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Synthesis of congeners of migrastatin and dorrigocin A from D-xylose

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ABSTRACT

Migrastatin and dorrigocin A analogues have potential as anti-metastatic agents that act by targeting the actin-bundling protein, fascin. Syntheses of close structural analogues of these agents have been achieved. Wittig and Ando olefination reactions with an aldehyde obtained from D-xylose, respectively, gave two trisubstituted alkene intermediates that were then elaborated into either macrolactone or macrolactam analogues of migrastatin or to an acyclic dorrigocin A analogue.

Tumour metastasis is the primary cause of death of cancer patients and the development of therapeutic agents that would inhibit this process would be of major benefit. Migrastatin (**1**), a macrolide natural product first isolated from a cultured broth of *Streptomyces*, is an inhibitor of tumour cell migration.[1] Dorrigocin A (**2**), a naturally occurring antifungal antibiotic, is structurally related to migrastatin by a lactone hydrolysis and alkene isomerisation and it also displays interesting biological properties. Dorrigocin A inhibits the carboxymethyltransferase involved in ras processing[2] and reverses the morphology of ras-transformed NIH/3T3 cells.[3] Importantly, simpler analogues of migrastatin, such as the macrolide **3a** (Fig. 1), are ~1000-fold more active than migrastatin itself in cell migration assays in vitro.[4] The macrolactam **3b**, macroketone **3c** and a macroether (not shown) inhibit the metastasis of highly metastatic tumour cells in mouse models.[5] An analogue of dorrigocin A **6** showed the ability to inhibit potently, gastric tumour cell migration in vitro.[6] Related natural products such as isomigrastatin and lactimidomycin are also active cell migration inhibitors.[7] Very recently, the macroketone **3c** was shown to target the actin-bundling protein, fascin, providing a mechanism by which migrastatin analogues and possibly dorrigocin A analogues inhibit tumour metastasis.[8] Therefore, the development of synthetic routes to new migrastatin and dorrigocin A analogues is important.[9]

The migrastatin and dorrigocin A analogues **5** and **6** have been prepared previously from D-glucal.[7] Structurally, these analogues differ from migrastatin and dorrigocin A in that they lack the glutarimide-containing side chain at C-13 and the methyl substituent at C-12. They contain a hydroxy group instead of a methyl group at C-10 with the opposite configuration to that found in the natural compounds. Herein, we report the synthesis of **4a**, macrolactam **4b** and acyclic dorrigocin A analogue **7** from the inexpensive D-xylose. Compound **4a** differs from **3a** in having a hydroxy substituent at C-10 instead of the methyl group; the stereochemistry is the same as in **3a**.

The retrosynthetic analysis (Scheme 1) revealed that macrolactone **4a** and dorrigocin A analogue **7** could be assembled from **8** and **9**, respectively. We envisaged that both **8** and **9** would be obtained from the aldehyde **10**; the reaction of **10** with an Ando phosphonate[10] would give **8**, whereas the reaction of **10** with the appropriate Wittig reagent[11] would give **9**. The aldehyde **10** was envisaged to be prepared from D-xylose.[12]

The synthesis began with the conversion of D-xylose into the key intermediate **10** (Scheme 2). The D-xylofuranoside derivative **11** was prepared in three steps. Hence the reaction of D-xylose with allyl alcohol in the presence of pyridinium *p*-toluenesulfonate to

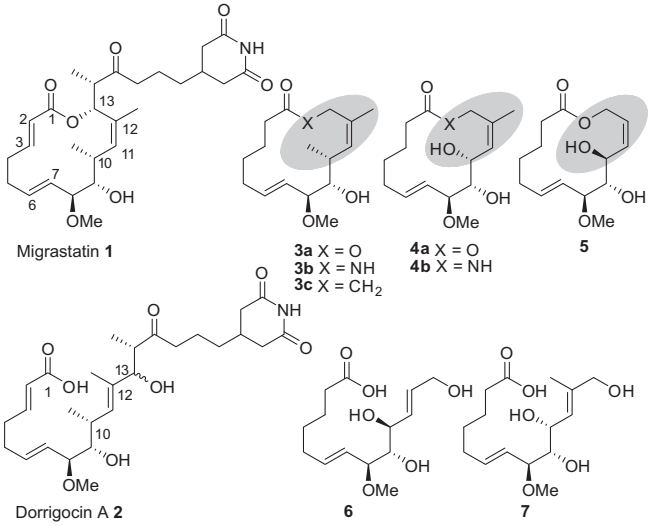

Figure 1. Structures of natural products **1**–**2** and synthetic analogues **3**–**7**.

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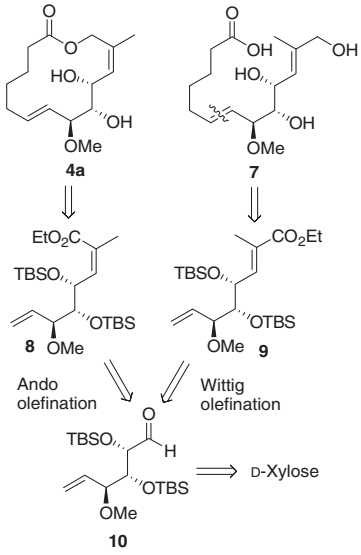
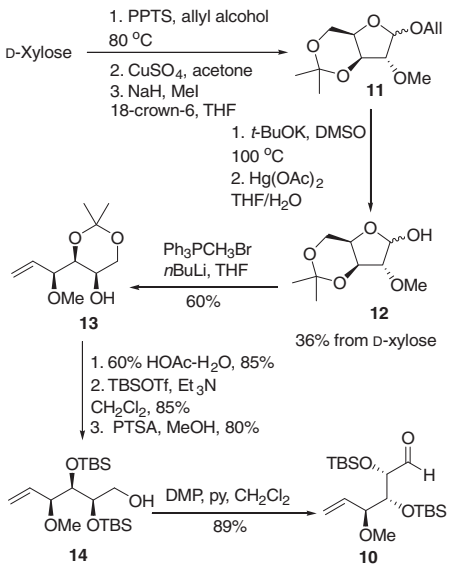
give an allyl xylofuranoside was followed by introduction of an isopropylidene group at C-3 and C-5,[13] and then methylation of the hydroxy group at C-2 to give **11**. The hemiacetal **12** was obtained from **11** (36% from D-xylose) by the removal of the allyl ether using the conditions reported by Gigg and Warren.[14] The reaction of **12** with the Wittig reagent obtained from the reaction of methyltriphenylphosphonium bromide with a base in anhydrous THF at −50 °C gave the olefin **13**. Removal of the acetonide gave a triol which when reacted with an excess of TBSOTf in the presence of a base gave a fully silylated intermediate. Subsequent regioselective removal of the TBS group at the primary position led to the formation of alcohol **14**. This alcohol was then converted into aldehyde **10** by Dess–Martin oxidation.

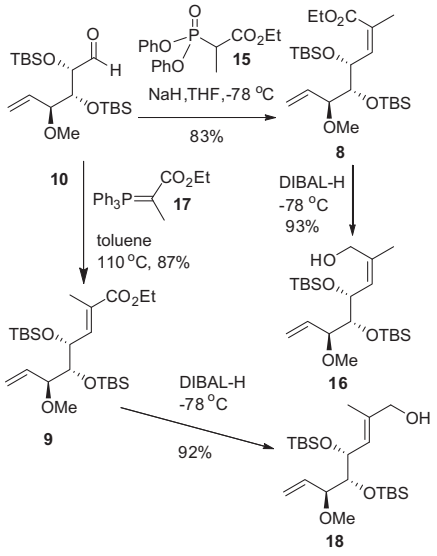
The conversion of **10** into the key intermediates **8** and **9** was next investigated (Scheme 3). Firstly, the aldehyde **10** was reacted with the Ando phosphonate **15**[8] in a variation of the Horner–Wadsworth–Emmons (HWE) olefination, which gave the trisubstituted alkene **8** as the major product. This reaction proceeded with acceptable *Z*-selectivity (*Z*:*E* = 92:8) and hence gave also a small amount of **9**. The mixture of isomers was then converted into a mixture of the allylic alcohols **16** and **18** using diisobutylaluminum hydride (DIBAL-H). In this mixture the ratio of **87**:**13** was 85:15 and it was difficult to separate these two isomers by chromatography. This problem was resolved during subsequent manipulations (Schemes 4 and 5). When the aldehyde **10** was treated with Wittig reagent **17**[9] the trisubstituted alkene derivative **9** was obtained as the major product (*E*:*Z* = 98:2). In this case, a small amount of the unreacted aldehyde **10** was difficult to separate from the alkene product, but purification was achieved after the reductive step. Hence reduction of **9** using DIBAL-H gave the allylic alcohol **18** in high yield.



Scheme 1. Retrosynthetic analysis of **4a** and **7**.



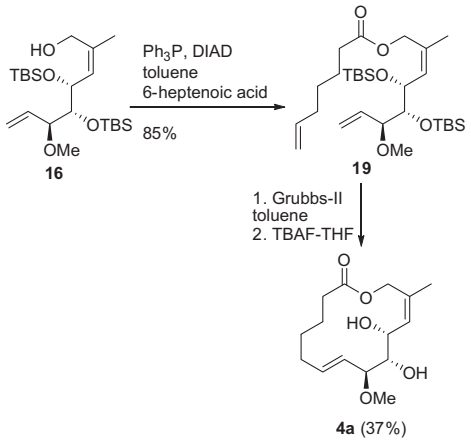
Scheme 2. Synthesis of **10**.



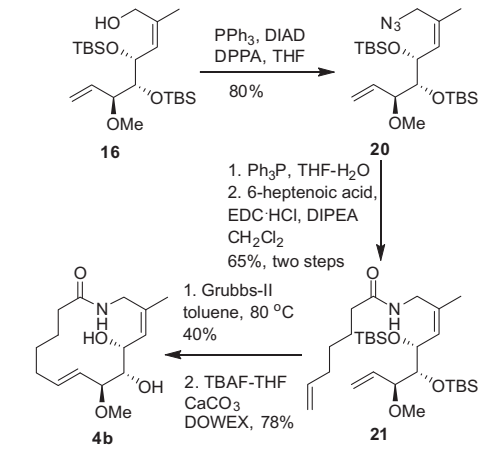
Scheme 3. Synthesis of alkenes **8**, **9**, **16** and **18**.

With **16** in hand the synthesis of **4a**[15] was then completed. Esterification with 6-heptenoic acid promoted by triphenylphosphine and diisopropyl azodicarboxylate gave **19**.[16] Stereoselective ring-closing metathesis[17] was then achieved using the Grubbs second generation catalyst and removal of the TBS groups gave **4a**.[18]

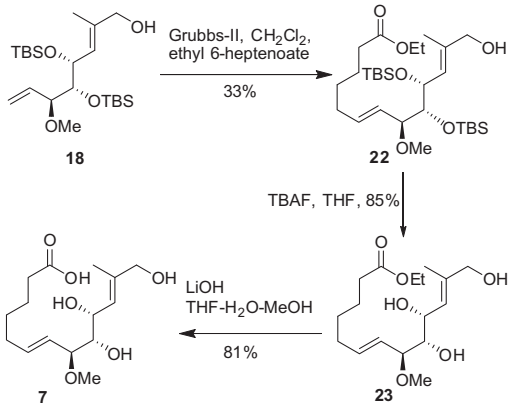
Next, the synthesis of the macrolactam **4b** was carried out. The reaction of **16** with diphenylphosphoryl azide in the presence of triphenylphosphine and diisopropyl azodicarboxylate (DIAD) led to the exchange of the free hydroxy group for an azide group and gave **20** in 80% yield (Scheme 5). The azide **20** was reduced via Staudinger reaction, and the resulting amine was coupled to 6-heptenoic acid using EDC in the presence of a base to give **21**



Scheme 4. Synthesis of migrastatin analogue **4a**.



Scheme 5. Synthesis of macrolactam **4b**.



Scheme 6. Synthesis of dorrigocin A analogue **7**.

(65% yield over two steps). The ring-closing metathesis of **21** in the presence of Grubbs second generation catalyst and the subsequent removal of the TBS groups using TBAF/THF, as recently described by Kaburagi and Kishi,[19] gave the macrolactam **4b**.

Finally, the preparation of the dorrigocin A analogue **7**[20] was achieved from **18**. The synthesis of the C1–C13 fragment of 2,3-dihydrodorrigocin A has been reported by Brazidec et al.[21] They sequentially employed the Julia–Kocienski coupling, an aldol addition and a Wittig reaction to introduce the desired alkenes and to achieve stereocontrol. Herein, we completed the preparation of a similar C1–C13 fragment using the primary alcohol **18**. Thus the cross metathesis[22] of **18** with both 6-heptenoic acid and ethyl 6-heptenoate was investigated, respectively. The reaction with the acid was unproductive but **22** was obtained (33%) from the ester (Scheme 6) using the Grubbs second generation catalyst in dichloromethane at 40 °C; the yield of **22** was low, but the starting compound **18** was also recovered in ~30% yield. Removal of the TBS-protecting groups using TBAF/THF (85%) and the subsequent saponification gave **7** (81%).

In conclusion, the synthesis of close structural analogues of migrastatin and dorrigocin A core structures has been achieved. D-Xylose was employed to generate an aldohexene intermediate with three stereocentres, with a similar stereochemical arrangement to that found in the natural products. The Ando and Wittig olefinations of this aldehyde were used to respectively prepare, in a stereocontrolled manner, the two trisubstituted alkene intermediates that were elaborated to macrolactone, macrolactam and acyclic target compounds, differing from the core structures by having a hydroxy group instead of a methyl group. The biological properties of these new agents are currently being investigated and will be reported in due course.

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Supplementary data

Supplementary data (selected NMR spectra for key intermediates and final compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.141.

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20. Analytical data for **7**: $[\alpha]_D$ +10.8 (c 0.66, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 5.81–5.70 (m, 2H), 5.51 (dd, 1H, J = 9.2 Hz, 1.3 Hz), 5.49–5.44 (m, 1H), 4.47 (dd, 1H, J = 9.2 Hz, 5.8 Hz), 3.96 (s, 2H), 3.59 (dd, 1H, J = 8.5 Hz, 4.3 Hz), 3.28 (t, 1H, J = 2.4 Hz), 3.21 (s, 3H), 2.20–2.10 (m, 4H), 3.45 (s, 3H), 1.64 (td, 2H, J = 15.2 Hz, 7.5 Hz), 1.47 (td, 2H, J = 14.7 Hz, 7.3 Hz); ^{13}C NMR (CD_3OD, 125 MHz): δ 182.4 (C), 139.7 (C), 137.4 (CH), 128.5 (CH), 125.6 (CH), 83.9 (CH), 78.7 (CH), 69.4 (CH), 68.2 (CH_2), 56.3 (CH_3), 38.8 (CH_2), 33.3 (CH_2), 30.4 (CH_2), 27.1 (CH_2), 14.2 (CH_3); ESI/MS- (m/z): 325.2 (M+Na)$^+$; HRMS-ESI: calcd for $C_{15}H_{26}O_6Na$ (M+Na)$^+$: 325.1627. Found: 325.1613.
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