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

Ying Zhou, Paul V. Murphy *

School of Chemistry, National University of Ireland, Galway, University Road, Galway, Ireland
Centre for Synthesis and Chemical Biology and School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland

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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

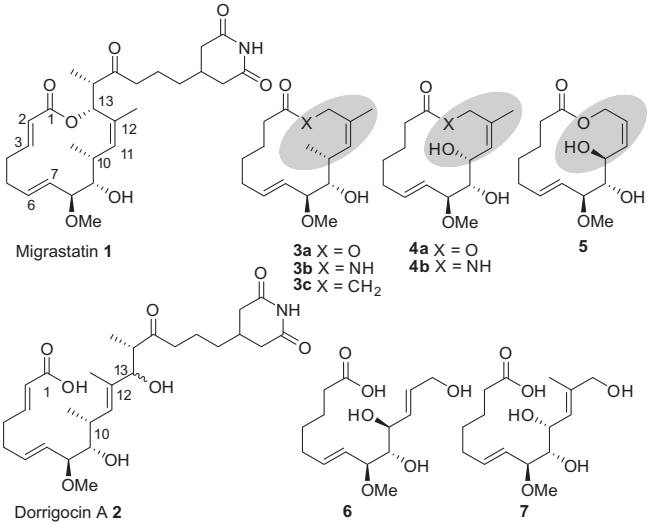

Figure 1. Structures of natural products **1**–**2** and synthetic analogues **3**–**7**.

* Corresponding author. Tel.: +353 91 492465; fax: +353 91 525700.
E-mail address: paul.v.murphy@nuigalway.ie (P.V. Murphy).

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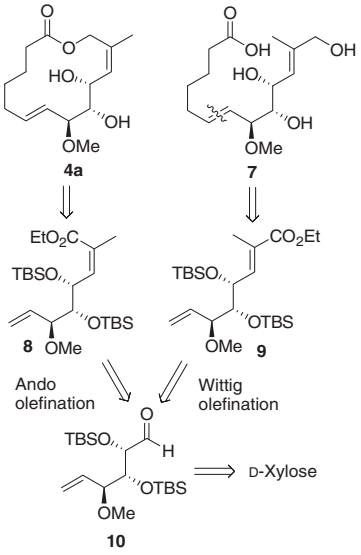
give an allyl xylofuranoside was followed by introduction of an isopropylidene group at C-3 and C-5,[13] and then methylation of the hydroxy group at C-2 to give **11**. The hemiacetal **12** was obtained from **11** (36% from D-xylose) by the removal of the allyl ether using the conditions reported 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.

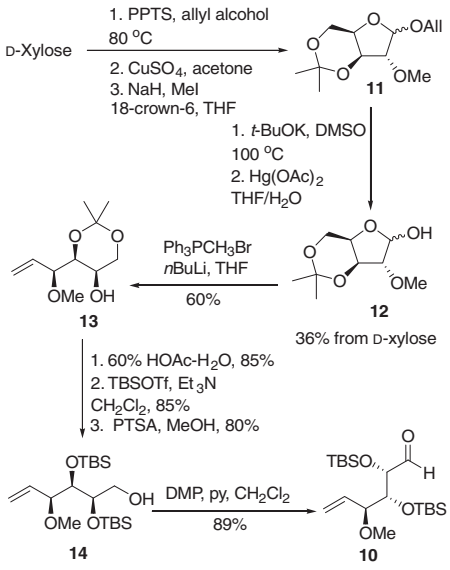
The conversion of **10** into the key intermediates **8** and **9** was next investigated (Scheme 3). Firstly, the aldehyde **10** was reacted with the Ando phosphonate **15**[8] in a variation of the Horner–Wadsworth–Emmons (HWE) olefination, which gave the trisubstituted alkene **8** as the major product. 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.

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]

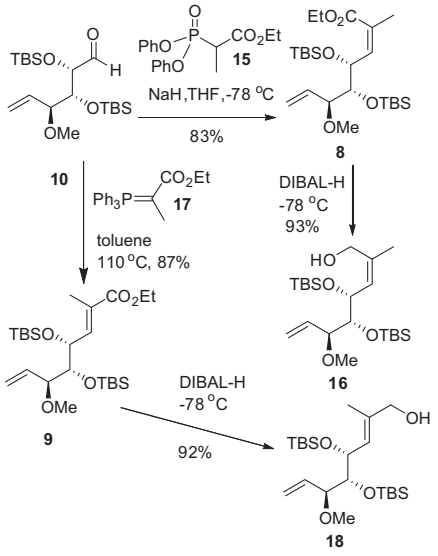
Next, the synthesis of the macrolactam **4b** was carried out. The reaction of **16** with diphenylphosphoryl azide in the presence of triphenylphosphine and diisopropyl azodicarboxylate (DIAD) led to the exchange of the free hydroxy group for an azide group and gave **20** in 80% yield (Scheme 5). The 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**



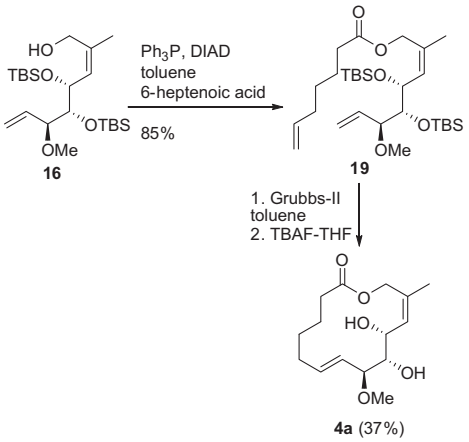
Scheme 1. Retrosynthetic analysis of **4a** and **7**.



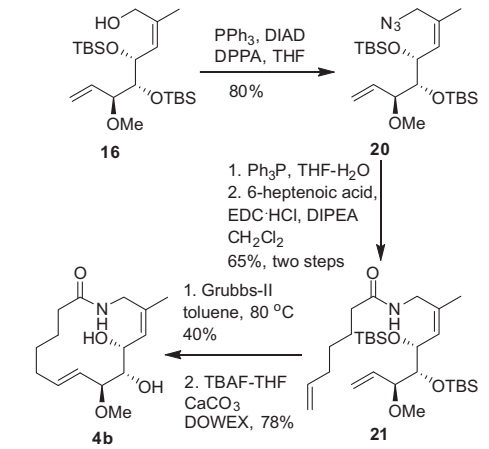
Scheme 2. Synthesis of **10**.



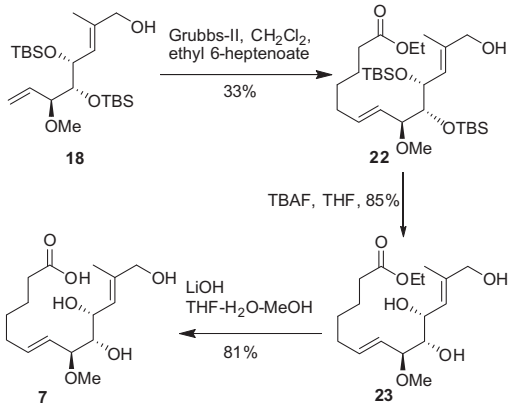
Scheme 3. Synthesis of alkenes **8**, **9**, **16** and **18**.



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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