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Enantiopure hydroxylactones from D-xylose. A novel approach to the enantiodivergent synthesis of (+)- and (−)-muricatacin suitable for the preparation of 7-oxa analogues

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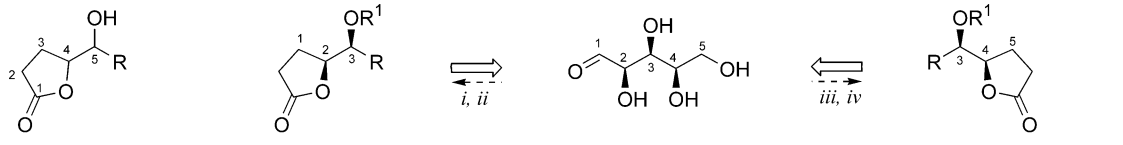
Abstract—A new route towards enantiopure hydroxylactones **3** and *ent*-**3**, the final chiral precursors in an enantiodivergent synthesis of (+)- and (−)-muricatacin, has been developed starting from D-xylose.

Hydroxylactones of type **1** (Scheme 1) are naturally occurring 5-hydroxyalkylbutan-4-olides that show different biological activity depending on the length of the alkyl chain and absolute configuration of the stereocenters. One such molecule that has attracted considerable attention since its isolation from the seeds of *Anona muricata*[1] is muricatacin (5-hydroxy-4-heptadecanolide), an acetogenin derivative that shows cytotoxic activity against certain human tumor cell lines. Interestingly, the isolated sample was a mixture of enantiomers **4a** and **4b** with the (−)-(*R*,*R*)-isomer **4b** being predominant (ee, ca. 25%). Both (+)- and (−)-muricatacin show the same antitumor activity.[1,2] The biological activity of muricatacin and other related compounds, has stimulated significant interest in the synthesis of 5-hydroxyalkylbutan-4-olides. Many syntheses of (+)- and/or (−)-muricatacin from various non-carbohydrate precursors have been reported,[2,3] along with a number of carbohydrate based approaches,[4,5] most being target oriented. Herein we report on a novel general approach to an enantiodivergent synthesis of (+)- and (−)-muricatacin from D-xylose, that is suitable for elaboration to a variety of 7-oxa analogues.

As outlined in Scheme 1, (+)-muricatacin **4a** might be prepared by a sequence that will ensure the introduction of the C-2 and C-3 stereocenters of D-xylose into the target structure **4a** via the aldehydo-lactone **2**. It was further assumed that the key intermediate **2** should be available from a suitably protected D-xylose derivative through the following steps: (i) 'CH_2CO_2R'—introduction at C-1 followed by γ-lactonization, and (ii)



Scheme 1. (a) Naturally occurring 5-hydroxyalkylbutan-4-olides (conventional numbering); (b) enantiodivergent strategy for preparation of (+)- and (−)-muricatacin by chirality transfer from D-xylose (sugar numbering).

Keywords: 5-hydroxyalkylbutan-4-olides; D-xylose; muricatacin; enantiodivergent synthesis; Wittig reaction.
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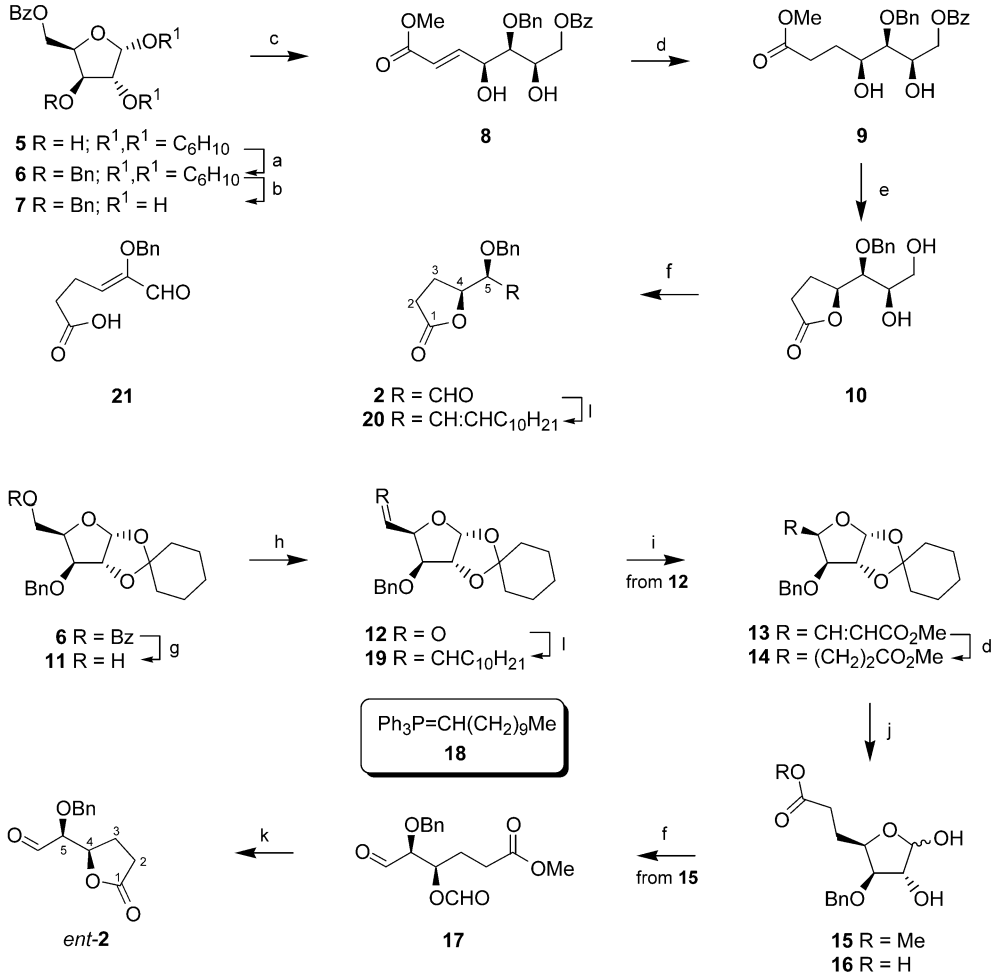
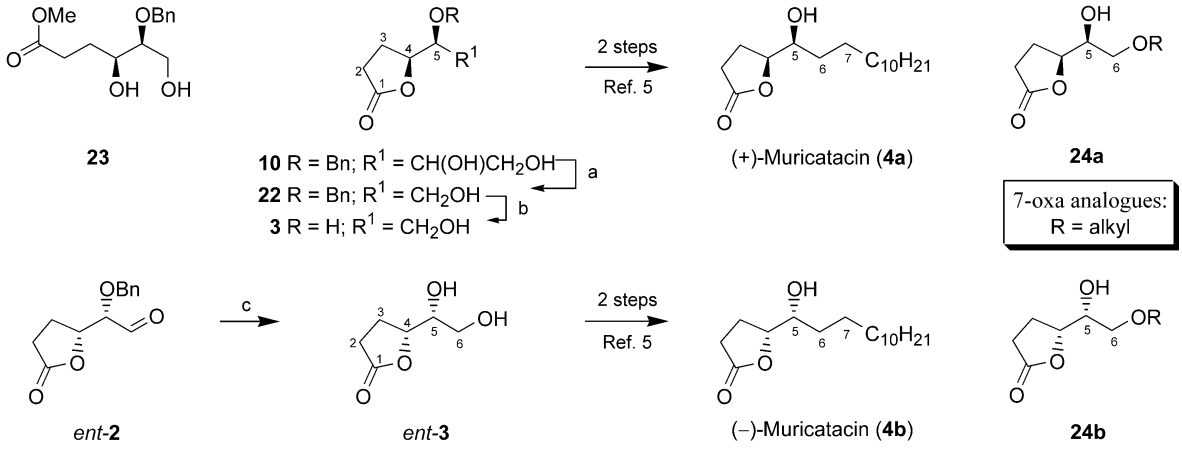
oxidative glycol cleavage of the C_4–C_5 bond. An alternative sequence that involves (iii) 'CH_2CO_2R'—elongation at C-5 followed by γ-lactonization, and (iv) C_1–C_2 glycol cleavage, should provide access to the aldehydo-lactone *ent*-**2** bearing the C_3–C_4 chiral segment of D-xylose. It was also assumed that both **2** and *ent*-**2** can be converted to the targets **4a** and **4b** by a Wittig elongation/catalytic reduction process. Alternatively, the chiral synthons **2** and *ent*-**2** may be first converted to the dihydroxylactones **3** and *ent*-**3** and finally to the targets **4a** and **4b** through a known two-step sequence.[5]

The syntheses of **2** and *ent*-**2** are summarized in Scheme 2. The preparation of **2** started with 5-*O*-benzoyl-1,2-*O*-cyclohexylidene-α-D-xylofuranose **5** which was readily available from D-xylose in three steps.[6,7] Treatment of **5** with benzyl bromide in DMF, in the presence of NaH as a base, followed by removal of the cyclohexylidene protective group with dilute acetic acid gave the corresponding lactol **7**. Wittig olefination of **7** with (carbomethoxymethylidene)triphenylphosphorane in DMF took place stereospecifically to afford the (*E*)-unsaturated ester **8** (83%) as the only isolable product. The *E*-selectivity of this step was essential, because it is well known that similar (*Z*)-α,β-unsaturated esters rapidly undergo a sequential lactonization/Michael ring-closure process.[8] Catalytic hydrogenation of **8** over PtO_2 in ethanol yielded the corresponding saturated ester **9**, which upon treatment with sodium methoxide in methanol furnished the hydroxylactone **10** in 82% yield. Oxidative cleavage of the diol functionality in **10** was achieved by treatment with $NaIO_4$-impregnated wet silica in dichloromethane, whereby the aldehydo-lactone **2**[9] was obtained. In the light of its stereochemical features the molecule **2** fully corresponds to the chiral lactone core of (+)-muricatacin **4a**, and to the related 5-hydroxyalkylbutan-4-olides of type **1**.



Scheme 2. *Reagents and conditions*: (a) BnBr, NaH, DMF, 0°C→rt, 1.5 h, 74%; (b) 7:3 AcOH–H_2O, reflux, 5.5 h, 85%; (c) Ph_3P:$CHCO_2Me$, DMF, 60–70°C, 3.5 h, 83%; (d) H_2/PtO_2, EtOH, rt, 16 h for **8**, 76% of **9**, 19 h for **13**, 92% of **14**; (e) (i) NaOMe, MeOH, rt, 1.5 h, (ii) 2:1 TFA–H_2O, rt, 10 min, 82%; (f) aq. $NaIO_4$, silica gel, CH_2Cl_2, rt, 1 h, 89% of **2**, 52% of **17**; (g) NaOMe, MeOH, 0°C→rt, 1 h, 86%; (h) DMSO, DCC, anh. H_3PO_4, Py, rt, 5.5 h, 76% (83% based on recovered **11**); (i) Ph_3P:$CHCO_2Me$, CH_2Cl_2, rt, 2 h, 97%; (j) 1:1 AcOH–H_2O, reflux, 1.5 h, 58% of **15** (64% based on recovered **14**), 7.5% of **16**; (k) 2:1 TFA–H_2O, rt, 2 h, 77% from **15**; (l) $[Ph_3PCH_2(CH_2)_9Me]^+$ Br^-, LiHMDS, THF, −78°C→rt, 20 h for **12**, 3 days for **2**; 43% of **19**, 6.5% of **20**.



Scheme 3. *Reagents and conditions*: (a) (i) aq. $NaIO_4$, silica gel, CH_2Cl_2, rt, 1 h, (ii) $NaBH_4$, MeOH, 0°C→rt, 1.5 h, (iii) 2:1 TFA–MeOH, 0°C→rt, 1.5 h, 64% (73% based on recovered **2**); (b) H_2–Pd/C, EtOAc, rt, 19 h, 69%; (c) (i) $NaBH_4$, MeOH, 0°C→rt, 2 h, (ii) 2:1 TFA–MeOH, 0°C→rt, 1.5 h, (iii) H_2–Pd/C, rt, 19 h, 71%.

The 5-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-cyclohexylidene-α-D-xylofuranose **6** was conveniently used as an intermediate for the preparation of *ent*-**2**. Treatment of **6** with sodium methoxide in methanol afforded the primary alcohol **11** in 86% yield (64% from **5**). However, when the last two steps (**5**→**6**→**11**) were carried out as an one-pot procedure, the intermediate **11** was obtained in 89% overall yield with respect to **5**. Oxidation of the primary hydroxyl group in **11** gave **12**, which was further treated with (carbomethoxymethylidene)triphenylphosphorane in dry dichloromethane to afford the expected unsaturated ester **13** as a 2:1 mixture of the corresponding *Z*- and *E*-isomers. Catalytic hydrogenation of **13**, followed by hydrolytic removal of the cyclohexylidene protective group, gave a 58% yield of the corresponding lactol **15** (64% based on recovered **14**), accompanied with a small amount of the carboxylic acid **16** (7.5%). Oxidative cleavage of purified diol **15** with sodium periodate on silica afforded the formate **17**, which upon treatment with aqueous trifluoroacetic acid yielded the γ-lactone *ent*-**2**,[10] with the absolute configuration of both stereocenters corresponding to (–)-muricatacin **4b**. Spectral data (^1H and ^{13}C NMR) and physical constants of *ent*-**2** were in good agreement with values recorded for its enantiomer **2**.

With the requisite chirons **2** and *ent*-**2** in hand, we next focused on their C_{11}-elongation in order to elaborate the muricatacin side chain. According to the initial plan, Wittig olefination of **2** and *ent*-**2** with the appropriate C_{11}–ylide should enable us to resolve this problem. However, in order to avoid wasting valuable intermediates (**2** and *ent*-**2**), the Wittig reaction was first explored on aldehyde **12** as a model compound. Thus, aldehyde **12** was reacted with ylide **18** (generated in situ from undecyltriphenylphosphonium bromide and LiHMDS in THF at −78°C),[11] to give an acceptable yield of the corresponding (*Z*)-olefin **19** (43%), as the only isolable product. The aldehydo-lactone **2** under the same reaction conditions also gave the desired unsaturated derivative **20** but in only 6.5% yield. Traces of the elimination product **21** were also isolated from a complex reaction mixture. All our attempts to improve the yield of **20** were unsuccessful and afforded only the elimination product **21**. We were therefore forced to find an alternative methodology for elaboration of the muricatacin side chain. According to our plan (Scheme 1), conversion of both **2** and *ent*-**2** to the corresponding diols **3** and *ent*-**3** (Scheme 3) represents a possible alternative route for completion of the synthesis.

The preparation of **3** began with the synthesis of the primary alcohol **22** from dihydroxy-lactone **10**. Oxidative cleavage of the terminal diol in **10** provided the aldehydo-lactone **2**, which was isolated in pure form after the usual work-up and used in the next step without further purification. Subsequent reduction of crude **2** with sodium borohydride gave the expected primary alcohol **22** along with an equal amount of ester **23**. The mixture was not separated (except for characterization purposes), but was further treated with trifluoroacetic acid to complete the lactonization of **23** to **22**. The intermediate **22** was thus obtained in a 64% overall yield with respect to the starting compound **10** (73% based on recovered **2**). Catalytic hydrogenolysis of **22** (10% Pd/C) furnished the known diol **3**, a key intermediate in the synthesis of conformationally constrained analogues of diacylglycerol.[12] The ^1H and ^{13}C NMR spectral data (Table 1) and the optical rotation[13] of **3** thus obtained were in reasonable agreement with reported values.[12] Compound **3** can be converted to (+)-muricatacin according to the reported procedure.[5] The intermediate *ent*-**2** was converted to the dihydroxylactone *ent*-**3** by using an one-pot procedure that involved a reduction of the aldehyde group ($NaBH_4$ in MeOH) in *ent*-**2**, followed by subsequent hydrogenolytic removal of the benzyl ether protective group (10% Pd/C) under the acidic conditions (2:1 TFA–MeOH). This procedure provided the desired intermediate *ent*-**3** in 71% overall yield. The ^1H and ^{13}C NMR spectral data (Table 1), as well as the value of optical rotation[14] for *ent*-**3** were fully consistent with those reported previously.[5] Since (–)-muricatacin **4b** has already been synthesized from diol *ent*-**3**,[5] the preparation of *ent*-**3** formally represents a novel synthesis of (–)-**4b** from D-xylose.

Table 1. NMR spectral data for compounds **3** and *ent*-**3**

Compound	Solvent	δ_H (ppm)				δ_C (ppm)						Reference
		2×H-2	2×H-3	H-4	H-5 and 2×H-6	C-1	C-2	C-3	C-4	C-5	C-6	
3	$CDCl_3$	2.57	2.26	4.59	3.65	178.21	28.45	23.90	80.77	73.56	63.27	This work
	Methanol-d_4	2.53	2.25	4.68	3.60	180.44	29.34	24.68	81.79	74.53	63.77	Ref. 12
ent-**3**	$CDCl_3$	2.60	2.28	4.60	3.75	177.31	28.31	23.89	80.62	73.42	63.28	This work
	$CDCl_3$	2.52	2.23	4.57	3.69	178.00	28.40	23.90	80.70	73.50	63.30	Ref. 5

In conclusion, a new and flexible strategy for the synthesis of enantiopure 5-hydroxyalkylbutan-4-olides by chirality transfer from D-xylose has been developed. The synthetic pathway that provided an access to (+)- and (−)-5,6-dihydroxy-4-hexanolides **3** and *ent*-**3** formally represents a new enantiodivergent synthesis of (+)- and (−)-muricatacin. This approach is potentially useful for the preparation of hitherto unknown 7-oxa (+)- and (−)-muricatacin analogues **24a** and **24b** (via **22** and *ent*-**22**).

Acknowledgements

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9. Selected data for **2**: mp 93–94°C (from CH_2Cl_2–hexane), $[\alpha]_D$ +135.8 (*c* 1.05 in $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.92–2.68 (m, 4H, 2×CH_2), 3.78 (dd, 1H, $J_{4,5}=2.7$, $J_{5,6}=1.5$ Hz, H-5), 4.58 (d, 1H, $J_{gem}=11.9$ Hz, PhC*H*-a), 4.74–4.85 (m, 2H, H-4 and PhC*H*-b), 7.33 (m, 5H, Ph), 9.68 (d, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 23.63 and 27.77 (2×CH_2), 73.53 (Ph*C*H_2), 78.88 (C-4), 84.02 (C-5), 128.20, 128.52, 128.69 and 136.18 (Ph), 176.56 (C-1), 201.57 (C-6).
10. Selected data for *ent*-**2**: mp 93–94°C (from CH_2Cl_2–hexane), $[\alpha]_D$ −129.8 (*c* 1.0 in $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.90–2.65 (m, 4H, 2×CH_2), 3.76 (dd, 1H, $J_{4,5}=2.7$, $J_{5,6}=1.5$ Hz, H-5), 4.60 (d, 1H, $J_{gem}=11.9$ Hz, PhC*H*-a), 4.72–4.84 (m, 2H, H-4 and PhC*H*-b), 7.37 (m, 5H, Ph), 9.69 (d, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 23.53 and 27.72 (2×CH_2), 73.45 (Ph*C*H_2), 78.84 (C-4), 83.94 (C-5), 128.19, 128.42, 128.61 and 136.16 (Ph), 176.57 (C-1), 201.84 (C-6).
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13. Compound **3** (syrup): $[\alpha]_D$ +57.99 (*c* 2.01 in MeOH); Ref. 12: $[\alpha]_D$ +58.18 (*c* 2.03 in MeOH); ^1H and ^{13}C NMR data in Table 1.
14. Compound *ent*-**3** (syrup): $[\alpha]_D$ −40.03 (*c* 2.07 in MeOH); Ref. 5: $[\alpha]_D$ −43.3 (*c* 0.9 in MeOH); ^1H and ^{13}C NMR data in Table 1.