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A short synthesis of the common dihydropyran segment of the antifungal agents ambruticin and jerangolid A

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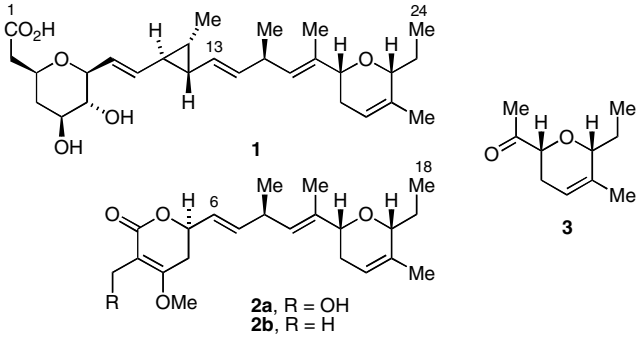
Abstract—The dihydropyranyl segment common to ambruticin and jerangolid A was prepared in six steps (31.7% yield) from (*S*)-2-benzyloxypropanal via silyloxydiene cyclocondensation, followed by C-glycosidation, and eventual epimerization at C18.

Ambruticin (**1**, Scheme 1) is a structurally unique carboxylic acid isolated from *Polyangium cellulosum var. fulvum*, which exhibits potent oral antifungal activity against *Coccidioides immitis*, *Histoplasma capsulatum* and *Blastomyces dermititidis*.[1] Extensive spectral analysis revealed that the structure of **1** consists of a tetrahydropyranyl ring, a dihydropyranyl ring and a divinylcyclopropane ring. More recently, the jerangolids A and D (**2a**,**b**), isolated from a strain of *Sorangium cellulosum* (So ce 307), were found to exhibit antifungal activity similar to that of **1**.[2] The structure of **2** from C6–C18 is identical with the C13–C24 segment of ambruticin, and similar antibiotic spectrum of **1** and **2** suggests that these segments are responsible for their biological activity. The complex array of diverse functionality present in **1** has generated considerable synthetic interest,[3] including total syntheses by the groups of Kende et al.,[4] Martin and co-workers,[5] Lee et al.[6] and Liu and Jacobsen.[7] To our knowledge, there are no reported syntheses of the jerangolids. As part of our interest in the preparation of *C*-glycosides,[8] we herein report the enantioselective preparation of the common dihydropyranyl segment **3**, an intermediate in the Martin synthesis of **1**.[5]



Scheme 1.

Construction and elaboration of the oxane ring was envisioned by means of a Lewis acid catalyzed diene–aldehyde cyclocondensation reaction,[9] followed by a C-glycosidation of the derived pseudoglycal. Since C-glycosidation generally proceeds via axial attack on an oxonium ion to afford *trans*-2,6-disubstituted pyrans, it was anticipated that a subsequent epimerization at C18 (ambruticin numbering) would be necessary to generate the desired *cis*-18,22 relative stereochemistry. To this end, reaction of 2(*S*)-benzyloxypropanal (**4**)[10] with 1-methoxy-2-methyl-3-(trimethylsiloxy)-1,3-butadiene (**5**)[11] in the presence of BF_3-etherate, followed by work-up with TFA gave an inseparable mixture of diastereomeric dihydropyrones **6** and **7** (Scheme 2). The relative stereochemistry of **6** and **7** was assigned on the basis of their ^{1}H NMR spectral data.[12] In particular, the signals for H17 and $H19_{eq}$ (ambruticin numbering) of **6** (δ 3.69 and 2.36 ppm, respectively), appear upfield of the corresponding signals for **7** (δ 3.81 and 2.56 ppm, respectively). These relative chemical shifts are quite characteristic of diastereomeric dihydropyrones with an α-alkoxy group.[13] Cyclocondensation of **4** with **5** in the presence of $MgBr_2$, followed by work-up with

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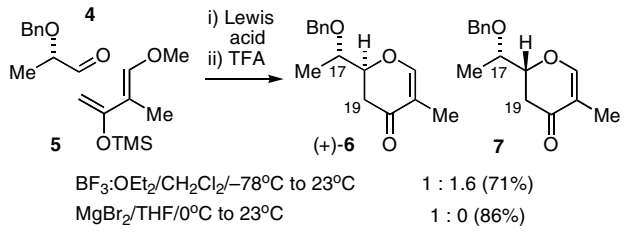
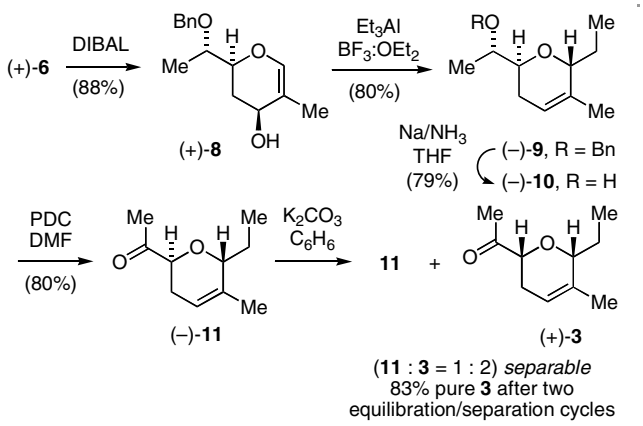


Scheme 2.

TFA gave only dihydropyrone (+)-**6**. The *S* configuration at C18 (ambruticin numbering) of **6** is the result of approach of the diene in an *exo* sense on the less hindered face of the Mg^{2+} chelated form of optically active aldehyde **4**.

Reduction of **6** gave the pseudoglycal (+)-**8** as a single diastereomer (Scheme 3). We[8a] and others[14] have reported that the reaction of glycals with trialkylaluminium reagents is useful for the preparation of *C*-alkyl glycosides. To this end, treatment of pseudoglycal **8** with the weak nucleophile triethylaluminium, in the presence of boron trifluoride etherate, gave a mixture of *trans*- and *cis*-dihydropyrans (8:1 ratio). The major product arises via axial attack of the weak nucleophile on the cyclic oxonium ion generated by ionization of **8**. The pure *trans*-isomer, (−)-**9**, was obtained in good yield after column chromatography. Removal of the benzyl protecting group, followed by oxidation gave (−)-**11**.[15] Base-catalyzed epimerization of the *trans*-ketone, in benzene, gave a separable mixture of (−)-**11** and (+)-**3** (1:2 ratio).[16] Two equilibration/separation cycles gave pure (+)-**3** in 83% combined yield. The NMR spectral data obtained for **3** was identical with that previously reported.[5]

In summary, the synthesis of the dihydropyranyl segment (**3**), common to ambruticin and the jerangolids, from optically active aldehyde **4**, was accomplished in six steps (31.7% overall yield). The length and yield of our synthetic route is competitive with that reported by Martin and co-workers.[5]



Scheme 3.

Acknowledgements

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12. Compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 6H), 4.70 (d, J = 11.7 Hz, 1H), 4.53 (d, J = 11.7 Hz, 1H), 4.34 (ddd, J = 14.7, 3.8, 3.6 Hz, 1H), 3.69 (qd, J = 6.5, 4.7 Hz, 1H), 2.79 (dd, J = 16.4, 14.7 Hz, 1H), 2.36 (dd, J = 16.7, 3.2 Hz, 1H), 1.68 (d, J = 1.2 Hz, 3H), 1.30

(d, J = 6.5 Hz, 3H). Compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.27 (m, 6H), 4.67 (d, J = 11.7 Hz, 1H), 4.59 (d, J = 12.0 Hz, 1H), 4.33 (ddd, J = 14.4, 3.8, 3.8 Hz, 1H), 3.81 (qd, J = 6.5, 4.1 Hz, 1H), 2.68 (dd, J = 16.7, 14.4 Hz, 1H), 2.56 (dd, J = 16.7, 3.5 Hz, 1H), 1.70 (d, J = 1.2 Hz, 3H), 1.27 (d, J = 6.5 Hz, 3H).

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15. Compound **11**: $[\alpha]_D^{23}$ −129.2 (c 0.3320, $CHCl_3$); IR (neat): 2967, 2934, 2876, 1717, 1453, 1355, 1120, 1053, 924 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.49 (ddd, J = 6.2, 3.5, 1.8 Hz, 1H), 4.06 (dd, J = 7.9, 5.9 Hz, 1H), 4.00 (br d, J = 9.7 Hz, 1H), 2.24 (s, 3H), 2.22–2.14 (m, 2H), 1.70 (s, 3H), 1.74–1.49 (m, 2H), 1.02 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.6, 136.0, 118.1, 78.1, 73.3, 26.8, 26.2, 24.7, 20.1, 10.7; EI-HRMS m/z 168.1150 (calcd for $C_{10}H_{16}O_2$ m/z 168.1136). Compound **3**: $[\alpha]_D^{23}$ +172 (c 0.248, $CHCl_3$); IR (neat): 2966, 2936, 2879, 1721, 1435, 1352, 1229, 1116, 1058, 927 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.60–5.33 (m, 1H), 4.13–4.05 (m, 1H), 3.92 (dd, J = 10.4, 4.4 Hz, 1H), 2.25 (s, 3H), 2.21–2.00 (m, 2H), 1.81 (ddq, J = 14.9, 10.9, 3.5 Hz, 1H), 1.60 (ddd, J = 2.4, 2.4, 1.4 Hz, 3H), 1.54 (ddq, J = 14.1, 7.0, 7.0 Hz, 1H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.0, 135.7, 119.7, 79.0, 78.5, 27.6, 26.1, 25.9, 19.2, 9.0.
16. Notably, ab initio calculations (6-31G* basis set) of the two stereoisomers indicated that the *cis*-isomer (**3**) is 0.77 kcal mol^{-1} lower in energy compared to the *trans*-isomer (**11**).