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Original scientific paper

A formal synthesis of (+)-muricatacin from D-xylose

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Abstract: A multistep route towards the aldehydo-lactone **19**, the final chiral precursor in a new stereospecific synthesis of (+)-muricatacin, has been developed starting from D-xylose. The key step of the synthesis involves an *E*-selective Wittig olefination of the lactol **6** with methoxycarbonylmethylidene triphenylphosphorane, followed by successive catalytic reduction and γ-lactonisation processes. Subsequent selective functional groups interconversions furnished the key six-carbon intermediate **19**, which can be converted into the (+)-muricatacin *via* a three-step sequence already described in the chemical literature.

Keywords: muricatacin, Wittig reaction, γ-lactone, stereospecific synthesis, D-xylose.

INTRODUCTION

Muricatacin (5-hydroxyheptadecan-4-olide) is an acetogenin related γ-lactone which has attracted considerable attention since its recent isolation from the seeds of *Anona muricata*[1] owing to its cytotoxic activity against certain human tumour cells. Remarkably, the natural muricatacin is a mixture of (+)-(4*S*,5*S*)-5-hydroxyheptadecan-4-olide (**1**, Scheme 1) and its (–)-(4*R*,5*R*)-entantiomer, with the latter being predominant (ee of *ca.* 25 %). Both (+)- and (–)-muricatacin have shown the same antitumour activity.[1,2] The biological activity of muricatacin and other related compounds has stimulated a significant interest in the synthesis of this type of 5-hydroxyalkylbutan-4-olides. Many syntheses of (+)- and (–)-muricatacin and congeners from various non-carbohydrate precursors have been reported,[3] as well as a number of carbohydrate based approaches to the (–)-muricatacin.[4] However, only two syntheses of (+)-muricatacin (**1**) from carbohydrate precursors have been described so far. A stereoselective approach from L-glyceraldehyde,[5] as well as a stereospecific synthesis of (+)-**1** based on chirality transfer from D-glucose.[6] Herein an alternative route to the final chiral precursor in a new stereospecific synthesis of (+)-muricatacin (**1**) from D-xylose is reported.[7]

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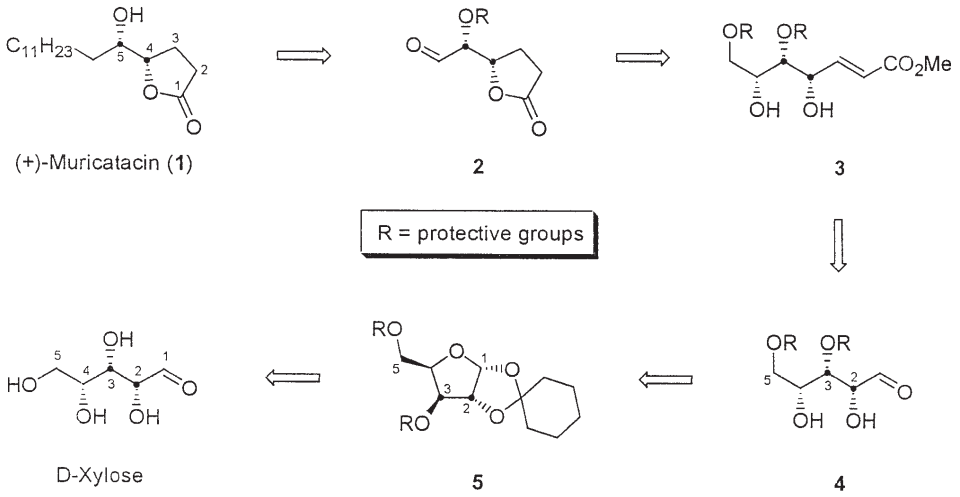


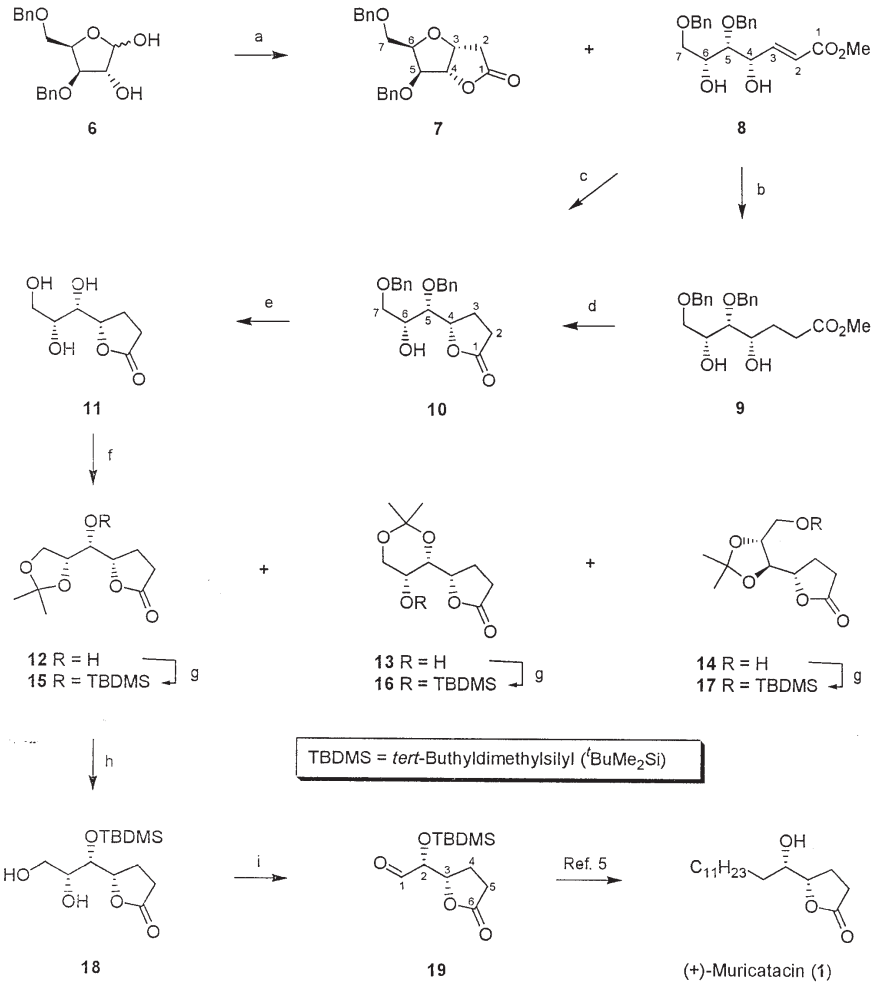
Scheme 1. Retrosynthetic analysis of (+)-muricatacin (**1**).

RESULTS AND DISCUSSION

The retrosynthetic analysis of (+)-muricatacin (**1**) outlined in Scheme 1 shows that this molecule might be available from an advanced intermediate of type **2** *via* a sequential Wittig elongation/catalytic hydrogenation manoeuvre followed by deprotection. Further disconnection of **2** shows that it can be derived from the enoate **3** by a number of selective transformations that involve successive catalytic hydrogenation, γ-lactonisation, 7-*O*-deprotection and an oxidative 6,7-glycol-cleavage process. Compound **3** can be further traced retrosynthetically to the 3,5-di-*O*-protected D-xylose derivative **4** *via* an *E*-selective Wittig transformation. Compounds of type **4** are readily available from D-xylofuranose derivatives of type **5** after hydrolytic removal of the 1,2-*O*-cyclohexylidene protective group. Accordingly, the 3,5-di-*O*-benzyl-D-xylose (**6**, Scheme 2), earlier prepared in our laboratory starting from D-xylose,[8] was chosen as a suitable starting compound in this work.

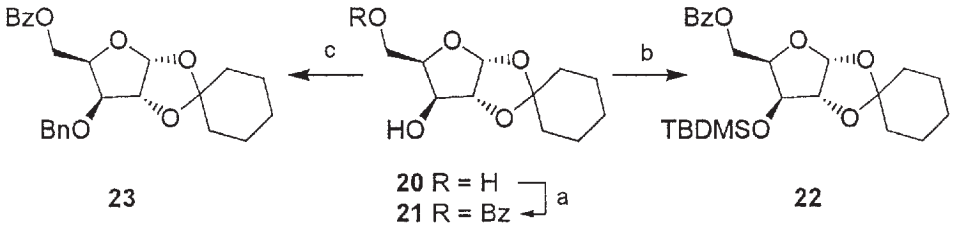
The crucial problem for elaboration of the 5-hydroxy-γ-lactone moiety in target (+)-**1** was the two-carbon homologation of **6** by the Wittig reaction with methoxycarbonylmethylidene triphenylphosphorane. The *E*-selectivity of the process is essential, because it is well known that some related *Z*-unsaturated esters may undergo a sequential lactonisation/Michael ring closure process.[9] Indeed, the preliminary experiments carried out with the lactol **6** confirmed that, depending on reaction conditions, the expected *E*-unsaturated derivative **8** was accompanied with variable amounts of the bicyclic lactone **7**, while the corresponding *Z*-stereoisomer could not be detected in the reaction mixtures. A reasonable chemoselectivity (**8**:**7** = 6:1) was achieved when the reaction was carried out in *N*,*N*-dimethylformamide at 65 ºC, whereupon the desired product **8** was isolated in 74 % yield.

Catalytic hydrogenation of **8** over PtO_2 in ethanol yielded the expected saturated ester **9**, which on exposure to 2:1 trifluoroacetic acid – water gave the γ-lactone **10** in an almost quantitative yield. Alternatively, catalytic reduction of **8** over the Adams catalyst in glacial



Scheme 2. (a) Ph_3P:$CHCO_2Me$, DMF, 60–70 ºC, 24 h; (b) H_2, PtO_2, EtOH, r.t. 24 h; (c) H_2, PtO_2, AcOH, r.t. 51 h; (d) 2:1 TFA–H_2O, r.t. 3 h; (e) H_2, 5 % Pd/C, r.t. 20 h; (f) $Me_2C(OMe)_2$, TsOH, DMF, r.t. 3.5 h; (g) $^tBuMe_2SiCl$, imidazole, DMF, r.t. 24 h; (h) 7:3 AcOH–H_2O, 50 ºC, 3 h; (i) 0.65 M aq. $NaIO_4$, silica gel, CH_2Cl_2, r.t. 0.5 h.

acetic acid gave directly the lactone **10** in 48 % yield. Obviously, the two-step sequence (**8**→**9**→**10**) represents a more convenient route toward the intermediate **10** since it provided a considerably higher overall yield (61 % from **8**). Catalytic debenzylation of **10** over 10 % Pd/C in ethanol furnished in 91 % yield the corresponding triol **11**, which was subsequently treated with 2,2-dimethoxypropane in the presence of catalytic amounts of *p*-toluenesulphonic acid to afford a mixture of isopropylidene derivatives **12**, **13** and **14** in an approximate ratio of 3:2:1, respectively. The desired product **12** was isolated in pure form by flash column chromatography (31.5 %) along with small amount of its regioisomer **13** (5 %). The structures of **12** and **13** were easily distinguished by comparison of



Scheme 3. (a) BzCl, Py, CH_2Cl_2, –22 ºC, 69 h, then r.t. 24 h; (b) $^tBuMe_2SiCl$, imidazole, DMF, r.t. 24 h; (c) BnBr, NaH, DMF, 0 ºC→r.t. then 2.5 h at r.t.

the ^{13}C-NMR data related to the resonance of both methyl groups from their isopropylidene functionalities (compound **12**: δ_{Me} 25.22 and 26.56 ppm; compound **13**: δ_{Me} 18.24 and 29.25 ppm). The small difference between the chemical shifts ($\Delta\delta_{Me}$ 1.34 ppm) along with the down-field position of the quaternary carbon signal in the spectrum of **12** (δ_C 109.36) clearly indicated that molecule **12** contains a 1,3-dioxolane five-membered ring.[10] Conversely, the large difference between the methyl carbon signals ($\Delta\delta_{Me}$ 11.01 ppm), as well as the high-field position of the quaternary carbon signal in the spectrum of **13** (δ_C 99.30) definitely confirmed the presence of a six-membered isopropylidene function in the molecule.[10] Since the regioisomer **14** could not be obtained free of **12** and **13**, it was therefore indirectly characterized after its conversion to the corresponding 7-*O*-silyl ether **17**. Namely, silylation of the mixture **12**, **13** and **14** with *tert*-butyldimethylsilyl chloride followed by chromatographic purification enabled the isolation of pure **17**, while the isomeric silylated products **15** and **16** could not be separated by column chromatography as they had the same mobility in different solvent systems. Reaction of pure **12** with *tert*-butyldimethylsilyl chloride and imidazole in DMF gave the corresponding silyl ether **15** (81 %), which was subsequently hydrolysed with 70 % aqueous acetic acid (50 ºC) to the expected diol **18**. Oxidative fission of the diol **18** was achieved by treatment with $NaIO_4$–impregnated wet silica in dichloromethane, whereupon the known[5] aldehyde **19** was obtained with the absolute configuration of all stereocentres corresponding to (+)-muricatacin. The ^{1}H and ^{13}C-NMR spectral data (Table I), as well as the optical rotation of the thus obtained **19** were in good agreement with the reported data.[5] Since the aldehyde **19** was earlier converted to (+)-muricatacin (**1**) in three synthetic steps,[5] the preparation of **19** formally represents a new stereospecific synthesis of (+)-**1** from D-xylose.

In the final stage of this study, the synthesis of several fully protected D-xylose derivatives of type **5** (Scheme 1) was achieved. Namely, the aim of this part of the work was to prepare the 1,2-*O*-cyclohexylidene derivatives bearing different protective groups at C-3 and C-5, in order to avoid the low-selectivity acetonation step in the presented route (**11**→**12**). Thus, 1,2-*O*-cyclohexylidene-α-D-xylofuranose[11] (**20**, Scheme 3) was selectively benzoylated to afford a high yield of the corresponding 5-*O*-benzoyl derivative **21** (84 %). Compound **21** was earlier described in the chemical literature[12] as an oil, $[\alpha]_D$ + 12.1º. However, our sample was a crystalline solid (m.p. 101.5–102 ºC) that showed a rather different value of optical rotation {$[\alpha]_D$ – 3.19º (*c* 1.0 in $CHCl_3$) }. In spite of this

disagreement, all spectral data of the thus obtained product were fully consistent with structure **21**. Further treatment of **21** with *tert*-butyldimethylsilyl chloride under standard reaction conditions furnished the corresponding 3-*O*-silyl ether **22** in 77 % yield. Finally, reaction of **21** with benzyl bromide in DMF, in the presence of sodium hydride as a base, gave the expected 3-*O*-benzyl derivative **23** in 64 % yield. According to the retrosynthetic analysis (Scheme 1), the synthesized compounds **22** and **23** also represent possible intermediates in a modified approach to (+)-muricatacin (**1**), hoping that the presence of different protective groups at C-3 and C-5 would provide a better chemoselectivity of the alternative synthetic routes, which are currently under study in our laboratory.

TABLE I. NMR spectral data for aldehyde **19** (in $CDCl_3$)

	Chemical shift (δ) and *J* (Hz)								
	H-1	H-2	H-3	H-4a	H-4b	2×H-5	$SiMe_2$	$SiCMe_3$	
This work	9.66	4.01	4.85	2.17	2.36	2.55	0.11	0.93	
Ref. 5	9.67	4.04	4.88	2.19	2.37	2.57	0.12	0.95	
	$J_{1,2}$	$J_{2,3}$	$J_{3,4a}$	$J_{3,4b}$					
This work	1.2	2.6	5.3	8.0					
Ref. 5	1.3	2.6	5.4	8.1					
	C-1	C-2	C-3	C-4	C-5	C-6	$SiMe_2$	$SiCMe_3$	$SiCMe_3$
This work	202.1	79.3	79.7	23.3	27.8	176.5	–5.1 and –4.6	18.0	25.6
Ref. 5	201.9	79.2	79.6	23.2	27.7	176.5	–5.2 and –4.7	18.0	25.5

In conclusion, a stereospecific route toward the aldehydo-lactone **19**, the known[5] chiral precursor of (+)-muricatacin, has been developed that may enable the preparation of the target **1** in 14 steps starting from D-xylose. The most recent synthesis of **1** has been accomplished in 15 synthetic steps starting from D-glucose.[6] Although this new synthesis of **19** consists of more synthetic steps than the earlier preparation from L-glyceraldehyde,[5] it uses conventional reagents and a less expensive starting material.

EXPERIMENTAL

General methods

Melting points were determined on a Büchi SMP 20 apparatus and were not corrected. Optical rotations were measured on a Polamat A (Carl-Zeiss, Jena) automatic polarimeter at room temperature. IR spectra were recorded with a Specord 75IR spectrophotometer and the band positions are given in cm^{-1}. NMR spectra were recorded on a Bruker AC 250 E instrument and the chemical shifts are expressed in ppm downfield from Me_4Si. Chemical ionisation mass spectra were recorded on Finnigan-MAT 8230 spectrometer with isobutane as the reagent gas. FAB mass spectra were taken on a VG AutoSpec instrument. TLC was performed on DC Alufolien Kieselgel 60 F_{254} (E. Merck). Flash column chromatography was performed using ICN silica 32-63. Column chromatography was carried out using Kieselgel 60 (under 0.063 mm; E. Merck). All organic extracts were dried with anhydrous Na_2SO_4. Organic solutions were concentrated in a rotary evaporator under reduced pressure at a bath temperature below 30 ºC.

*3,6-Anhydro-5,7-di-*O*-benzyl-2-deoxy-D-*ido*-heptono-1,4-lactone (**7**) and methyl (*E*)-5,7-di-*O*-benzyl-2,3-di-deoxy-D-*xylo*-hept-2-enonate (**8**)*

A solution of **6** (0.1078 g, 0.33 mmol) and methoxycarbonylmethylidene triphenylphosphorane (0.1395 g, 0.42 mmol) in dry DMF (40 mL) was stirred at 60–70 ºC for 24 h. The solvent was evaporated and the residue was chromatographed on a column of flash silica (Et_2O) to separate the reaction products from the Ph_3PO. Repeated chromatographic purification on a silica gel column (20 g, 3:7 hexane–Et_2O) gave pure lactone **7** (0.0139 g, 12 %). Crystallization from MeOH afforded an analytical sample of **7**, m.p. 90 ºC; $[\alpha]_D$ +8.60º (*c* 1.19 in $CHCl_3$); R_F 0.62 (4:1 hexane–Et_2O); ^{1}H-NMR ($CDCl_3$): δ 2.71 (*m*, 2H, $J_{2a,3}$ = 4,4, $J_{2b,3}$ = 2.9 Hz, H-2), 3.73 (*d*, 2H, $J_{6,7}$ = 5.5 Hz, 2×H-7), 4.22 (*dd*, 1H, $J_{4,5}$ = 0.6, $J_{5,6}$ = 4.1 Hz, H-5), 4.31 (*m*, 1H, H-6), 4.59 and 4.64 (2 partially overlapped 2×*d*, 4H, J_{gem} = 11.9 Hz, 2×C*H*$_2$Ph), 4.93 (*dd*, 1H, $J_{3,4}$ = 4.8 Hz, H-4), 4.96 (*m*, 1H, H-3), 7.26–7.42 (*m*, 10 H, 2×Ph); ^{13}C-NMR ($CDCl_3$): δ 36.05 (C-2), 68.19 (C-7), 72.79 and 73.65 (2×*C*H$_2$Ph), 76.95 (C-3), 79.73 (C-6), 81.62 (C-5), 85.55 (C-4), 127.84, 127.87, 128.23, 128.52, 128.67, 137.26 and 138.01 (2×Ph), 175.46 (C=O); CI MS: *m*/*z* 355 (M^+ +H), 263 (M^+ –Bn). Anal. Found: C, 70.89; H, 6.39. Calcd. for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Further eluting of the column gave pure **8** (0.0938 g, 74 %) as a colourless oil, $[\alpha]_D$ –188.88º (*c* 1.08 in $CHCl_3$); R_F 0.50 (4:1 hexane–Et_2O); IR (film): ν_{max} 3430 (OH), 1730 (C=O), 1670 (C=C), 1610 (Ph); ^{1}H-NMR ($CDCl_3$): δ 2.81 and 3.22 (2×*d*, 1H each, exchangeable with D_2O, *J* = 6.1 Hz, 2×OH), 3.52 (*dd*, 1H, $J_{6,7a}$ = 5.6, $J_{7a,7b}$ = 9.7 Hz, H-7a), 3.60 (*dd*, 1H, $J_{6,7b}$ = 5.7, H-7b), 3.62 (*t*, 1H, $J_{4,5}$ = $J_{5,6}$ = 4.1 Hz, H-5), 3.76 (*s*, 3H, OMe), 3.97 (*m*, 1H, H-6), 4.50 (*m*, 1H, $J_{3,4}$ = 4.3, $J_{2,4}$ = 2 Hz, H-4), 4.51 (*s*, 2H, C*H*$_2$Ph), 4.61 (2×*d*, 2H, J_{gem} = 11.3 Hz, C*H*$_2$Ph), 6.16 (*dd*, 1H, $J_{2,3}$ = 15.6 Hz, H-2), 7.03 (*dd*, 1H, H-3), 7.25–7.42 (*m*, 10 H, 2×Ph); ^{13}C-NMR ($CDCl_3$): δ 51.54 (OMe), 70.67 (C-4), 70.76 (C-6), 71.09 (C-7), 73.45 and 74.70 (2×*C*H$_2$Ph), 80.64 (C-5), 121.11 (C-2), 127.87, 128.06, 128.16, 128.43, 128.45, 137.32 and 137.39 (2×Ph), 147.48 (C-3), 166.67 (C=O); CI MS: *m*/*z* 387 (M^+ +H), 355 (M^+ – OMe).

*Methyl 5,7-di-*O*-benzyl-2,3-dideoxy-D-*xylo*-heptonate (**9**)*

A solution of **8** (1.9443 g, 5.28 mmol) in EtOH (40 mL) was hydrogenated over PtO_2 (0.1076 g) for 24 h at room temperature. The mixture was filtered and the catalyst washed with EtOH. The filtrate and washings were combined and evaporated. The syrupy residue (1.9282 g) was purified by flash chromatography (7:3 Et_2O–cyclohexane) to give pure **9** (1.2164 g, 62 %) as a colourless oil, $[\alpha]_D$ –23.37º (*c* 1.16 in $CHCl_3$); R_F 0.20 (7:3 Et_2O–cyclohexane); IR (film): ν_{max} 3430 (OH), 1740 (C=O), 1610 (Ph); ^{1}H-NMR ($CDCl_3$) δ 1.84 (pseudo *q*, 2H, $J_{2,3a}$ = $J_{2,3b}$ = 7.3, $J_{3,4}$ = 6.4 Hz, 2×H-3), 2.43 (*dd*, 1H, $J_{2a,2b}$ = 16.5 Hz, H-2a), 2.52 (*dd*, 1H, H-2b), 2.71 (*bs*, 2H, exchangeable with D_2O, 2×OH), 3.48 (*t*, 1H, $J_{4,5}$ = $J_{5,6}$ = 3.7 Hz, H-5), 3.56 (*dd*, 1H, $J_{7a,7b}$ = 9.6, $J_{6,7a}$ = 5.8 Hz, H-7a), 3.60 (*dd*, 1H, $J_{6,7b}$ = 5.8, H-7b), 3.67 (*s*, 3H, OMe), 3.75 (*m*, 1H, H-4), 3.99 (*m*, 1H, H-6), 4.54 and 4.76 (2×*s*, 2H, each, 2×PhC*H*$_2$), 7.32–7.80 (*m*, 10H, 2×Ph); ^{13}C-NMR ($CDCl_3$): δ 28.74 (C-3), 30.24 (C-2), 51.40 (OCH_3), 70.57 (C-6), 70.78 (C-7), 70.82 (C-4), 73.14 and 74.74 (2×Ph*C*H$_2$), 80.90 (C-5), 127.23, 127.33, 127.55, 127.68, 127.97, 128.08, 128.16, 128.22, 137.52 and 137.65 (2×Ph), 174.15 (C=O); CI MS: *m*/*z* 389 (M^+ +H), 357 (M^+ –OMe).

*5,7-Di-*O*-benzyl-2,3-dideoxy-D-*xylo*-heptono-1,4-lactone (**10**)*

(*A*) A solution of **8** (0.1059 g, 0.29 mmol) in glacial AcOH (3 mL) was hydrogenated over PtO_2 (0.0058 g) for 3 h at room temperature. The flow of hydrogen was terminated and stirring at room temperature was continued for an additional 48 h. The suspension was filtered through a Celite pad and the catalyst was washed with ethanol. The combined filtrate and washings were evaporated and traces of AcOH were removed by co-distillation with toluene. Silica gel column chromatography (10 g; 3:2 Et_2O–cyclohexane) of the residue afforded pure **10** (49.1 mg, 48 %) as a colourless syrup, R_F 0.29 (7:3 Et_2O–cyclohexane).

(*B*) A solution of **9** (1.3268 g; 3.42 mmol) in a mixture of 2:1 TFA–H_2O (30 mL) was stirred at room temperature for 3 h and then evaporated. Traces of acid and water were removed by co-distillation with toluene and the oily residue (1.2744 g) was purified by flash chromatography (49:1 CH_2Cl_2–MeOH) to afford pure **10** (1.1874 g; 98 %) as a colourless oil, $[\alpha]_D$ +31.7º (*c* 0.86 in CH_3OH), R_F 0.29 (7:3 Et_2O–cyclohexane). ^{1}H-NMR ($CDCl_3$): δ 1.98 and 2.35 (2×*m*, 2H, 2×H-3), 2.50 (*m*, 3H, 2×H-2 and OH), 3.52 (*dd*, 1H,

$J_{6,7a}$ = 5.8, $J_{7a,7b}$ = 9.5 Hz, H-7a), 3.58 (*m*, 2H, $J_{5,6}$ = 3.1 Hz, H-7b and H-5), 3.92 (*td*, 1H, H-6), 4.51 (*s*, 2H, PhCH_2), 4.65 and 4.82 (2×*d*, J_{gem} = 11.4 Hz, PhCH_2), 4.75 (*m*, 1H, H-4), 7.27–7.47 (*m*, 10H, 2×Ph); ^{13}C-NMR ($CDCl_3$): δ 24.65 (C-3), 28.33 (C-2), 69.72 (C-6), 70.82 (C-7), 73.45 and 74.46 (2×PhCH_2), 80.13 (C-5), 81.07 (C-4), 127.90, 127.99, 128.22, 128.43, 128.46 and 137.63 (2×Ph), 177.09 (C=O); CI MS: *m*/*z* 357 (M^+ + H); FAB MS: *m*/*z* 379 (M^+ + Na), 357 (M^+ + H).

2,3-Dideoxy-D-xylo-*heptono-1,4-lactone* ***(11)***

A solution of **10** (1.1874 g, 3.34 mmol) in EtOH (50 mL) was hydrogenated over 5 % Pd/C (0.9705 g) for 20 h at room temperature. The mixture was filtered and the catalyst washed with EtOH. The filtrate washings were combined and evaporated. The syrupy residue (0.6390 g) was purified by flash chromatography (5:1 CH_2Cl_2–MeOH) to give pure **11** (0.5360 g, 91 %) as a colourless oil, $[\alpha]_D$ +48.61º (*c* 0.98 in Me_2CO); R_F 0.18 (47:3 EtOAc–MeOH); ^{1}H-NMR (pyridine-d_6): δ 2.23 (*m*, 2H, $J_{3,4}$ = 7.1, $J_{2,3}$ = 8 Hz; 2×H-3), 2.38–2.73 (*m*, 2H, $J_{2a,2b}$ = 16.5 Hz, 2×H-2), 4.17 (*t*, 1H, $J_{4,5}$ = $J_{5,6}$ = 4.4 Hz, H-5), 4.20–4.36 (*m*, 3H, $J_{7a,7b}$ = 11.6, $J_{6,7a}$ = 4.6 Hz, 2×H-7 and H-6), 5.09 (*td*,1H, H-4), 5.20–7.00 (*bs*, 3H, exchangeable with D_2O, 3×OH); ^{13}C-NMR (pyridine-d_6): δ 24.72 (C-3), 31.06 (C-2), 64.22 (C-7), 72.11 (C-6), 74.45 (C-5), 81.77 (C-4), 177.90 (C=O); CI MS: *m*/*z* 177 (M^+ + H), 159 (M^+ – OH); FAB MS: *m*/*z* 199 (M^+ + Na), 177 (M^+ + H), 159 (M^+ – OH).

*2,3-Dideoxy-6,7-*O-*isopropylidene-D*-xylo-*heptono-1,4-lactone* ***(12)*** *and*
*2,3-dideoxy-5,7-*O-*isopropylidene-D*-xylo-*heptono-1,4-lactone* ***(13)***

To a solution of **11** (0.5111 g; 2.90 mmol) in dry DMF (5 mL) were added TsOH×H_2O (0.006 g; 0.03 mmol) and 2,2-dimethoxypropane (1.3 mL; 10.36 mmol). The mixture was stirred for 3.5 h at room temperature and then neutralized by stirring with Amberlite IRA-400 resin at room temperature for 30 min. The mixture was filtered and the resin was washed with dry MeOH. The combined organic solutions were evaporated to an oil (0.5726 g), which was purified by flash chromatography (47:3 toluene–MeOH). Pure **12** (0.1976 g; 31.5 %) was first isolated as a white solid. Recrystallization from CH_2Cl_2-cyclohexane gave an analytical sample **12** as colourless needles, m.p. 94 ºC; $[\alpha]_D$ +44.92º (*c* 1.25 in $CHCl_3$); R_F 0.69 (47:3 EtOAc–MeOH); ^{1}H-NMR ($CDCl_3$): δ 1.37 and 1.44 (2×*s*, 3H each, CMe_2), 2.20–2.39 (*m*, 2H, $J_{2a,3}$ = 8.6, $J_{2b,3a}$ = 7.2, $J_{2b,3b}$ = 9.2, $J_{3,4}$ = 7 Hz, 2×H-3), 2.47 (*dd*, 1H, $J_{2a,2b}$ = 17.4 Hz, H-2a), 2.54–2.77 (*m*, 2H, H-2b and OH), 3.58 (*m*, after treatment with D_2O *dd*, 1H, $J_{5,6}$ = 5.9, $J_{4,5}$ = 3.2 Hz, H-5), 3.82 (*dd*, 1H, $J_{7a,7b}$ = 8.3, $J_{6,7a}$ = 6.4 Hz, H-7a), 4.09 (*dd*, 1H, $J_{6,7b}$ = 6.6 Hz, H-7b), 4.27 (pseudo *q*, 1H, H-6), 4.49 (*td*, 1H, H-4); ^{13}C-NMR ($CDCl_3$): δ 23.95 (C-3), 25.22 and 26.56 (CMe_2) 28.10 (C-2), 65.79 (C-7), 73.56 (C-5), 75.57 (C-6), 79.56 (C-4), 109.86 (CMe_2), 177.17 (C=O); CI MS: *m*/*z* 217 (M^+ + H); FAB MS: *m*/*z* 455 ($2M^+$ + Na), 433 ($2M^+$ + H), 239 (M^+ + Na), 217 (M^+ + H). Anal Found: C, 56.11; H, 7.51. Calcd. for $C_{10}H_{16}O_5$: C, 55.85; H, 7.46. Further elution of the column gave first a mixture of regioisomers **12**, **13** and **14** (0.2605 g; 41 %), followed by small amount of pure **13** (0.0322 g, 5 %) as a colourless oil, R_F 0.28 (47:3 EtOAc–MeOH); ^{1}H-NMR ($CDCl_3$): δ 1.46 (*s*, 6H, CMe_2), 1.91 (*m*, 1H, H-3a), 2.39 (*m*, 1H, H-3b), 2.54 (*m*, 2H, 2×H-2), 2.95 (*bs*, 1H, exchangeable with D_2O, OH), 3.48 (*bs*, 1H, $J_{6,7a}$ = 1.9, $J_{6,7b}$ = 1.2, $J_{5,6}$ = 3 Hz, H-6), 3.82 (*dd*, 1H, $J_{7a,7b}$ = 12.5 Hz, H-7a), 3.86 (*bd*, 1H, $J_{4,5}$ = 8.9 Hz, H-5), 4.06 (*dd*, 1H, H-7b), 4.61 (*m*, 1H, H-4); ^{13}C-NMR ($CDCl_3$): δ 18.24 and 29.25 (CMe_2), 23.67 (C-3), 28.29 (C-2), 62.95 (C-6), 65.56 (C-7), 74.64 (C-5), 80.44 (C-4), 99.30 (CMe_2), 176.62 (C=O); CI MS: *m*/*z* 217 (M^+ + H).

*5-*O-*(*tert-*Butyldimethylsilyl)-2,3-dideoxy-6,7-*O-*isopropylidene-D*-xylo-*heptono-1,4-lactone* ***(15)***

A solution of **12** (0.1888 g; 0.87 mmol), *tert*-butyldimethylsilyl chloride (0.5157 g; 3.42 mmol) and imidazole (0.2512 g, 3.69 mmol) in dry DMF (13 mL) was stirred for 24 h at room temperature. The mixture was evaporated and the residue (0.7762 g) purified by flash column chromatography (49:1 toluene-MeOH). Pure **15** (0.2328 g; 81 %) was obtained as an oil which crystallized from hexane as colourless prisms, m.p. 76–77 ºC; $[\alpha]_D$ +49.76º (*c* 1.16 in $CHCl_3$); R_F 0.18 (CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): δ 0.12 and 0.13 (2×*s*, 3H each, SiMe_2), 0.89 (*s*, 9H, SiCMe_3), 1.34 and 1.41 (2×*s*, 3H each, CMe_2), 2.10–2.69 (*m*, 4H, 2×H-2 and 2×H-3), 3.71 (*dd*, 1H, $J_{5,6}$ = 5.8, $J_{4,5}$ = 3.3 Hz, H-5), 3.80 (*t*, 1H, $J_{6,7a}$ = $J_{7a,7b}$ = 8 Hz, H-7a), 4.03 (*dd*, 1H,

$J_{6,7b}$ = 6.4 Hz, H-7b), 4.19 (*m*, 1H, H-6), 4.52 (*m*, 1H, $J_{3a,4}$ = 6.4, $J_{3b,4}$ = 7.6 Hz, H-4); ^{13}C-NMR ($CDCl_3$): δ –4.76 and –4.32 ($SiMe_2$), 18.18 (Si*C*Me_3), 23.81 (C-3), 25.31 and 26.37 (C*Me*$_2$), 25.78 (SiC*Me*$_3$), 28.02 (C-2), 65.56 (C-7), 74.90 (C-5), 76.55 (C-6), 79.91 (C-4), 109.27 (*C*Me_2), 177.05 (C=O); CI MS: *m*/*z* 331 (M^+ + H); FAB MS: *m*/*z* 353 (M^+ + Na), 331 (M^+ + H), 315 (M^+ – Me). Anal. Found: C, 58.31; H, 9.41. Calcd. for $C_{16}H_{30}O_5Si$: C, 58.15; H, 9.15.

6-O-*(*tert-*Butyldimethylsilyl)-2,3-dideoxy-5,7*-O-*isopropylidene-D*-xylo-*heptono-1,4-lactone (**16**)*

A solution of **13** (0.032 g; 0.15 mmol), *tert*-butyldimethylsilyl chloride (0.0720 g; 0.51 mmol) and imidazole (0.0482 g, 0.71 mmol) in dry DMF (1.5 mL) was stirred for 24 h at room temperature. The mixture was evaporated and the residue purified by flash column chromatography (49:1 CH_2Cl_2–MeOH). Pure **16** (0.0361 g; 79 %) was obtained as a colourless oil, $[\alpha]_D$ +0.19º (*c* 1.1 in $CHCl_3$); R_F 0.18 (CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): δ 0.12 and 0.69 (2×*s*, 3 H each, Si*Me*$_2$), 0.91 (*s*, 9 H, SiC*Me*$_3$), 1.42 and 1.44 (2×*s*, 3 H each, CMe$_2$), 1.93 (*m*, 1 H, H-3a), 2.30 (*m*, 1 H, H-3b), 2.46–2.61 (*m*, 2H, 2×H-2), 3.64–3.83 (*m*, 3 H, $J_{4,5}$ = 8.2, $J_{5,6}$ = 1.8, $J_{7a,7b}$ = 12.5, $J_{6,7a}$ = 3 Hz, H-5, H-6 and H-7a), 3.95 (*dd*, 1 H, $J_{6,7b}$ = 2.7 Hz, H-7b), 4.66 (*m*, 1 H, $J_{3a,4}$ = 6.4, $J_{3b,4}$ = 8.9 Hz, H-4); ^{13}C-NMR ($CDCl_3$): δ –4.66 and –3.84 ($SiMe_2$), 18.09 (Si*C*Me_3), 23.52 (C-3), 19.61 and 28.14 (C*Me*$_2$), 25.64 (SiC*Me*$_3$), 28.41 (C-2), 64.50 (C-7), 64.72 (C-6), 74.81 (C-5), 80.34 (C-4), 98.96 (*C*Me_2), 176.54 (C=O).

7-O-*(*tert-*Butyldimethylsilyl)-2,3-dideoxy-5,6*-O-*isopropylidene-D*-xylo-*heptono-1,4-lactone (**17**)*

A solution of a mixture containing **12**, **13** and **14** (0.1504 g; 0.70 mmol), *tert*-butyldimethylsilyl chloride (0.4068 g; 2.70 mmol) and imidazole (0.2067 g, 3.04 mmol) in dry DMF (2.5 mL) was stirred for 24 h at room temperature. The mixture was evaporated and the residue (0.5216 g) purified by flash column chromatography (97:3 toluene–MeOH). Pure **17** (0.0630 g; 27 %) was obtained as a colourless oil, $[\alpha]_D$ +23.07º (*c* 0.7 in $CHCl_3$); R_F 0.52 (19:1 toluene–MeOH); ^{1}H-NMR ($CDCl_3$): δ 0.79 (*s*, 6 H, Si*Me*$_2$), 0.90 (*s*, 9 H, SiC*Me*$_3$), 1.38 and 1.39 (2×*s*, 3 H each, CMe$_2$), 2.20–2.81 (*m*, 4 H, 2×H-2 and 2×H-3), 3.70 (*dd*, 1 H, $J_{6,7a}$ = 6.5, $J_{7a,7b}$ = 10.5 Hz, H-7a), 3.88 (*dd*, 1 H, $J_{6,7b}$ = 3.9 Hz, H-7b), 3.97 (*dd*, 1 H, $J_{4,5}$ = 1.7, $J_{5,6}$ = 8 Hz, H-5), 4.15 (*ddd*, 1 H, H-6), 4.61 (*ddd*, 1 H, $J_{3a,4}$ = 6.1, $J_{3b,4}$ = 4.4 Hz, H-4); ^{13}C-NMR ($CDCl_3$): δ –5.46 ($SiMe_2$), 18.27 (Si*C*Me_3), 24.78 (C-3), 25.84 (SiC*Me*$_3$), 26.34 and 27.22 (C*Me*$_2$), 27.89 (C-2), 63.46 (C-7), 76.20 (C-6), 77.43 (C-4), 81.58 (C-5), 109.73 (*C*Me_2), 177.62 (C=O). Further elution of the column gave an inseparable mixture of the regioisomers **15** and **16** (0.1548 g; 67 %) as a colourless syrup, R_F 0.18 (CH_2Cl_2).

5-O-*(*tert-*Butyldimethylsilyl)-2-3-dideoxy-D*-xylo-*heptono-1,4-lactone (**18**)*

A solution of **15** (0.2828 g, 0.86 mmol) in 70 % aq. AcOH (5 mL) was stirred for 3 h at 50 ºC. The mixture was evaporated and the residual AcOH was removed by co-distillation with toluene. Flash column chromatography (93:7 CH_2Cl_2–cyclohexane) of the residue (0.2755 g) yielded pure **18** (0.2264 g, 91 %) as a white solid. Recrystallization from CH_2Cl_2–cyclohexane gave colourless crystals, m.p. 79–80 ºC; $[\alpha]_D$ +33.86º (*c* 0.5 in $CHCl_3$); R_F 0.39 (23:2 CH_2Cl_2–MeOH); ^{1}H-NMR ($CDCl_3$): δ 0.11 and 0.14 (2×*s*, 3 H each, Si*Me*$_2$), 0.89 (*s*, 9 H, SiC*Me*$_3$), 2.06 (*m*, 1 H, H-3a), 2.31 (*m*, 1 H, H-3b), 2.54 (*m*, 2 H, 2×H-2), 2.62 and 2.90 (2×*bs*, 2 H, exchangeable with D_2O, 2×OH), 3.54–3.72 (*m*, 3 H, H-6 and 2×H-7), 3.76 (*dd*, 1 H, $J_{4,5}$ = 4.8, $J_{5,6}$ = 2.9 Hz, H-5), 4.67 (*td*, 1 H, $J_{3,4}$ = 7.3 Hz, H-4); ^{13}C-NMR ($CDCl_3$): δ –4.64 and –4.49 ($SiMe_2$), 18.08 (Si*C*Me_3), 24.06 (C-3), 25.77 (SiC*Me*$_3$), 28.42 (C-2), 63.05 (C-7), 71.34 (C-6), 74.16 (C-5), 80.03 (C-4), 177.13 (C=O); CI MS: *m*/*z* 291 (M^+ + H), 273 (M^+ + H – OH). Anal. Found: C, 54.01; H, 9.21. Calcd. for $C_{13}H_{26}O_5Si$: C, 53.76; H, 9.02.

2-O-*(*tert-*Butyldimethylsilyl)-4,5-dideoxy-L*-threo-*hexurono-6,3-lactone (**19**)*

Partially protected lactone **18** (0.0458 g, 0.16 mmol) was dissolved in CH_2Cl_2 (1 mL) and treated with a 0.65 M aqueous $NaIO_4$ solution (0.5 ml) and chromatography grade silica gel (0.063 – 0.200 mm, 0.3 g). The resulting heterogeneous mixture was vigorously stirred for 0.5 h at room temperature then filtered and evaporated to afford chromatographically pure **19** as a white solid (0.0397 g, 97 %). Recrystallization from hexane gave colourless crystals, m.p. 71–72 ºC; $[\alpha]_D$ +101.28º (*c* 2.1 in $CHCl_3$); lit.[5] $[\alpha]_D$ +96.3 (*c* 1.2 in $CHCl_3$); R_F 0.80 (47:3 EtOAc–MeOH). ^{1}H and ^{13}C-NMR data are presented in Table I. FAB MS: *m*/*z* 259 (M^+ + H), 201 (M^+ – CMe_3).

5-O-*Benzoyl-1,2*-O-*cyclohexylidene*-α-*D*-*xylofuranose* ***(21)***

To a cold solution (–22 ºC) of **20** (4.6 g, 20 mmol) in dry CH_2Cl_2 (40 mL) and pyridine (5 mL) was added benzoyl chloride (2.5 mL, 21.54 mmol) previously cooled to –22 ºC. The mixture was left at –22 ºC for 69 h and then at room temperature for an additional 24 h. The reaction mixture was poured into 4 M aq. HCl (100 mL), the organic layer was washed with brine (3×100 mL), dried and evaporated to a yellow syrup. The residue was purified by flash chromatography (19:1 CH_2Cl_2–EtOAc) to give pure **21** (5.6254 g, 84 %) as a white solid. Recrystallization from hexane afforded colourless crystals, m.p. 101.5–102 ºC; $[\alpha]_D$ –3.19º (c 1.0 in $CHCl_3$); lit.[12] $[\alpha]_D$ +12.1º; R_F 0.32 (19:1 CH_2Cl_2–EtOAc); IR (KBr): ν_{max} 3460–3400 (OH), 1720 (C=O), 1610 (Ph); ^{1}H-NMR ($CDCl_3$): δ 1.32–1.77 (*m*, 10 H, C_6H_{10}), 3.53 (*bs*, 1H, exchangeable with D_2O, OH), 4.22 (*d*, 1 H, $J_{3,4}$ = 2.1 Hz, H-3), 4.39 (*m*, 1 H, $J_{4,5a}$ = 5.4, $J_{4,5b}$ = 8.8 Hz, H-4), 4.42 (*dd*, 1 H, $J_{5a,5b}$ = 13 Hz, H-5a), 4.58 (*d*, 1 H, $J_{1,2}$ = 3.6 Hz, H-2), 4.76 (*dd*, 1 H, H-5b), 5.97 (*d*, 1 H, H-1), 7.39–8.09 (*m*, 5 H, Ph); ^{13}C-NMR ($CDCl_3$); δ 23.47, 23.80, 24.78, 35.50 and 36.32 (5×CH_2 from C_6H_{10}), 61.56 (C-5), 74.45 (C-3), 78.40 (C-4), 84.53 (C-2), 104.28 (C-1), 112.44 (qC from C_6H_{10}), 128.37, 129.20, 129.78 and 133.40 (Ph), 167.20 (C=O); CI MS: *m*/*z* 335 (M^+ + H).

5-O-*Benzoyl-3*-O-tert-*butyldimethylsilyl-1,2*-O-*cyclohexylidene-a-D-xylofuranose* ***(22)***

A solution of **21** (0.40 g; 1.20 mmol), *tert*-butyldimethylsilyl chloride (0.3644 g; 2.42 mmol) and imidazole (0.2436 g, 3.6 mmol) in dry DMF (2 mL) was stirred for 23 h at room temperature. The mixture was evaporated and the residue (0.7762 g) purified by flash column chromatography (7:1 toluene–CH_2Cl_2). Pure **22** (0.4123 g; 77 %) was obtained as colourless crystals, m.p. 75–76 ºC; $[\alpha]_D$ –31.1º (*c* 0.99 in $CHCl_3$); R_F 0.67 (9:1 toluene–EtOAc); IR (KBr) ν_{max} 1730 (C=O), 1600 (Ph); ^{1}H-NMR ($CDCl_3$): δ 0.10 and 0.15 (2×*s*, 3 H each, Si*Me*$_2$), 0.91 (*s*, 9 H, SiC*Me*$_3$), 1.33–1.78 (*m*, 10 H, C_6H_{10}), 4.32 (*bs*, 1 H, $J_{3,4}$ = 2 Hz, H-3), 4.39 (*d*, 1 H, $J_{1,2}$ = 3.7 Hz, H-2), 4.43–4.57 (*m*, 3 H, H-4 and 2×H-5), 5.97 (*d*, 1 H, H-1), 7.38–8.11 (*m*, 5 H, Ph); ^{13}C-NMR ($CDCl_3$): δ –5.20 and –4.70 ($SiMe_2$), 17.97 (Si*C*Me$_3$), 23.56, 23.88, 24.86, 35.82 and 36.55 (5×CH_2 from C_6H_{10}), 25.61 (SiC*Me*$_3$), 62.69 (C-5), 75.75 (C-3), 78.72 (C-4), 85.00 (C-2), 104.75 (C-1), 112.58 (qC from C_6H_{10}), 128.29, 129.70, 129.77, 129.87 and 133.00 (Ph), 166.26 (C=O); CI MS: *m*/*z* 449 (M^+ + H).

5-O-*Benzoyl-3*-O-*benzyl-1,2*-O-*cyclohexylidene*-α-*D*-*xylofuranose* ***(23)***

To a cooled (0 ºC) and stirred solution of **21** (1.3482 g, 4 mmol) in dry DMF (20 mL) were added successively NaH (0.2633 g, 9.8 mmol) and BnBr (0.72 mL, 6 mmol). The mixture was stirred for 2.5 h at room temperature and then evaporated. The oily residue was partitioned between CH_2Cl_2 (50 mL) and 10 % aqueous NH_4Cl (45 mL). The organic layer was washed with water (2×45 mL), dried and evaporated to a yellow syrup. The residue was purified by flash column chromatography (CH_2Cl_2–light petroleum) to afford pure **23** (1.0841 g, 64 %) as a pale yellow oil, $[\alpha]_D$ –68.8º (*c* 1.02 in $CHCl_3$); R_F 0.76 (4:1 toluene–EtOAc); IR (film): ν_{max} 1720 (C=O), 1610 (Ph); ^{1}H-NMR ($CDCl_3$): δ 1.35–1.81 (*m*, 10 H, C_6H_{10}), 4.08 (*d*, 1 H, $J_{3,4}$ = 2.7 Hz, H-3), 4.50–4.78 (*m*, 6 H, J_{gem} = 12 Hz, Ph*C*H$_2$, H-2, H-4 and 2×H-5), 6.02 (*d*, 1 H, $J_{1,2}$ = 3.8 Hz, H-1), 7.23–8.07 (*m*, 10 H, Ph); ^{13}C-NMR ($CDCl_3$); δ 23.51, 23.80, 24.80, 35.64 and 36.35 (5×CH_2 from C_6H_{10}), 62.37 (C-5), 72.00 (Ph*C*H$_2$), 77.98 (C-4), 81.55 (C-2 and C-3), 104.81 (C-1), 112.49 (qC from C_6H_{10}), 127.63, 127.91, 128.23, 128.44, 129.68, 129.75, 132.97 and 137.11 (2×Ph), 166.18 (C=O); CI MS: *m*/*z* 425 (M^+ + H).

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ИЗВОД

ФОРМАЛНА СИНТЕЗА (+)-МУРИКАТАЦИНА ИЗ D-КСИЛОЗЕ

ВЕЛИМИР ПОПСАВИН[a], САЊА ГРАБЕЖ[a], ИВАНА КРСТИЋ[a], МИРЈАНА ПОПСАВИН[a] и ДЕЈАН ЂОКОВИЋ[б]

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У раду је остварена вишефазна синтеза алдехидо-лактона **19**, финалног хиралног прекурсора у новој стереоспецифичној синтези (+)-мурикатацина, полазећи из D-ксилозе. Кључну етапу синтезе представља *E*-стереоселективна Wittig-ова реакција лактола **6**, са метоксикарбонилметилиден-трифенилфосфораном, праћена накнадном каталитичком редукцијом и γ-лактонизацијом. Низом селективних интерконверзија присутних функционалних група награђен је кључни шесто-угљенични интермедијер **19**, који се може превести у (+)-мурикатацин трофазном синтетичком секвенцом која је раније описана у литератури.

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