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ORIGINAL PAPER

Stereoselective synthesis of the polar part of mycestericins E and G

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5-*O*-(*t*-Butyldimethylsilyl)-3-deoxy-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-3-(methoxycarbonylamino)-α-D-xylofuranose *IV* has been proved to be an appropriate building block in the stereoselective synthesis of methyl (4*S*)-4-[(1′*R*)-1′-acetoxy-4′-oxobutyl]-3-benzyl-2-oxooxazolidine-4-carboxylate *III* representing the polar part of the naturally occurring mycestericins E and mycestericins G.

Keywords: mycestericins, α-amino acid, stereoselective synthesis, immunosuppressant

Introduction

Mycestericin E (*I*) and mycestericin G (*II*) (Fig. 1), two members of the mycestericin family, were isolated from the culture broth of *Mycelia sterilia* (ATCC 20349) as potent immunosuppressants (Sasaki et al., 1994; Fujita et al., 1996). Other mycestericins, including A, B, D, and F, obtained from the same natural source (Sasaki et al., 1994; Fujita et al., 1996), have been reported to exhibit similar immunosuppressive activity (Sasaki et al., 1994; Fujita et al., 1996). From a structural standpoint, the above-mentioned compounds possess an attractive α-susbstituted α-amino acid moiety and are structurally related to myriocin (Fig. 1; for recent syntheses see: Oishi et al., 2002 (see also references herein); Jones & Marsden, 2008) which is a well-known inhibitor (Miyake et al., 1995) of serine palmitoyltransferase (SPT) (Hanada, 2003; Delgado et al., 2006) as well as a very strong immunosuppressant (Oishi et al., 2002; Jones & Marsden, 2008 (see also references herein)). Although these naturally occurring sphingolipid-based molecules exhibit remarkable bioactivity as well as unique structure, only few total syntheses in the mycestericin family have been reported so far (Shibata et al., 1996; Nishide et al., 2000; Sato et al., 2008; Yamanaka et al., 2009).

We wish to report a stereoselective synthesis of the polar segment of mycestericin E (*I*) (Fujita et al., 1995; Iwabuchi et al., 2001) and mycestericin G (*II*) (Fujita et al., 1995), with its two contiguous stere-

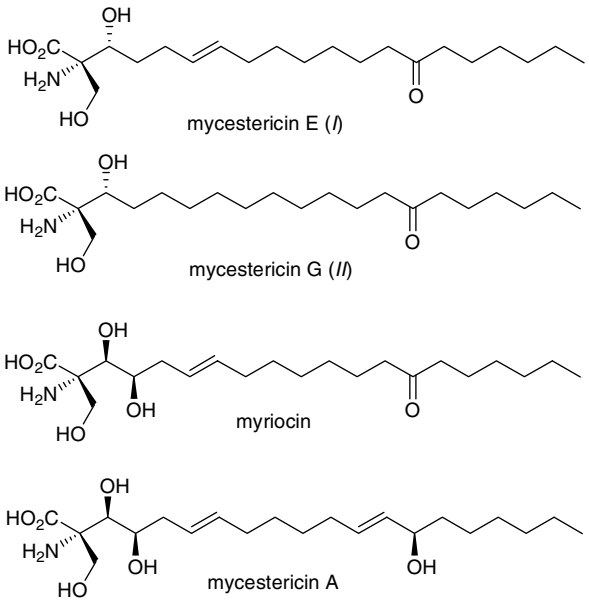

Fig. 1. Structures of mycestericin E and mycestericin G, and related natural compounds.

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ogenic centers as its construction is obviously the most difficult part of the total synthesis at present.

Experimental

All commercially available reagents were purchased in the highest available purity from Aldrich, Fluka, Merck, or Acros Organics (Slovakia), and were used without further purification. Solvents were dried and purified before use according to standard procedures. Flash chromatography purifications were run using Kieselgel 60 (0.040–0.063 mm, 230–400 mesh, Merck, Slovakia). Flash chromatography solvents (hexane, ethyl acetate, methanol, dichloromethane) were distilled before use. Thin-layer chromatography was performed on Merck silica gel 60 F_{254} analytical plates; detection was carried out with either ultraviolet light (254 nm) or spraying with a solution of phosphomolybdic acid, basic potassium permanganate solution or a solution of concentrated H_2SO_4, employing subsequent heating. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or in CD_3OD at ambient temperature on a Varian Mercury Plus 400 FT NMR (400.13 MHz for ^{1}H and 100.6 MHz for ^{13}C) or a Varian Premium COMPACT 600 (599.87 MHz for ^{1}H and 150.84 MHz for ^{13}C) spectrometer using TMS as the internal reference. Chemical shifts, δ, are given in parts per million (ppm) relative to tetramethylsilane (TMS) as the internal standard. Coupling constants, J, were obtained by first-order analysis and measured in Hertz (Hz). ^{13}C NMR signal multiplicity was determined using DEPT experiments; assignments were derived from COSY and H/C correlation spectra. Optical rotations were measured on a P3002 Krüss polarimeter and are referred to as $[\alpha]_D$ (c in grams per 100 mL of solvent). Melting points were recorded on a Kofler hot block, and are uncorrected. Small quantities of reagents (μL) were measured with appropriate syringes (Hamilton, Slovakia). All reactions were performed under an atmosphere of nitrogen, unless otherwise noted.

(3aR,4′S,5S,6aR)-5-[(t-Butyldimethylsilyloxy) methyl]-2,2-dimethyldihydro-3aH- spiro[furo [2,3-d][1,3]dioxole-6,4′-oxazolidin]-2′-one (V)

To a solution of *IV* (Martinková et al., 2007) (10.0 g, 26.0 mmol) in dry THF (129 mL) pre-cooled to 0 ℃, NaH (2.07 g, 86.0 mmol, 60 % dispersion in mineral oil, freed of oil using anhydrous THF) was added. The reaction mixture was stirred at 0 ℃ for 10 min and at room temperature for another 30 min. Then, the mixture was partitioned between CH_2Cl_2 (118 mL) and ice water (55 mL), and the water layer was further extracted with portions of CH_2Cl_2 (2 × 118 mL). After drying of the combined organic layers over Na_2SO_4, the solvent was evaporated, and the residue was chromatographed on silica gel (hexane–ethyl acetate, φ_r = 2 : 1) to afford 8.36 g (91 %) of compound *V* as a colorless oil. $[\alpha]_D^{25}$ = +31.2° (c = 2.2 g L^{-1}, $CHCl_3$).

(3aR,4′S,5S,6aR)-5-(Hydroxymethyl)-2,2-dimethyldihydro-3aH-spiro[furo[2,3-d][1,3] dioxole-6,4′-oxazolidin]-2′-one (VI)

To a solution of *V* (8.31 g, 23.0 mmol) in dry THF (210 mL), activated 4Å powdered molecular sieves (4.3 g) were added. The suspension was treated with a 1 M solution of Bu_4NF (23 mL, 23 mmol) in THF at 0 ℃. The resulting reaction mixture was stirred at 0 ℃ for 10 min and then at room temperature for 50 min. The solid material was removed by filtration and the solvent was distilled under reduced pressure. The residue was partitioned between EtOAc (105 mL) and water (77 mL); the water layer was extracted twice with EtOAc (2 × 105 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated, and the residue was chromatographed on silica gel (hexane–ethyl acetate, φ_r = 1 : 5) to afford 5.61 g (99 %) of crystalline compound *VI*. $[\alpha]_D^{25}$ = +58.1° (c = 2.5 g L^{-1}, CH_3OH).

(3aR,4′S,5S,6aR)-2,2-Dimethyl-2′-oxodihydro-3aH-spiro[furo[2,3-d][1,3]dioxole-6,4′-oxazolidine]-5-carbaldehyde (VII)

To an alcohol solution of *VI* (1.44 g, 5.87 mmol) in CH_3CN (53 mL), *o*-iodoxybenzoic acid (2.47 g, 8.82 mmol) was added and the resulting mixture was stirred for 50 min at reflux. After the starting material was completely consumed (monitored by TLC), the reaction mixture was cooled to room temperature. Insoluble materials were removed by filtration, the solvent was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel (hexane–ethyl acetate, φ_r = 2 : 1) to give 1.35 g (95 %) of aldehyde *VII* as a colorless oil that was used immediately in the next step.

(E)-Ethyl-3-{(3aR,4′S,5R,6aR)-2,2-dimethyl-2′-oxodihydro-3aH- spiro[furo[2,3-d][1,3] dioxole-6,4′-oxazolidine]-5-yl}acrylate (VIIIa) and (Z)-ethyl-3-{(3aR,4′S,5R,6aR)-2,2-dimethyl-2′-oxodihydro-3aH-spiro[furo[2,3-d] [1,3]dioxole-6,4′-oxazolidine]-5-yl}acrylate (VIIIb)

To a solution of aldehyde *VII* (1.35 g, 5.55 mmol) in dry CH_3CN (33 mL), stabilized ylides $Ph_3P{=}CHCO_2Et$, (2.32 g, 6.66 mmol) and LiBr (2.88 g, 33.3 mmol) were added. The reaction mixture was stirred at room temperature for 30 min. After filtration of insoluble materials, the solvent was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel (hexane–ethyl acetate, φ_r = 0.5). The amount of 1.11 g (64 %) of α,β-

unsaturated esters *VIII* as an amorphous solid mixture of *E*/*Z* isomers *VIIIa* and *VIIIb* (molar ratio of *E* : *Z* of 10 : 3, estimated from ^{1}H NMR spectrum) was obtained.

A small amount of this mixture of unsaturated esters was separated by column chromatography on silica gel (hexane–ethyl acetate, $\varphi_r = 0.5$) to give only (*E*)-isomer *VIIIa* in pure form. $[\alpha]_D^{25} = +82.9°$ (c = 3.0 g L^{-1}, $CHCl_3$).

Ethyl 3-{(3aR,4′S,5R,6aR)-2,2-dimethyl-2′-oxodihydro-3aH-spiro[furo[2,3-d][1,3]-dioxole-6,4′-oxazolidine]-5-yl}propanoate (IX)

To a solution of α,β-unsaturated ester *VIII* (1.11 g, 3.54 mmol) in absolute EtOH (28 mL), 10 % palladium on carbon (123 mg) was added. The resulting mixture was stirred under hydrogen atmosphere for 16 h at room temperature, and filtered through a pad of Celite. The resulting solution was concentrated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (hexane–ethyl acetate, $\varphi_r = 0.5$) to afford 0.95 g (85 %) of crystalline ester *IX*. $[\alpha]_D^{25} = +173.3°$ (c = 2.7 g L^{-1}, $CHCl_3$).

(3aR,4′S,5R,6aR)-5-(3-Hydroxypropyl)-2,2-dimethyldihydro-3aH-spiro[furo[2,3-d][1,3]dioxole-6,4′-oxazolidin]-2′-one (X)

To a solution of *IX* (0.94 g, 2.98 mmol) in dry CH_2Cl_2 (13 mL), pre-cooled to –15 °C, $BF_3 \cdot OEt_2$ (0.46 mL, 3.60 mmol) was added and the reaction mixture was stirred at the same temperature for 5 min. Then, diisobutylaluminum hydride (8.9 mL of 1.2 M toluene solution) was added dropwise. The solution was then stirred at −5 °C for 2 h before being quenched with MeOH (2 mL). The mixture was warmed to room temperature and poured into a 30 % aqueous K/Na-tartrate solution (45 mL). After being stirred for 30 min, the mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated under reduced pressure, and the residue was subjected to flash column chromatography on silica gel (hexane–ethyl acetate, $\varphi_r = 1 : 5$) to afford 0.60 g (74 %) of crystalline alcohol *X*. $[\alpha]_D^{25} = +115.1°$ (c = 4.9 g L^{-1}, CH_3OH).

(3aR,4′S,5R,6aR)-3′-Benzyl-5-[3-(benzyloxy)propyl]-2,2-dimethyldihydro-3aH-spiro[furo[2,3-d][1,3]dioxole-6,4′-oxazolidin]-2′-one (XI)

To a solution of *X* (0.594 g, 2.174 mmol) in dry DMF (5.5 mL), pre-cooled to 0 °C, NaH (0.26 g, 10.83 mmol, 60 % dispersion in mineral oil, freed of oil with anhydrous THF) was added. The reaction mixture was stirred at 0 °C for 15 min, and then benzyl bromide (0.78 mL, 6.52 mmol) and tetrabutylammonium iodide (0.16 g, 0.43 mmol) were added at the same temperature. The resulting mixture was stirred at 0 °C for 10 min. The mixture was allowed to warm to room temperature and it was stirred for another 3 h. Then, the mixture was partitioned between ice water (5.5 mL) and diethyl ether (20 mL). The aqueous layer was extracted with an additional portion of Et_2O (20 mL), the combined organic extracts were dried over Na_2SO_4, and the solvent was removed. The residue was purified by flash chromatography on silica gel (hexane–ethyl acetate, $\varphi_r = 3 : 1$) to afford 0.94 g (95 %) of compound *XI* as a colorless oil. $[\alpha]_D^{25} = +170.5°$ (c = 2.6 g L^{-1}, $CHCl_3$).

(5S,6R,8R&S,9R)-1-Benzyl-6-[3-(benzyloxy)propyl]-8,9-dihydroxy-3,7-dioxa-1-azaspiro[4.4]nonan-2-one (XII)

Compound *XI* (0.937 g, 2.066 mmol) was treated with a mixture of TFA–H_2O ($\varphi_r = 9 : 1$, 17.3 mL) at room temperature for 5 h. The solvent was removed under reduced pressure, and the residue was passed through a short flash chromatography column of silica gel (hexane–ethyl acetate, $\varphi_r = 3 : 1$) to afford 0.554 g (65 %) of furanoses *XII* (amorphous solid) as an inseparable mixture of anomers which were then acetylated.

(5S,6R,8R,9R)-1-Benzyl-6-[3-(benzyloxy)propyl]-2-oxo-3,7-dioxa-1-azaspiro[4.4]nonane-8,9-diyl diacetate (XIIIa) and (5S,6R,8S,9R)-1-benzyl-6-[3-(benzyloxy)propyl]-2-oxo-3,7-dioxa-1-azaspiro[4.4]nonane-8,9-diyl diacetate (XIIIb)

To a solution of furanoses *XII* (46 mg, 0.11 mmol) in pyridine (0.8 mL), DMAP (2.7 mg, 0.02 mmol) and acetic anhydride (0.03 mL, 0.32 mmol) were added at room temperature. The resulting mixture was stirred overnight. Then, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane–ethyl acetate, $\varphi_r = 2 : 1$) to afford 46 mg (83 %) of an inseparable mixture of anomers. *XIII* was obtained as an amorphous solid. ^{1}H and ^{13}C NMR spectra of this mixture were analyzed and all signals were assigned to anomer *XIIIa* or anomer *XIIIb*, respectively.

(4S)-3-Benzyl-4-[(1′R)-4′-(benzyloxy)-1′-(formyloxy)butyl]-2-oxooxazolidine-4-carboxylic acid (XIV)

To a solution of furanoses *XII* (0.508 g, 1.23 mmol) in CH_3OH (15 mL), a solution of sodium metaperiodate (0.315 g, 1.47 mmol) in water (2.5 mL) was added. The resulting mixture was stirred at room

Table 1. Characterization data of the newly prepared compounds

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%				Yield	M.p.
			C	H	N	S	%	°C
III	$C_{18}H_{21}NO_7$	363.36	59.50	5.83	3.85	–	85	–
			59.44	5.86	3.80			
V	$C_{16}H_{29}NO_6Si$	359.49	53.46	8.13	3.90	–	91	–
			53.49	8.17	3.94			
VI	$C_{10}H_{15}NO_6$	245.23	48.98	6.17	5.71	–	99	227–228
			48.91	6.21	5.76			
VII	$C_{10}H_{13}NO_6$	243.21	49.38	5.39	5.76	–	95	–
			49.33	5.44	5.80			
VIIIa	$C_{14}H_{19}NO_7$	313.30	53.67	6.11	4.47	–		48–50
			53.62	6.16	4.52			
IX	$C_{14}H_{21}NO_7$	315.32	53.33	6.71	4.44	–	85	138–140
			53.28	6.65	4.40			
X	$C_{12}H_{19}NO_6$	273.28	52.74	7.01	5.13	–	74	149–151
			52.69	7.06	5.17			
XI	$C_{26}H_{31}NO_6$	453.53	68.86	6.89	3.09	–	95	–
			68.92	6.80	3.13			
XIIIa, *XIIIb*	$C_{27}H_{31}NO_8$	497.54	65.18	6.28	2.82	–	83	–
XV	$C_{24}H_{27}NO_7$	441.47	65.29	6.16	3.17	–	87	–
			65.25	6.19	3.12			
XVI	$C_{23}H_{27}NO_6$	413.46	66.81	6.58	3.39	–	94	76–77
			66.84	6.54	3.42			
XVII	$C_{25}H_{29}NO_7$	455.50	65.92	6.42	3.08	–	94.5	–
			65.88	6.38	3.12			
XVIII	$C_{18}H_{23}NO_7$	365.38	59.17	6.34	3.83	–	91	–
			59.22	6.37	3.79			

temperature for 2 h. The precipitate was filtered off and washed with CH_3OH. The resulting solution was dried over Na_2SO_4. The solvent was removed under reduced pressure to give crude aldehyde which was used immediately without further purification.

A solution of $NaClO_2$ (1.03 g, 11.35 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (1.28 g, 8.19 mmol) in water (7 mL) was added dropwise to the solution of the crude aldehyde (0.506 g, 1.23 mmol) in CH_3CN–*t*-butanol–2-methylbut-2-ene (28 mL, $\varphi_r = 4 : 4 : 1$) at 0 °C for over 10 min. The resulting mixture was stirred at 0 °C for further 3 h, and then at room temperature for 14 h. Ethyl acetate (20 mL) was added to the reaction mixture which was then washed with brine (20 mL). The aqueous layer was extracted with an additional portion of EtOAc (20 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated under reduced pressure, and the residue was subjected to flash chromatography through a very short column of silica gel (CH_2Cl_2–MeOH, $\varphi_r = 9 : 1$) to afford 0.353 g (67 %; in two steps) of carboxylic acid *XIV*. To avoid potential problems of instability, compound *XIV* was used immediately in the next step.

Methyl (4S)-3-benzyl-4-[(1′R)-4′-(benzyloxy)-1′-(formyloxy)butyl]-2-oxooxazolidine-4-carboxylate (XV)

To a stirred solution of carboxylic acid *XIV* (0.353 g, 0.826 mmol) in dry DMF (1.5 mL), K_2CO_3 (0.171 g, 1.24 mmol) and CH_3I (77 μL, 1.24 mmol) were added at room temperature. After 30 min, no starting compound was detected (TLC) in the reaction mixture which was then poured into ice water (1 mL) and extracted with Et_2O (2 × 16 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated in vacuo, and the residue was chromatographed on silica gel (hexane–ethyl acetate, $\varphi_r = 2 : 1$) to afford 0.32 g (87 %) of ester *XV* as a colorless oil. $[\alpha]_D^{25} = +28.4°$ ($c = 1.5$ g L^{-1}, $CHCl_3$).

Methyl (4S)-3-benzyl-4-[(1′R)-4′-(benzyloxy)-1′-hydroxybutyl]-2-oxooxazolidine-4-carboxylate (XVI)

To a solution of *XV* (0.317 g, 0.718 mmol) in CH_3OH (6 mL), pre-cooled to 0 °C, K_2CO_3 (19.4 mg, 0.14 mmol) was added. After 20 min, as no starting compound was detected (monitored by TLC), the reaction mixture was neutralized with Amberlite IR-120

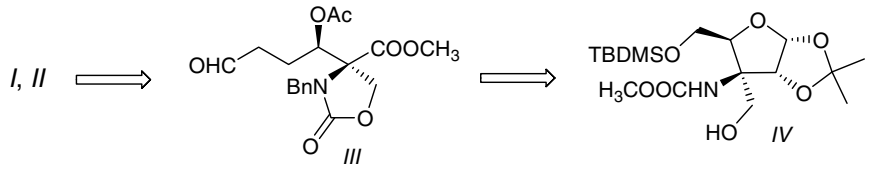

Fig. 2. Retrosynthetic route to the polar fragment of mycestericins E and G.

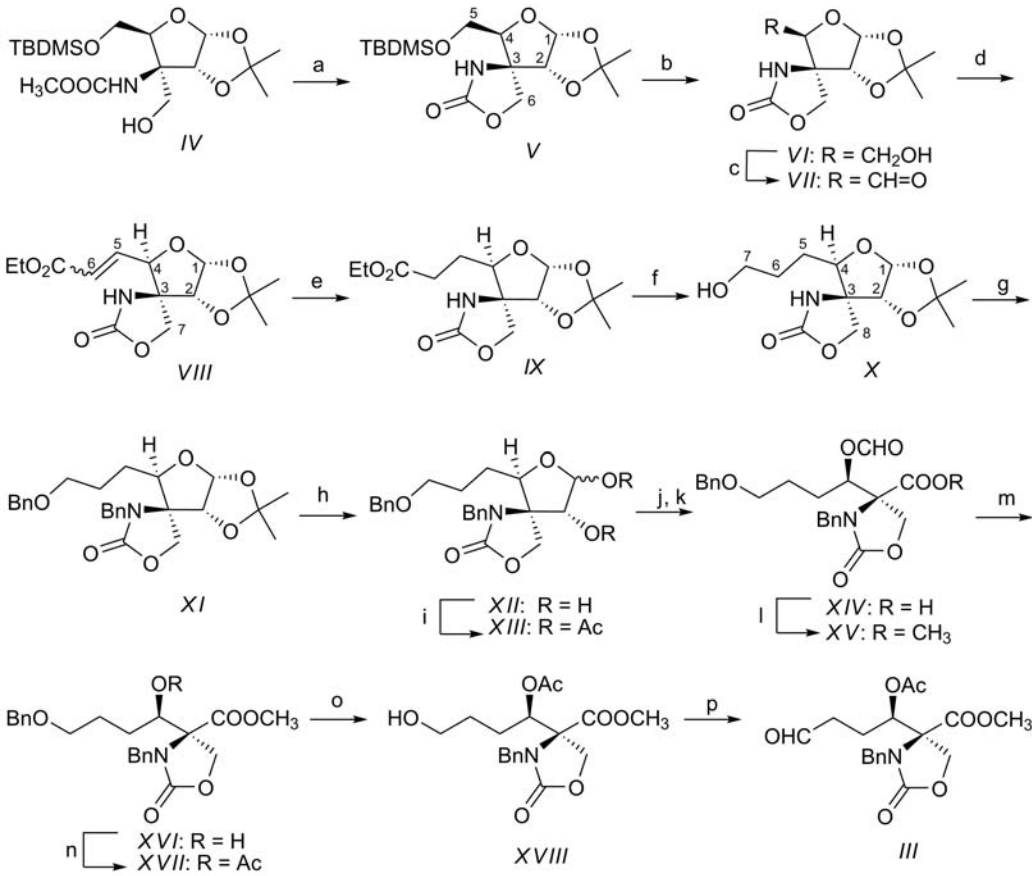

Fig. 3. Synthesis of aldehyde *III*. Reagents and conditions: (a) THF, NaH, 0 °C to r.t., 91 %; (b) TBAF, THF, 0 °C to r.t., 99 %; (c) IBX, CH_3CN, reflux, 95 %; (d) $Ph_3P{=}CHCO_2Et$, LiBr, CH_3CN, r.t., 64 %; (e) H_2, 10 % Pd/C, EtOH, r.t., 85 %; (f) DIBAL-H, CH_2Cl_2, $BF_3 \cdot OEt_2$, –15–(–5) °C, 74 %; (g) NaH, BnBr, TBAI, DMF, 0 °C to r.t., 95 %; (h) TFA–H_2O (9 : 1), r.t., 65 %; (i) Ac_2O, pyridine, DMAP, r.t., 83 %; (j) $NaIO_4$, MeOH–H_2O, r.t.; (k) $NaClO_2$, CH_3CN–*t*-BuOH–2-methylbut-2-ene, 0 °C to r.t.; 67 %; (l) CH_3I, K_2CO_3, DMF, r.t., 87 %; (m) K_2CO_3, CH_3OH, 0 °C, 94 %; (n) Ac_2O, pyridine, DMAP, r.t., 94 %; (o) H_2, 10 % Pd/C, CH_3OH, r.t., 91 %; (p) IBX, CH_3CN, reflux, 85 %. TBDMS = *t*-butyldimethylsilyl, Et = ethyl, Bn = benzyl, Bu = butyl.

(H^+). Insoluble materials were removed by filtration, washed with CH_3OH, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (hexane–ethyl acetate, $\varphi_r = 1 : 1$) to afford 0.28 g (94 %) of crystalline alcohol *XVI*. $[\alpha]_D^{25} = -47.5°$ ($c = 2.4$ g L^{-1}, $CHCl_3$).

Methyl (4S)-4-[(1′R)-1′-acetoxy-4′-(benzyloxy)butyl]-3-benzyl-2-oxooxazolidine-4-carboxylate (XVII)

To a solution of *XVI* (0.279 g, 0.675 mmol) in pyridine (5 mL), acetic anhydride (95.5 μL, 1.01 mmol), and DMAP (8.19 mg, 0.067 mmol) were added at room temperature. After 30 min, the solvent was removed and the residue was purified by flash chromatography on silica gel (hexane–ethyl acetate, $\varphi_r = 3 : 1$) to afford 0.29 g (94 %) of compound *XVII* as a colorless oil. $[\alpha]_D^{25} = -69.2°$ ($c = 2.4$ g L^{-1}, $CHCl_3$).

Methyl (4S)-4-[(1′R)-1′-acetoxy-4′-hydroxybutyl]-3-benzyl-2-oxooxazolidine-4-carboxylate (XVIII)

To a solution of *XVII* (0.304 g, 0.668 mmol) in absolute EtOH (7.5 mL), 10 % palladium on carbon

Table 2. Spectral data of the newly prepared compounds

Compound	Spectral data
III	^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.58–1.68 (m, 1H, $H_{2'}$), 1.79 (dtd, 1H, $J_{2',1'}$ = 2.4 Hz, $J_{3',2'}$ = 7.3 Hz, $J_{3',2'}$ = 7.4 Hz, $J_{2',2'}$ = 9.6 Hz, $H_{2'}$), 2.09 (s, 3H, CH_3), 2.48–2.64 (m, 2H, 2 × $H_{3'}$), 3.26 (s, 3H, OCH_3), 4.27 (d, 1H, $J_{H,H}$ = 16.1 Hz, NCH_2), 4.45 (d, 1H, $J_{5,5}$ = 9.2 Hz, H_5), 4.70 (d, 1H, $J_{H,H}$ = 16.1 Hz, NCH_2), 4.72 (d, 1H, $J_{5,5}$ = 9.1 Hz, H_5), 5.59 (dd, 1H, $J_{2',1'}$ = 2.4 Hz, $J_{2',1'}$ = 10.4 Hz, $H_{1'}$), 7.22–7.25 (m, 3H, Ph), 7.28–7.32 (m, 2H, Ph), 9.72 (t, 1H, $J_{3',CHO}$ = 0.7 Hz, CHO) ^{13}C NMR (100 MHz, $CDCl_3$), δ: 20.7 (CH_3), 21.6 (CH_2), 39.9 (CH_2), 45.8 (NCH_2), 52.8 (OCH_3), 65.3 (CH_2), 68.4 (C), 69.8 (CH), 127.6 (3 × CH), 128.4 (2 × CH), 136.3 (C), 157.8 (CO), 168.1 ($COOCH_3$), 170.1 ($COCH_3$), 199.9 (CHO)
V	^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.08 (s, 6H, 2 × CH_3), 0.90 (s, 9H, 3 × CH_3), 1.33 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.80 (dd, 1H, $J_{5,4}$ = 8.5 Hz, $J_{5,5}$ = 10.3 Hz, H_5), 3.94 (dd, 1H, $J_{5,4}$ = 4.4 Hz, $J_{5,5}$ = 10.3 Hz, H_5), 4.03 (dd, 1H, $J_{5,4}$ = 4.4 Hz, $J_{5,4}$ = 8.5 Hz, H_4), 4.45 (d, 1H, $J_{6,6}$ = 9.3 Hz, H_6), 4.48 (d, 1H, $J_{2,1}$ = 3.7 Hz, H_2), 4.65 (d, 1H, $J_{6,6}$ = 9.3 Hz, H_6), 5.85 (d, 1H, $J_{2,1}$ = 3.7 Hz, H_1), 6.37 (br s, 1H, NH) ^{13}C NMR (100 MHz, $CDCl_3$), δ: –5.8 (CH_3), –5.7 (CH_3), 18.1 (C), 25.8 (3 × CH_3), 26.2 (CH_3), 26.6 (CH_3), 60.4 (CH_2), 66.7 (CH_2), 67.4 (C), 78.9 (CH), 85.6 (CH), 103.7 (CH), 112.8 (OCO), 159.5 (CO)
VI	^{1}H NMR (400 MHz, CD_3OD), δ: 1.32 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 3.70–3.77 (m, 2H, 2 × H_5), 4.01 (t, 1H, $J_{5,4}$ = 6.0 Hz, $J_{5,4}$ = 6.0 Hz, H_4), 4.34 (d, 1H, $J_{6,6}$ = 9.5 Hz, H_6), 4.51 (d, 1H, $J_{2,1}$ = 3.7 Hz, H_2), 4.61 (d, 1H, $J_{6,6}$ = 9.5 Hz, H_6), 5.84 (d, 1H, $J_{2,1}$ = 3.7 Hz, H_1) ^{13}C NMR (100 MHz, CD_3OD), δ: 26.5 (CH_3), 26.9 (CH_3), 60.7 (CH_2), 67.4 (CH_2), 68.6 (C), 81.6 (CH), 87.0 (CH), 105.5 (CH), 113.9 (OCO), 161.3 (CO)
VII	^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.36 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 4.29 (br s, 1H, H_4), 4.52 (d, 1H, $J_{5,5}$ = 9.8 Hz, H_5), 4.59 (d, 1H, $J_{2,1}$ = 3.4 Hz, H_2), 4.72 (d, 1H, $J_{5,5}$ = 9.8 Hz, H_5), 6.11 (d, 1H, $J_{2,1}$ = 3.4 Hz, H_1), 6.62 (br s, 1H, NH), 9.75 (br s, 1H, CHO)
VIIIa	^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.31 (t, 3H, J = 7.1 Hz, CH_3), 1.35 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 4.18–4.23 (m, 2H, CH_2), 4.24 (d, 1H, $J_{7,7}$ = 9.7 Hz, H_7), 4.55 (dd, 1H, $J_{6,4}$ = 1.6 Hz, $J_{5,4}$ = 4.8 Hz, H_4), 4.59 (d, 1H, $J_{2,1}$ = 3.7 Hz, H_2), 4.70 (d, 1H, $J_{7,7}$ = 9.8 Hz, H_7), 5.96 (d, 1H, $J_{2,1}$ = 3.7 Hz, H_1), 6.20 (dd, 1H, $J_{6,4}$ = 1.7 Hz, $J_{6,5}$ = 15.7 Hz, H_6), 6.71 (br s, 1H, NH), 6.92 (dd, 1H, $J_{5,4}$ = 4.8 Hz, $J_{6,5}$ = 15.7 Hz, H_5) ^{13}C NMR (100 MHz, $CDCl_3$), δ: 14.0 (CH_3), 26.2 (CH_3), 26.5 (CH_3), 60.9 (CH_2), 65.1 (CH_2), 68.6 (C), 79.0 (CH), 84.8 (CH), 103.8 (CH), 113.1 (OCO), 125.3 (CH), 138.7 (CH), 158.2 (CO), 165.8 (COOEt)
IX	^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.26 (t, 3H, J = 7.1 Hz, CH_3), 1.32 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.78–1.95 (m, 2H, 2 × H_5), 2.46–2.62 (m, 2H, 2 × H_6), 3.94 (dd, 1H, $J_{5,4}$ = 2.7 Hz, $J_{5,4}$ = 9.8 Hz, H_4), 4.09–4.15 (m, 2H, CH_2), 4.15 (d, 1H, $J_{7,7}$ = 9.9 Hz, H_7), 4.50 (d, 1H, $J_{2,1}$ = 3.8 Hz, H_2), 4.66 (d, 1H, $J_{7,7}$ = 9.8 Hz, H_7), 5.87 (d, 1H, $J_{2,1}$ = 3.8 Hz, H_1), 6.71 (br s, 1H, NH) ^{13}C NMR (100 MHz, $CDCl_3$), δ: 14.2 (CH_3), 23.0 (CH_2), 26.2 (CH_3), 26.4 (CH_3), 30.6 (CH_2), 60.6 (CH_2), 65.6 (CH_2), 67.8 (C), 79.0 (CH), 85.1 (CH), 103.6 (CH), 112.6 (OCO), 159.0 (C=O), 172.9 (COOEt)
X	^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.32 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.63–1.80 (m, 4H, 2 × H_5, 2 × H_6), 3.49 (m, 1H, OH), 3.62–3.70 (m, 2H, 2 × H_7), 3.90 (dd, 1H, $J_{5,4}$ = 2.7 Hz, $J_{5,4}$ = 8.5 Hz, H_4), 4.10 (d, 1H, $J_{8,8}$ = 9.8 Hz, H_8), 4.51 (d, 1H, $J_{2,1}$ = 3.8 Hz, H_2), 4.63 (d, 1H, $J_{8,8}$ = 9.8 Hz, H_8), 5.88 (d, 1H, $J_{2,1}$ = 3.8 Hz, H_1), 7.39 (br s, 1H, NH) ^{13}C NMR (100 MHz, $CDCl_3$), δ: 24.2 (CH_2), 26.2 (CH_3), 26.4 (CH_3), 29.3 (CH_2), 61.9 (CH_2), 65.8 (CH_2), 67.9 (C), 80.6 (CH), 85.1 (CH), 103.6 (CH), 112.4 (OCO), 159.3 (CO)
XI	^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.09 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.61–1.81 (m, 3H, 2 × H_5, H_6), 1.86–1.96 (m, 1H, H_6), 3.48 (ddd, 1H, $J_{7,6}$ = 5.5 Hz, $J_{7,6}$ = 6.6 Hz, $J_{7,7}$ = 9.4 Hz, H_7), 3.54 (ddd, 1H, $J_{7,6}$ = 5.3 Hz, $J_{7,6}$ = 6.4 Hz, $J_{7,7}$ = 9.4 Hz, H_7), 3.93 (dd, 1H, $J_{5,4}$ = 3.3 Hz, $J_{5,4}$ = 9.5 Hz, H_4), 3.96 (d, 1H, $J_{8,8}$ = 10.0 Hz, H_8), 4.13 (d, 1H, $J_{2,1}$ = 3.9 Hz, H_2), 4.16 (d, 1H, $J_{H,H}$ = 15.8 Hz, NCH_2), 4.48 (d, 1H, $J_{H,H}$ = 12.0 Hz, $PhCH_2O$), 4.52 (d, 1H, $J_{H,H}$ = 12.0 Hz, $PhCH_2O$), 4.52 (d, 1H, $J_{8,8}$ = 9.9 Hz, H_8), 4.93 (d, 1H, $J_{H,H}$ = 15.8 Hz, NCH_2), 5.62 (d, 1H, $J_{2,1}$ = 3.9 Hz, H_1), 7.27–7.37 (m, 10H, 2 × Ph) ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.0 (CH_2), 25.8 (CH_3), 26.2 (CH_3), 26.7 (CH_2), 46.7 (NCH_2), 64.3 (CH_2), 69.5 (CH_2), 70.7 (C), 72.9 ($PhCH_2O$), 82.5 (CH), 83.2 (CH), 103.8 (CH), 111.9 (OCO), 127.6 (3 × CH), 127.7 (2 × CH), 128.0 (CH), 128.4 (2 × CH), 128.7 (2 × CH), 137.4 (C), 138.3 (C), 158.6 (CO)
XIIIa	^{1}H NMR (600 MHz, $CDCl_3$), δ: 1.62–1.91 (m, 4H, 2 × H_5, 2 × H_6), 1.95 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 3.42–3.53 (m, 2H, 2 × H_7), 4.03 (dd, 1H, $J_{5,4}$ = 2.6 Hz, $J_{5,4}$ = 9.5 Hz, H_4), 4.09 (d, 1H, $J_{8,8}$ = 9.7 Hz, H_8), 4.23 (d, 1H, $J_{H,H}$ = 16.0 Hz, NCH_2), 4.46–4.51 (m, 3H, $PhCH_2O$, H_8), 4.94 (d, 1H, $J_{H,H}$ = 16.0 Hz, NCH_2), 5.04 (d, 1H, $J_{2,1}$ = 4.9 Hz, H_2), 6.29 (d, 1H, $J_{2,1}$ = 4.9 Hz, H_1), 7.26–7.38 (m, 10H, 2 × Ph) ^{13}C NMR (150 MHz, $CDCl_3$), δ: 20.0 (CH_3), 20.8 (CH_3), 26.0 (CH_2), 26.5 (CH_2), 46.9 (NCH_2), 66.8 (CH_2), 68.9 (C), 69.4 (CH_2), 73.0 ($PhCH_2O$), 73.7 (CH), 85.0 (CH), 92.7 (CH), 127.4 (2 × CH), 127.7 (2 × CH), 127.8 (CH), 128.4 (3 × CH), 128.9 (2 × CH), 136.7 (C), 138.3 (C), 158.1 (CO), 168.6 (CO), 168.8 (CO)
XIIIb	^{1}H NMR (600 MHz, $CDCl_3$), δ: 1.62–1.91 (m, 4H, 2 × H_5, 2 × H_6), 2.00 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 3.42–3.53 (m, 2H, 2 × H_7), 3.91 (dd, 1H, $J_{5,4}$ = 3.2 Hz, $J_{5,4}$ = 9.3 Hz, H_4), 4.02 (d, 1H, $J_{8,8}$ = 9.7 Hz, H_8), 4.37 (d, 1H, $J_{8,8}$ = 9.7 Hz, H_8), 4.46–4.51 (m, 2H, $PhCH_2O$), 4.55 (d, 1H, $J_{H,H}$ = 16.3 Hz, NCH_2), 4.85 (d, 1H, $J_{H,H}$ = 16.3 Hz, NCH_2) 5.28 (d, 1H, $J_{2,1}$ = 2.1 Hz, H_2), 5.90 (d, 1H, $J_{2,1}$ = 2.1 Hz, H_1), 7.26–7.38 (m, 10H, 2 × Ph) ^{13}C NMR (150 MHz, $CDCl_3$), δ: 20.4 (CH_3), 20.9 (CH_3), 25.8 (CH_2), 26.4 (CH_2), 46.6 (NCH_2), 66.0 (CH_2), 68.7 (C), 69.3 (CH_2), 73.0 ($PhCH_2O$), 79.3 (CH), 85.8 (CH), 99.3 (CH), 127.0 (2 × CH), 127.6 (CH), 127.7 (3 × CH), 128.1 (2 × CH), 128.6 (2 × CH), 136.7 (C), 137.0 (C), 158.1 (CO), 168.9 (2 × CO)

Table 2. (continued)

Compound	Spectral data
XV	^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.45–1.69 (m, 4H, 2 × $H_{2'}$, 2 × $H_{3'}$), 3.12 (s, 3H, OCH_3), 3.38–3.50 (m, 2H, 2 × $H_{4'}$), 4.29 (d, 1H, $J_{H,H}$ = 16.2 Hz, NCH_2), 4.40 (d, 1H, $J_{5,5}$ = 9.1 Hz, H_5), 4.46 (m, 2H, $PhCH_2O$), 4.73 (d, 1H, $J_{5,5}$ = 9.1 Hz, H_5), 4.75 (d, 1H, $J_{H,H}$ = 16.0 Hz, NCH_2), 5.77 (dd, 1H, $J_{2',1'}$ = 2.5 Hz, $J_{2',1'}$ = 9.7 Hz, $H_{1'}$), 7.21–7.36 (m, 10H, 2 × Ph), 8.08 (s, 1H, CHO) ^{13}C NMR (100 MHz, $CDCl_3$), δ: 26.0 (2 × CH_2), 45.7 (NCH_2), 52.8 (OCH_3), 65.2 (CH_2), 68.3 (C), 68.8 (CH_2), 69.6 (CH), 72.9 ($PhCH_2O$), 127.5 (3 × CH), 127.6 (2 × CH), 127.7 (CH), 128.4 (4 × CH), 136.2 (C), 138.1 (C), 157.8 (CO), 159.7 (CHO), 168.0 (COOMe)
XVI	^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.13–1.25 (m, 1H, $H_{2'}$), 1.41–1.48 (m, 1H, $H_{2'}$), 1.60–1.70 (m, 1H, $H_{3'}$), 1.72–1.80 (m, 1H, $H_{3'}$), 2.88 (d, 1H, $J_{1',OH}$ = 3.4 Hz, OH), 3.37–3.47 (m, 2H, 2 × $H_{4'}$), 3.51 (s, 3H, OCH_3), 4.02–4.05 (m, 1H, $H_{1'}$), 4.27 (d, 1H, $J_{5,5}$ = 8.8 Hz, H_5), 4.48 (m, 2H, $PhCH_2O$), 4.56 (d, 1H, $J_{5,5}$ = 8.8 Hz, H_5), 4.56 (d, 1H, $J_{H,H}$ = 15.6 Hz, NCH_2), 4.66 (d, 1H, $J_{H,H}$ = 15.6 Hz, NCH_2), 7.25–7.37 (m, 10H, 2 × Ph) ^{13}C NMR (100 MHz, $CDCl_3$), δ: 26.3 (CH_2), 27.8 (CH_2), 46.1 (NCH_2), 52.6 (OCH_3), 65.3 (CH_2), 69.7 (CH), 69.8 (CH_2), 70.4 (C), 73.1 ($PhCH_2O$), 127.7 (2 × CH), 127.8 (CH), 128.1 (2 × CH), 128.4 (2 × CH), 128.7 (3 × CH), 137.3 (C), 137.8 (C), 158.5 (CO), 170.2 (COOMe)
XVII	^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.42–1.53 (m, 2H, 2 × $H_{2'}$), 1.58–1.68 (m, 2H, 2 × $H_{3'}$), 2.08 (s, 3H, CH_3), 3.16 (s, 3H, OCH_3), 3.40–3.49 (m, 2H, 2 × $H_{4'}$), 4.28 (d, 1H, $J_{H,H}$ = 16.3 Hz, NCH_2), 4.41 (d, 1H, $J_{5,5}$ = 9.1 Hz, H_5), 4.46 (m, 2H, $PhCH_2O$), 4.72–4.76 (m, H_5, NCH_2), 5.66 (dd, 1H, $J_{2',1'}$ = 4.3 Hz, $J_{2',1'}$ = 8.6 Hz, $H_{1'}$), 7.20–7.36 (m, 10H, 2 × Ph) ^{13}C NMR (100 MHz, $CDCl_3$), δ: 20.7 (CH_3), 25.9 (CH_2), 26.0 (CH_2), 45.6 (NCH_2), 52.6 (OCH_3), 65.2 (CH_2), 68.4 (C), 69.0 (CH_2), 69.9 (CH), 72.9 ($PhCH_2O$), 127.3 (2 × CH), 127.4 (CH), 127.6 (3 × CH), 128.4 (4 × CH), 136.5 (C), 138.2 (C), 157.7 (CO), 168.0 ($COOCH_3$), 170.0 ($COCH_3$)
XVIII	^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.45–1.53 (m, 2H, 2 × $H_{2'}$), 1.55–1.64 (m, 2H, 2 × $H_{3'}$), 2.10 (s, 3H, CH_3), 3.21 (s, 3H, OCH_3), 3.59–3.68 (m, 2H, 2 × $H_{4'}$), 4.28 (d, 1H, $J_{H,H}$ = 16.2 Hz, NCH_2), 4.42 (d, 1H, $J_{5,5}$ = 9.1 Hz, H_5), 4.73 (d, 1H, $J_{5,5}$ = 9.1 Hz, H_5), 4.74 (d, 1H, $J_{H,H}$ = 16.2 Hz, NCH_2), 5.67 (dd, 1H, $J_{2',1'}$ = 3.3 Hz, $J_{2',1'}$ = 9.1 Hz, $H_{1'}$), 7.21–7.32 (m, 5H, Ph), not seen (1H, OH) ^{13}C NMR (100 MHz, $CDCl_3$), δ: 20.8 (CH_3), 25.6 (CH_2), 28.5 (CH_2), 45.6 (NCH_2), 52.7 (OCH_3), 61.6 (C), 65.3 (CH_2), 68.4 (CH_2), 69.8 (CH), 127.5 (3 × CH), 128.4 (2 × CH), 136.4 (C), 157.8 (CO), 168.2 ($COOCH_3$), 170.1 ($COCH_3$)

(23 mg) was added and the resulting mixture was stirred under hydrogen atmosphere at room temperature for 17 h before being filtered through a pad of Celite. The resulting solution was concentrated under reduced pressure and the residue was subjected to flash column chromatography on silica gel (hexane–ethyl acetate, φ_r = 1 : 2) to give 0.222 g (91 %) of compound *XVIII* as a colorless oil. $[\alpha]_D^{25} = -30.9°$ (c = 2.5 g L^{-1}, $CHCl_3$).

Methyl (4S)-4-[(1′R)-1′-acetoxy-4′-oxobutyl]-3-benzyl-2-oxooxazolidine-4-carboxylate (III)

To a solution of alcohol *XVIII* (0.222 g, 0.608 mmol) in CH_3CN (3 mL), *o*-iodoxybenzoic acid (0.255 g, 0.91 mmol) was added and the resulting mixture was stirred for 30 min at reflux. After the starting material was completely consumed (TLC), the reaction was stopped and allowed to cool to the room temperature. Insoluble materials were removed by filtration, the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane–ethyl acetate, φ_r = 1 : 1) to afford 0.188 g (85 %) of aldehyde *III* as a colorless oil. $[\alpha]_D^{25} = +17.6°$ (c = 2.9 g L^{-1}, $CHCl_3$).

Results and discussion

Retrosynthetic analysis (Fig. 2) suggested that utilizing the functional group interconversions in the highly functionalized 3-*C*-hydroxymethyl-α-D-xylofuranose *IV* (Martinková et al., 2006, 2007) as the versatile building block developed and prepared on a multi-gram scale in our laboratory, with (*S*)-configuration on the tetrasubstituted carbon stereocentre, provides aldehyde *III* as the hydrophilic head group of both mycestericins *I* and *II*.

In order to develop a synthetic route to the desired polar fragment *III*, the conversion of *IV* into cyclic carbamate *V* was achieved using sodium hydride in anhydrous THF (91 %, Fig. 3). Exposure of *V* to tetrabutylammonium fluoride (TBAF) in THF gave the corresponding alcohol *VI* in a 99 % isolated yield (Fig. 3). Its oxidation with *o*-iodoxybenzoic acid (IBX) (Satam et al., 2010) in CH_3CN afforded aldehyde *VII* (95 %) which was, after flash chromatography and rapid ^{1}H NMR analysis, immediately used in the next reaction. Homologation of the resulting furanose derivative *VII* via the Wittig reaction ($Ph_3P{=}CHCO_2Et$, CH_3CN, LiBr) afforded the corresponding α,β-unsaturated esters *VIII* in a 64 % yield (Fig. 3) as a hardly separable mixture of isomers ($E : Z$ = 10 : 3 molar ratio, determined by ^{1}H NMR spectroscopy). A small amount of the mixture of unsaturated esters *VIII* was resolved using silica gel column chromatography to give only (*E*)-isomer *VIIIa* in pure form; its structure including geometry of the double bond was determined by ^{1}H and ^{13}C NMR spectroscopy.

Catalytic hydrogenation of the mixture of isolated esters *VIII* on Pd–C in EtOH resulted in the formation of saturated derivative *IX* in an 85 % yield (Fig. 3), its reduction with diisobutylaluminum hydride (DIBAL-H) in CH_2Cl_2 in the presence of $BF_3 \cdot OEt_2$ provided alcohol *X* (74 %, Fig. 3). Exposure of *X* to benzyl bromide in dry DMF using sodium hydride and catalytic amounts of tetrabutylammonium iodide (TBAI) produced completely protected derivative *XI* in a 95 % yield (Fig. 3). Acid hydrolysis of *XI* removed the acetonide protecting group to give the corresponding lactols *XIIa* and *XIIb* (65 %) as an inseparable anomers mixture, which were characterized as acetates *XIIIa* and *XIIIb* (Ac_2O, pyridine, DMAP, 83 %; $\alpha : \beta \approx 4 : 1$, molar ratio, estimated from ^{1}H NMR spectroscopy). Oxidative fragmentation of lactols *XII* with sodium metaperiodate ($NaIO_4$) in CH_3OH/H_2O, followed by $NaClO_2$ treatment and subsequent immediate esterification (K_2CO_3, CH_3I, DMF) (Muto & Mori, 2001) gave methyl ester *XV* (87 %, Fig. 3). After routine deprotection of *XV* under basic conditions (K_2CO_3, CH_3OH), the resulting alcohol *XVI* (94 %) was treated with acetic anhydride in dry pyridine in the presence of DMAP as the catalyst to provide protected compound *XVII* in a 94.5 % yield (Fig. 3). Finally, using 10 % Pd-C in CH_3OH, selective catalytic hydrogenolysis of the protecting group *O*-benzyl gave the corresponding alcohol *XVIII* in a 91 % yield (Fig. 3). The hydroxyl group of *XVIII* was subsequently oxidized using IBX (Satam et al., 2010) in CH_3CN to produce the desired polar fragment *III* (85 %) of mycestericins E (*I*) and G (*II*). All stereogenic centers of building block *III* have the expected absolute configuration. In addition, compound *III* contains an aldehyde group for coupling with the less polar C14 fragment via the Wittig or Julia olefination (Byun et al., 2006) thereby completing these new total syntheses of mycestericins E and G.

Conclusions

In summary, a new synthetic pathway to the polar part of two α-substituted α-amino acid natural products, *I* and *II*, has been found utilizing protected 3-*C*-hydroxymethyl-α-D-xylofuranose *IV* as an appropriate building block. Further studies towards the completion of the total synthesis of mycestericins E and G are in progress in our laboratory.

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