyde **4**. Alcohol **5** was then exposed to Sharpless asymmetric dihydroxylation[11] to install the C-2 and C-3 stereocentres. Unfortunately, treatment of the unprotected alcohol **5** with $(DHQD)_2PHAL$ ligand and potassium osmate as the oxidant provided the diastereomeric mixture of triols D-*xylo*-**6**/D-*lyxo*-**6** in low yield (21%) due to isolation problems. Therefore, alcohol **5** was O-silylated[12] to the corresponding TBS ether **7** in 96% yield; subsequent

SYNTHESIS 2014, 46, 0817–0821
Advanced online publication: 23.01.2014
DOI: 10.1055/s-0033-1338584; Art ID: SS-2013-T0742-OP

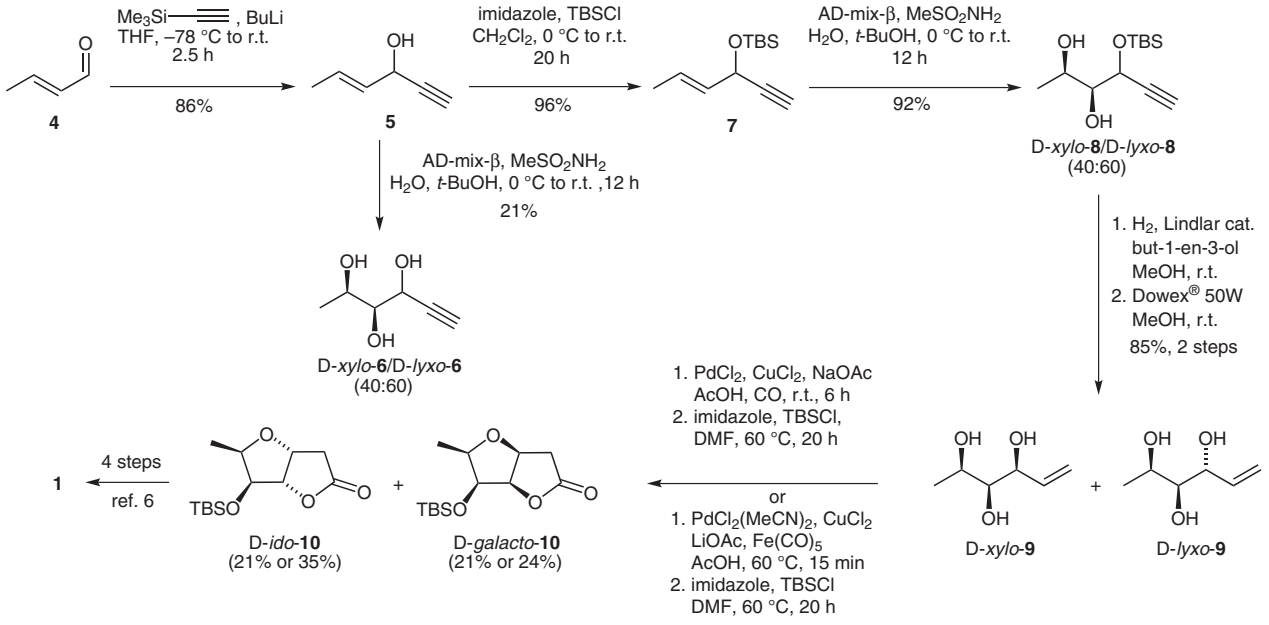


Scheme 1 Retrosynthetic analysis of pyrenolide D (**1**) and its 6,7-diastereomer **3**

asymmetric dihydroxylation of **7** using AD-mix-β in *tert*-butyl alcohol–water afforded the monoprotected diastereomeric triols D-*xylo*-**8**/D-*lyxo*-**8** in a 40:60 ratio with high enantioselectivity[13] in the *xylo* case and moderate enantioselectivity in the *lyxo* case (92% yield). The standards for GC determination of the optical purity, racemic *xylo*-**8**/*lyxo*-**8**, were prepared following the same synthetic procedure, with final dihydroxylation $\{K_2[OsO_2(OH)_4]$, $MeSO_2NH_2$, $K_3Fe(CN)_6$, $K_2CO_3\}$ of **7** providing racemic *xylo*-**8**/*lyxo*-**8** in 76% yield.

The first attempt to hydrogenate the alkynes **8** using Lindlar catalyst unfortunately resulted in the concomitant saturation of the generated C–C double bond, and the alkenes were obtained along with a remarkable quantity of the unwanted alkanes. A literature search aimed at reaction conditions that would suppress the formation of the saturated side products[14] resulted in a catalytic system consisting of 0.1 equivalent of Lindlar catalyst and 2 equivalents of but-1-en-3-ol in methanol under hydrogen (1 atm) at room temperature, which pleasingly selectively afforded a mixture of the alkenetriols D-*xylo*-**9**/D-*lyxo*-**9** after acidic hydrolysis using Dowex® 50W in methanol (85% yield from D-*xylo*-**8**/D-*lyxo*-**8**). Thus, the required intermediates for the subsequent bicyclisation, the unprotected triols D-*xylo*-**9**/D-*lyxo*-**9**, were available.

Finally, the diastereomers D-*xylo*-**9**/D-*lyxo*-**9** (40:60) were then subjected to the crucial transformation of the synthesis: a two-step sequence to convert the unsaturated triols D-*xylo*-**9**/D-*lyxo*-**9** into lactones D-*ido*-**10** and D-*galacto*-**10** with the 1,5-*threo* relationship. At first, the cyclisation reaction was carried out under standard reaction conditions[8a–e,9a,b] using $PdCl_2$ as a catalyst (0.1 equiv) with $CuCl_2$ (3 equiv) and NaOAc (3 equiv) in acetic acid under a carbon monoxide atmosphere (balloon). Subsequent treatment of the crude material with TBSCl and imidazole in *N*,*N*-dimethylformamide followed by flash chromatographic purification provided lactones D-*ido*-**10** (21%) and D-*galacto*-**10** (21%) with high regioselectivity and *threo* diastereoselectivity. As an alternative option to the standard cyclisation method, we decided to use a newly optimised, homogeneous palladium-catalysed carbonylation reaction using $Fe(CO)_5$,[15] since previous screening and optimisation of the reaction conditions pointed to better yields of isolated products **10** for the manipulation



Scheme 2 Formal synthesis of (+)-pyrenolide D

with iron pentacarbonyl compared to gaseous carbon monoxide. Thus, the reaction using $Fe(CO)_5$ (0.25 equiv) in the presence of $PdCl_2(MeCN)_2$ (0.1 equiv), $CuCl_2$ (4 equiv) and LiOAc (4 equiv) in acetic acid at 60 °C, followed by silyl protection of the free hydroxy group, provided the target lactones **10** in higher yields {D-*ido*-**10**: 35%, mp 91.7–92.5 °C (Lit.[6] 87.8–89 °C), $[\alpha]_D^{20}$ +29.4 (*c* 1, $CHCl_3$) [Lit.[6] $[\alpha]_D^{23}$ +26.2 (*c* 1, $CHCl_3$)]; D-*galacto*-**10**: 24%, $[\alpha]_D^{20}$ –28.2 (*c* 0.75, $CHCl_3$)}.[16] The enantiomeric purity of the target compounds, D-*ido*-**10** (er 93:7) and D-*galacto*-**10** (er 83:17), was determined by GC analysis with a Chirasil-Dex (permethylated β-cyclodextrin) stationary phase column (25 m, i.d. 0.25 mm, d_f 250 nm). The absolute configuration of D-*ido*-**10** was assigned by comparison of the specific rotation value with the literature data for the lactone D-*ido*-**10** prepared from D-xylose.[6] Additionally, the relative configuration at the C-1 and C-5 centres was also confirmed by positive NOE interactions of related protons.

In conclusion, we have described a concise assembly of the central 2,6-dioxabicyclo[3.3.0]octane core of pyrenolide D by employing a Sharpless asymmetric dihydroxylation and a palladium(II)-catalysed oxycarbonylative bicyclisation. Moreover, the lactone D-*galacto*-**10** represents a useful chiral synthon for the synthesis of 6,7-di-*epi*-pyrenolide D (**3**). The synthetic strategy described herein has a significant potential for further extension to other analogues of pyrenolide D and cephalosporolides.

All reactions involving organometallic or moisture-sensitive reagents were carried out under argon atmosphere using standard vacuum line techniques and glassware that was flame-dried and cooled under argon before use. Commercial reagents were used without further purification. All solvents were distilled before use. Hexanes refers to the fraction boiling at 60–65 °C. Flash column liquid chromatography (FLC) was performed on silica gel (Kieselgel 60, 40–63 μm, 230–400 mesh) and analytical thin-layer chromatography (TLC) was performed on aluminum plates precoated with either 0.2 mm (DC-Alufolien, Merck) or 0.25 mm silica gel 60 F254 (ALUGRAM® SIL G/UV254, Macherey-Nagel). The compounds were visualised by UV fluorescence and by dipping the plates in an aqueous H_2SO_4 solution of cerium sulfate/ammonium molybdate followed by charring with a heat gun. GC analyses were performed on an Agilent 5980 Series II gas chromatograph equipped with a split/splitless injector (250 °C, split ratio 1:50) and an FID detector (250 °C). Hydrogen with optimal velocity 40 cm/s was used as the carrier gas. The oven was operated under the temperature program 180 °C (25 min)–10 °C/min–240 °C (5 min). Enantiomeric excesses were determined with the same gas chromatograph using hydrogen with velocity 85 cm/s as the carrier gas, and the temperature program 60 °C (2 min)–3.5 °C/min–190 °C. Elemental analyses were run on a Fisons EA1108 instrument. Melting points were obtained using a Boetius apparatus and are uncorrected. Optical rotations were measured with a JASCO P-2000 polarimeter and are given in units of 10^{-1} deg·cm^2·g^{-1}. FTIR spectra were obtained on a Nicolet 5700 spectrometer (Thermo Electron) equipped with a Smart Orbit (diamond crystal ATR) accessory, using the reflectance technique (4000–400 cm^{-1}). NMR spectra were recorded in $CDCl_3$ on either a Varian Mercury Plus 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) or Varian Unity Inova 600 (600 MHz for ^{1}H, 151 MHz for ^{13}C) spectrometer. Chemical shifts (δ) are quoted in ppm and are referenced to TMS as internal standard. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Orbitrap Velos mass spectrometer with a heated electrospray ionisation (HESI) source. The mass spectrometer was operated with full scan (50–2000 amu) in positive or negative FT mode (at a resolution of 100000). The analyte was dissolved in MeOH and infused via syringe pump at a rate of 5 mL/min. The heated capillary was maintained at 275 °C with a source heater temperature of 50 °C, and the sheath, auxiliary and sweep gases were at 10, 5 and 0 units, respectively. The source voltage was set to 3.5 kV.

Hex-4-en-1-yn-3-ol (5)

Procedure A

To a suspension of Mg turnings (2.43 g, 100.00 mmol, 1 equiv) in anhydrous THF (200 mL) was added portionwise neat 1,2-dibromoethane (8.66 mL, 100.00 mmol, 1 equiv). The resulting mixture was stirred for 30 min at r.t., followed by refluxing for 30 min. This mixture was then treated at 0 °C with sodium acetylide (26.68 g, 18 wt % in xylene) and left to stir for 45 min at the same temperature. The resulting solution of sodium acetylide–$MgBr_2$ complex was then added at –35 °C to a solution of crotonaldehyde (**4**; 5.53 mL, 66.70 mmol, 0.67 equiv) in anhydrous THF (100 mL). The reaction mixture was allowed to warm to 0 °C over a 1-h period while being stirred, and then was quenched with saturated NH_4Cl solution (100 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (3 × 150 mL). The combined organic extracts were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Distillation of the residue (52–54 °C/12 mbar) provided 4.50 g of the desired product in 70% yield as a colourless oil.

Procedure B

To a stirred solution of (trimethylsilyl)acetylene (34.07 mL, 239.34 mmol, 1.1 equiv) in anhydrous THF (500 mL) was added at –78 °C a solution of 2.5 M *n*-BuLi in hexanes (100 mL, 250.21 mmol, 1.15 equiv). After 30 min of stirring at –78 °C, a solution of crotonaldehyde (**4**; 15.25 g, 217.58 mmol, 1 equiv) in anhydrous THF (100 mL) was added. The resulting mixture was left to stir at –78 °C for 2 h, followed by addition of MeOH (300 mL). The reaction mixture was left to warm to r.t. with stirring until complete desilylation was observed (TLC). The mixture was then concentrated in vacuo. The residue was diluted with Et_2O (1000 mL) followed by addition of saturated NH_4Cl solution (500 mL). After 30 min of stirring, the layers were separated and the aqueous phase was extracted with Et_2O (1 × 250 mL). The combined organic extracts were washed with brine (250 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Distillation of the residue (74–76 °C/34–38 mbar) afforded 17.92 g of the desired product in 86% yield as a colourless oil.

R_f = 0.4 (hexanes–EtOAc, 4:1).

IR (ATR): 3350, 3292, 2918, 1005, 962, 650 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75 (dd, *J* = 6.5, 1.6 Hz, 3 H, H-6), 2.02 (d, *J* = 6.0 Hz, 1 H, OH), 2.57 (d, *J* = 2.2 Hz, 1 H, H-1), 4.87–4.80 (m, 1 H, H-3), 5.64 (ddq, *J* = 15.2, 6.2, 1.6 Hz, 1 H, H-4), 5.94 (dqd, *J* = 15.2, 6.5, 1.2 Hz, 1 H, H-5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.7, 62.9, 74.2, 83.5, 129.5, 129.9.

***tert*-Butyl(hex-4-en-1-yn-3-yloxy)dimethylsilane (7)**

To a stirred solution of hex-4-en-1-yn-3-ol (**5**; 20.00 g, 203.79 mmol, 1 equiv) in anhydrous CH_2Cl_2 (250 mL) was added at 0 °C imidazole (18.73 g, 275.12 mmol, 1.35 equiv). After 5 min of stirring, TBSCl (36.85 g, 244.55 mmol, 1.2 equiv) was added in one portion and stirring was continued for 30 min at 0 °C. The resulting solution was then allowed to warm to r.t., and after 20 h of stirring the reaction mixture was concentrated in vacuo. The residue was taken up in Et_2O (350 mL), which was washed with H_2O (3 × 60 mL) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Distillation of the residue (77–79 °C/9–10 mbar) provided 41.12 g of silane **7** in 96% yield as a colourless oil.

R_f = 0.4 (hexanes–EtOAc, 19:1).

IR (ATR): 2929, 2858, 1054, 835, 776, 653 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.13 (s, 3 H, SiMe), 0.14 (s, 3 H, SiMe), 0.91 (s, 9 H, *t*-Bu), 1.74–1.70 (m, 3 H, H-6), 2.48 (d, *J* = 2.2 Hz, 1 H, H-1), 4.86–4.81 (m, 1 H, H-3), 5.55 (ddq, *J* = 15.2, 5.7, 1.6 Hz, 1 H, H-4), 5.82 (dqd, *J* = 15.0, 6.5, 1.3 Hz, 1 H, H-5).

^{13}C NMR (151 MHz, $CDCl_3$): δ = –4.6, –4.4, 17.6, 18.1, 26.0, 63.4, 73.1, 84.3, 129.1, 129.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{23}OSi$: 211.15182; found: 211.15118.

(2*R*,3*S*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)hex-5-yne-2,3-diol (D-*xylo*-8) and (2*R*,3*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)hex-5-yne-2,3-diol (D-*lyxo*-8)

A suspension of AD-mix-β (57.89 g, 1.40 g/1 mmol of olefin) and $MeSO_2NH_2$ (3.93 g, 41.35 mmol, 1 equiv) in H_2O (207 mL) and *t*-BuOH (207 mL) was stirred at r.t. until both phases became clear. Then, the mixture was cooled to 0 °C, whereupon the inorganic salts partially precipitated, and *tert*-butyl(hex-4-en-1-yn-3-yloxy)dimethylsilane (**7**; 8.70 g, 41.35 mmol, 1 equiv) was added in one portion. The resulting heterogeneous slurry was stirred overnight, the reaction was quenched at 0 °C by addition of sodium sulfite (62.03 g, 1.50 g/1 mmol of olefin) and the mixture was warmed to r.t. over a period of 1 h. The reaction mixture was extracted with EtOAc (3 × 250 mL), and the combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (hexanes–EtOAc, 100:0 to 80:20; then isocratic hexanes–EtOAc, 80:20) provided 9.31 g of the desired mixture of diastereomers (D-*xylo*/D-*lyxo*, 40:60 from ^1H NMR data) in 92% yield as a pale yellow oil.

D-*xylo*-8

R_f = 0.2 (hexanes–EtOAc, 4:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.16 (s, 3 H, SiMe), 0.19 (s, 3 H, SiMe), 0.91 (s, 9 H, *t*-Bu), 1.28 (d, *J* = 6.5 Hz, 3 H, H-1), 2.26 (br s, 1 H, OH), 2.49 (d, *J* = 2.1 Hz, 1 H, H-6), 2.75 (d, *J* = 5.0 Hz, 1 H, OH), 3.45–3.33 (m, 1 H, H-3), 4.00 (m, 1 H, H-2), 4.44 (dd, *J* = 6.4, 2.1 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.0, –4.2, 18.3, 20.4, 25.9, 64.6, 66.9, 75.0, 76.0, 82.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{25}O_3Si$: 245.15730; found: 245.15682; *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{24}NaO_3Si$: 267.13924; found: 267.13874.

D-*lyxo*-8

R_f = 0.2 (hexanes–EtOAc, 4:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.16 (s, 3 H, SiMe), 0.19 (s, 3 H, SiMe), 0.91 (s, 9 H, *t*-Bu), 1.24 (d, *J* = 6.5 Hz, 3 H, H-1), 2.52 (d, *J* = 2.2 Hz, 1 H, H-6), 2.78 (d, *J* = 8.6 Hz, 1 H, OH), 2.85 (br s, 1 H, OH), 3.43–3.35 (m, 1 H, H-3), 4.34 ('q', *J* = 6.4 Hz, 1 H, H-2), 4.55 (dd, *J* = 3.6, 2.2 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.2, –4.6, 18.2, 19.6, 25.8, 66.8, 67.2, 75.4, 77.6, 82.1.

(±)-4-(*tert*-Butyldimethylsilyloxy)hex-5-yne-2,3-diol (*xylo*-8/*lyxo*-8)

A suspension of $K_3Fe(CN)_6$ (2.35 g, 7.13 mmol, 3 equiv), K_2CO_3 (0.99 g, 7.13 mmol, 3 equiv), $K_2[OsO_2(OH)_4]$ (3.50 mg, 9.50 μmol, 0.004 equiv), pyridine (18.80 mg, 0.24 mmol, 0.1 equiv) and $MeSO_2NH_2$ (0.23 g, 2.38 mmol, 1 equiv) in H_2O (12 mL) and *t*-BuOH (12 mL) was stirred at r.t. until both phases became clear. Then, the mixture was cooled to 0 °C, whereupon the inorganic salts partially precipitated, and *tert*-butyl(hex-4-en-1-yn-3-yloxy)dimethylsilane (**7**; 0.50 g, 2.38 mmol, 1 equiv) was added in one portion. The resulting heterogeneous slurry was stirred overnight, the reaction was quenched at 0 °C by addition of sodium sulfite (3.57 g, 1.50 g/1 mmol of olefin) and the mixture was warmed to r.t. over a period of 1 h. The reaction mixture was extracted with EtOAc (3 × 30 mL), and the combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (hexanes–EtOAc, 100:0 to 80:20; then isocratic hexanes–EtOAc, 80:20) provided 0.44 g of the desired racemic mixture of diastereomers (*xylo*/*lyxo*) in 76% yield as a pale yellow oil; R_f = 0.2 (hexanes–EtOAc, 4:1).

(2*R*,3*S*,4*S*)-Hex-5-ene-2,3,4-triol (D-*xylo*-9) and (2*R*,3*S*,4*R*)-Hex-5-ene-2,3,4-triol (D-*lyxo*-9)

To a stirred solution of diastereomeric mixture D-*xylo*-**8**/D-*lyxo*-**8** (1.33 g, 5.44 mmol, 1 equiv) and but-1-en-3-ol (0.78 g, 10.89 mmol, 2 equiv) in MeOH (50 mL) was added Lindlar catalyst (130 mg, 10 wt % according to the mixture of alkynes). The flask was three times evacuated and filled with hydrogen via balloon and the mixture was left to vigorously stir at r.t. under hydrogen atmosphere (balloon) until full conversion (detected by TLC). The mixture was then filtered through fiberglass filter paper which was followed by addition of Dowex® 50W X8 (10.00 g) to the filtrate. The reaction mixture was stirred until full conversion (TLC), and then was filtered and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (hexanes–EtOAc, 100:0 to 0:100; then EtOAc) provided 0.61 g of the desired mixture of diastereomers (D-*xylo*/D-*lyxo*, 40:60 from ^1H NMR data) in 85% yield over two steps as a pale yellow oil.

D-*xylo*-9

R_f = 0.2 (EtOAc).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.4 Hz, 3 H, H-1), 2.84–2.74 (br s, 2 H, OH), 2.89 (br s, 1 H, OH), 3.30 (t, *J* = 3.6 Hz, 1 H, H-3), 3.95 (qd, *J* = 6.4, 3.4 Hz, 1 H, H-2), 4.28–4.21 (m, 1 H, H-4), 5.27 (dt, *J* = 10.5, 1.4 Hz, 1 H, H-6_a), 5.38 (dt, *J* = 17.3, 1.5 Hz, 1 H, H-6_b), 5.94 (ddd, *J* = 17.2, 10.5, 5.9 Hz, 1 H, H-5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2, 68.8, 74.5, 76.6, 117.3, 137.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_6H_{13}O_3$: 133.08647; found: 133.08585; *m*/*z* $[M + Na]^+$ calcd for $C_6H_{12}NaO_3$: 155.06841; found: 155.06771.

D-*lyxo*-9

R_f = 0.2 (EtOAc).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.5 Hz, 3 H, H-1), 1.78 (br s, 1 H, OH), 2.84–2.67 (br s, 1 H, OH), 2.89 (br s, 1 H, OH), 3.39 (t, *J* = 3.5 Hz, 1 H, H-3), 4.00 (qd, *J* = 6.5, 3.2 Hz, 1 H, H-2), 4.35–4.29 (m, 1 H, H-4), 5.28 (dt, *J* = 10.5, 1.5 Hz, 1 H, H-6_a), 5.38 (dt, *J* = 17.3, 1.5 Hz, 1 H, H-6_b), 5.93 (ddd, *J* = 17.3, 10.5, 5.8 Hz, 1 H, H-5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7, 67.2, 75.5, 76.1, 117.3, 136.7.

(1*S*,5*R*,7*R*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)-7-methyl-2,6-dioxabicyclo[3.3.0]octan-3-one (D-*ido*-10) and (1*R*,5*S*,7*R*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)-7-methyl-2,6-dioxabicyclo[3.3.0]octan-3-one (D-*galacto*-10)

Procedure A

A 10-mL round-bottom flask equipped with a side inlet with stopcock was charged with the diastereomeric mixture of alkenetriols D-*xylo*-**9**/D-*lyxo*-**9** (40:60; 0.30 g, 2.28 mmol, 1 equiv), NaOAc (0.56 g, 6.83 mmol, 3 equiv), anhydrous $CuCl_2$ (0.92 g, 6.83 mmol, 3 equiv) and $PdCl_2$ (0.04 g, 0.23 mmol, 0.1 equiv) in glacial AcOH (9 mL). The flask was evacuated and filled with gaseous CO, and the heterogeneous mixture was vigorously stirred at r.t. under CO atmosphere (balloon) until its colour changed from green to pale brown (overnight). The reaction mixture was concentrated in vacuo, suspended in EtOAc (50 mL), filtered through a pad of silica gel and concentrated in vacuo. The crude mixture of lactones was dissolved

in anhydrous DMF (9 mL), imidazole (0.54 g, 7.97 mmol, 3.5 equiv) and TBSCl (0.86 g, 5.69 mmol, 2.5 equiv) were added, and the mixture was stirred at 60 °C overnight, then cooled to r.t. EtOAc (20 mL) was added and the organic phase was washed with H_2O (3 × 15 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by FLC (hexanes–EtOAc, 100:0 to 85:15; then isocratic hexanes–EtOAc, 85:15) afforded pure lactones D-*ido*-**10** (133 mg, 21%) as a colourless solid and D-*galacto*-**10** (130 mg, 21%) as a colourless oil.

Procedure B

The diastereomeric mixture of alkenetriols D-*xylo*-**9**/D-*lyxo*-**9** (40:60; 0.71 g, 5.36 mmol, 1 equiv), anhydrous $CuCl_2$ (2.88 g, 21.43 mmol, 4 equiv) and anhydrous LiOAc (1.41 g, 21.43 mmol, 4 equiv) were stirred for 15 min in a closed vessel in glacial AcOH (21.43 mL, 0.25 M according to the substrate triols) at r.t. Then, $PdCl_2(MeCN)_2$ (0.14 g, 0.54 mmol, 0.1 equiv) and $Fe(CO)_5$ (181 μL, 1.34 mmol, 0.25 equiv) were added to the mixture, which was followed by stirring at 60 °C until there was no further colour change (15 min). Then, the reaction vessel was cooled to r.t. The reaction mixture was concentrated in vacuo, suspended in EtOAc (150 mL), filtered through a pad of silica gel and concentrated in vacuo. The crude mixture of lactones was dissolved in anhydrous DMF (21.43 mL), imidazole (0.95 g, 13.92 mmol, 2.6 equiv) and TBSCl (1.45 g, 9.64 mmol, 1.8 equiv) were added, and the mixture was stirred at 60 °C overnight, then cooled to r.t. EtOAc (250 mL) was added and the organic phase was washed with H_2O (3 × 100 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by FLC (hexanes–EtOAc, 100:0 to 85:15; then isocratic hexanes–EtOAc, 85:15) afforded pure lactones D-*ido*-**10** (511 mg, 35%) as a colourless solid and D-*galacto*-**10** (350 mg, 24%) as a colourless oil.

D-*ido*-10

Mp 91.7–92.5 °C (Lit.[6] 87.8–89 °C).

$[\alpha]_D^{20}$ +29.4 (*c* 1, $CHCl_3$) [Lit.[6] $[\alpha]_D^{23}$ +26.2 (*c* 1, $CHCl_3$)].

R_f = 0.3 (hexanes–EtOAc, 17:3).

IR (ATR): 2929, 2856, 1789, 1034, 836, 777 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.11 (s, 3 H, SiMe), 0.13 (s, 3 H, SiMe), 0.92 (s, 9 H, *t*-Bu), 1.22 (d, *J* = 6.3 Hz, 3 H, CH_3), 2.62 ('d', *J* = 18.7 Hz, 1 H, H-4_a), 2.71 (dd, *J* = 18.7, 6.1 Hz, 1 H, H-4_b), 4.14 (qd, *J* = 6.2, 2.9 Hz, 1 H, H-7), 4.20 ('d', *J* = 2.7 Hz, 1 H, H-8), 4.74 ('d', *J* = 4.4 Hz, 1 H, H-5), 4.91 ('t', *J* = 5.2 Hz, 1 H, H-1).

^{13}C NMR (151 MHz, $CDCl_3$): δ = –5.1, –5.0, 13.8, 18.1, 25.7, 36.1, 76.0, 76.1, 77.3, 88.7, 175.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{25}O_4Si$: 273.15221; found: 273.15169; *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{24}NaO_4Si$: 295.13416; found: 295.13355.

Anal. Calcd for $C_{13}H_{24}O_4Si$: C, 57.32; H, 8.88. Found: C, 57.38; H, 8.84.

D-galacto-10

$[\alpha]_D^{20}$ –28.2 (*c* 0.75, $CHCl_3$).

R_f = 0.1 (hexanes–EtOAc, 17:3).

IR (ATR): 2929, 2856, 1780, 1158, 1084, 838 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 0.09 (s, 3 H, SiMe), 0.13 (s, 3 H, SiMe), 0.92 (s, 9 H, *t*-Bu), 1.27 (d, *J* = 6.3 Hz, 3 H, CH_3), 2.63 (dd, *J* = 18.4, 4.5 Hz, 1 H, H-4_a), 2.72 (dd, *J* = 18.4, 8.2 Hz, 1 H, H-4_b), 3.92 (qd, *J* = 6.3, 2.9 Hz, 1 H, H-7), 4.12 (dd, *J* = 4.8, 3.0 Hz, 1 H, H-8), 4.66 (td, *J* = 7.8, 4.5 Hz, 1 H, H-5), 4.94 (dd, *J* = 7.4, 4.9 Hz, 1 H, H-1).

^{13}C NMR (151 MHz, $CDCl_3$): δ = –5.2, –4.8, 15.2, 18.3, 25.8, 36.6, 72.6, 75.2, 78.9, 82.9, 175.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{25}O_4Si$: 273.15221; found: 273.15170; *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{24}NaO_4Si$: 295.13416; found: 295.13348.

Anal. Calcd for $C_{13}H_{24}O_4Si$: C, 57.32; H, 8.88. Found: C, 57.28; H, 8.94.

Acknowledgment

This work was supported by the Slovak Grant Agencies (APVV, Bratislava, project no. APVV-0203-10 and ASFEU, Bratislava, ITMS project nos. 26240120001, 26240120025).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) Nukina, M.; Hirota, H. *Biosci., Biotechnol., Biochem.* **1992**, *56*, 1158.
(2) Nukina, M.; Iikeda, M.; Sassa, T. *Agric. Biol. Chem.* **1980**, *44*, 2761.
(3) Ackland, M. J.; Hanson, J. R.; Hitchcock, P. B.; Ratcliffe, A. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 843.
(4) Engstrom, K. M.; Mendoza, M. R.; Navarro-Villalobos, M.; Gin, D. Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 1128.
(5) Thirupathi, B.; Reddy, P. P.; Mohapatra, D. K. *J. Org. Chem.* **2011**, *76*, 9835.
(6) Zhang, Ch.; Liu, J.; Du, Y. *Tetrahedron Lett.* **2013**, *54*, 3278.
(7) (a) Pavlakos, E.; Georgiou, T.; Tofi, M.; Montagnon, T.; Vassilikogiannakis, G. *Org. Lett.* **2009**, *11*, 4556. (b) Montagnon, T.; Tofi, M.; Vassilikogiannakis, G. *Acc. Chem. Res.* **2008**, *41*, 1001.
(8) (a) Gracza, T.; Jäger, V. *Synlett* **1992**, 191. (b) Gracza, T.; Jäger, V. *Synthesis* **1994**, 1359. (c) Babjak, M.; Kapitán, P.; Gracza, T. *Tetrahedron Lett.* **2002**, *43*, 6983. (d) Babjak, M.; Kapitán, P.; Gracza, T. *Tetrahedron* **2005**, *61*, 2471. (e) Dixon, D. J.; Ley, S. V.; Gracza, T.; Szolcsányi, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 839. (f) Palík, M.; Karlubíková, O.; Lásiková, A.; Kožíšek, J.; Gracza, T. *Eur. J. Org. Chem.* **2009**, 709. (g) Karlubíková, O.; Palík, M.; Lásiková, A.; Gracza, T. *Synthesis* **2010**, 3449. (h) Szolcsányi, P.; Gracza, T.; Špánik, I. *Tetrahedron Lett.* **2008**, *49*, 1357. (i) Karlubíková, O.; Babjak, M.; Gracza, T. *Tetrahedron* **2011**, *67*, 4980.
(9) (a) Gracza, T.; Hasenohrl, T.; Stahl, U.; Jäger, V. *Synthesis* **1991**, 1108. (b) Gracza, T. In *Stereoselective Synthesis of Drugs & Natural Products*; Vol. 1; Andrushko, V.; Andrushko, N., Eds.; Wiley: Hoboken, **2013**, 421–440. (c) Babjak, M.; Remeň, Ľ.; Szolcsányi, P.; Zálupský, P.; Miklóš, D.; Gracza, T. *J. Organomet. Chem.* **2006**, *691*, 928.
(10) Spino, C.; Thibault, C.; Gingras, S. *J. Org. Chem.* **1998**, *63*, 5283.
(11) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(12) Yoshida, K.; Imamoto, T. *J. Am. Chem. Soc.* **2005**, *127*, 10470.
(13) The enantioselectivity of the AD reaction was identified retrospectively based on the ee values of lactones D-*ido*-**10** and D-*galacto*-**10**.
(14) Rawat, V.; Dey, S.; Sudalai, A. *Org. Biomol. Chem.* **2012**, *10*, 3988.
(15) Babjak, M.; Markovič, M.; Kandríková, B.; Gracza, T. *Synthesis* **2014**, *46*, 809.
(16) The racemic lactones *ido*-**10**/*galacto*-**10** were prepared from (±)-*xylo*-**8**/*lyxo*-**8** in a parallel synthesis.