

Marquette University

e-Publications@Marquette

Chemistry Faculty Research and Publications

Chemistry, Department of

8-2005

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

Julie Lukesh
Marquette University

William Donaldson
Marquette University, william.donaldson@marquette.edu

Follow this and additional works at: https://epublications.marquette.edu/chem_fac

 Part of the [Chemistry Commons](#)

Recommended Citation

Lukesh, Julie and Donaldson, William, "A short synthesis of the common dihydropyran segment of the antifungal agents ambruticin and jerangolid A" (2005). *Chemistry Faculty Research and Publications*. 58. https://epublications.marquette.edu/chem_fac/58

Marquette University

e-Publications@Marquette

Chemistry Faculty Research and Publications/College of Arts and Sciences

This paper is NOT THE PUBLISHED VERSION; but the author's final, peer-reviewed manuscript. The published version may be accessed by following the link in the citation below.

Tetrahedron Letters, Vol. 46, No. 33 (August 15, 2005): 5529-5531. [DOI](#). This article is © Elsevier and permission has been granted for this version to appear in [e-Publications@Marquette](#). Elsevier does not grant permission for this article to be further copied/distributed or hosted elsewhere without the express permission from Elsevier.

A Short Synthesis of The Common Dihydropyran Segment of The Antifungal Agents Ambruticin and Jerangolid A

Julie M. Lukesh

Department of Chemistry, Marquette University, Milwaukee, WI

William A. Donaldson

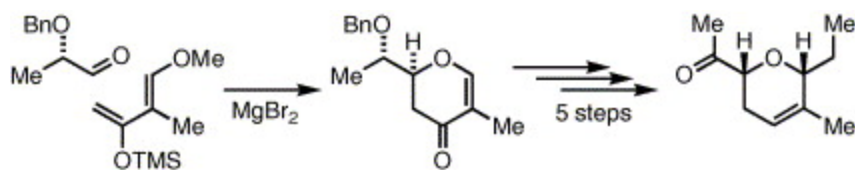
Department of Chemistry, Marquette University, Milwaukee, WI

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.

Graphical abstract

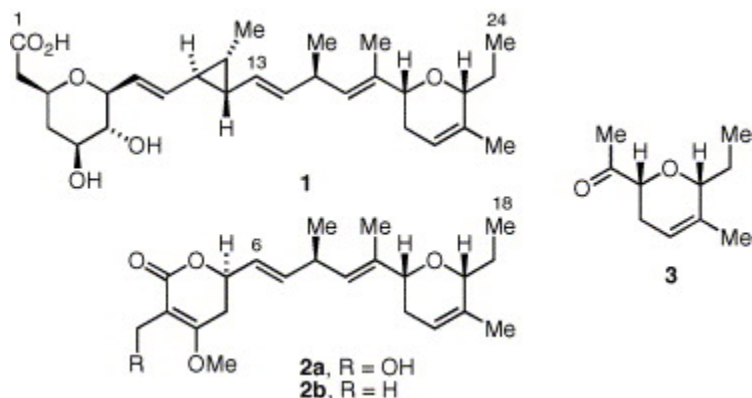
The title segment was prepared in six steps, 31.7% yield from (S)-2-benzyloxypropanal.



Keywords

Hetero-Diels–Alder cycloaddition, C-glycosidation

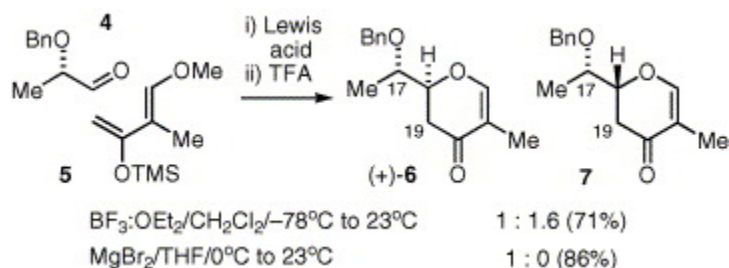
Ambruticin (**1**, Scheme 1) is a structurally unique carboxylic acid isolated from *Polyangium cellulosum* var. *fulvum*, which exhibits potent oral antifungal activity against *Coccidioides immitis*, *Histoplasma capsulatum* and *Blastomyces dermatitidis*.¹ Extensive spectral analysis revealed that the structure of **1** consists of a tetrahydropyran ring, a dihydropyran 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 dihydropyran ring segment **3**, an intermediate in the Martin synthesis of **1**.⁵



Scheme 1.

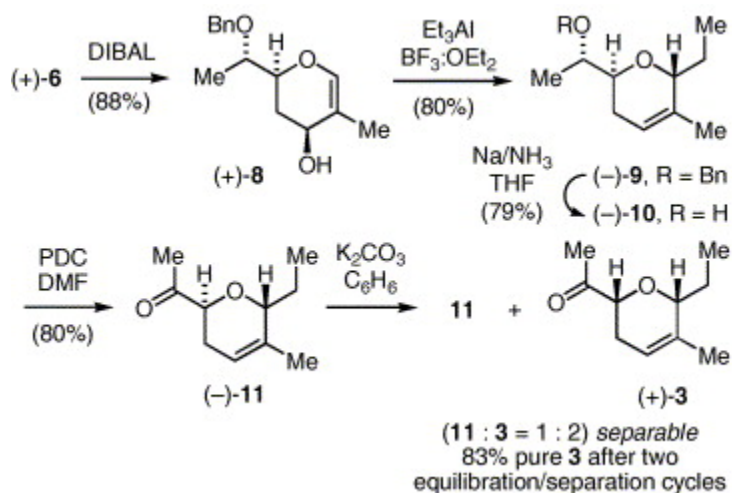
Construction and elaboration of the oxane ring was envisioned by means of a Lewis acid catalyzed diene–aldehyde cyclocondensation reaction,⁹ followed by a C-glycosidation of the derived pseudoglycal. Since C-glycosidation generally proceeds via axial attack on an oxonium ion to afford *trans*-2,6-disubstituted 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-(trimethylsilyloxy)-1,3-butadiene (**5**)¹¹ in the presence of BF₃–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 ¹H 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 MgBr₂, followed by work-up with 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 Mg²⁺ chelated form of optically active aldehyde **4**.



Scheme 2.

Reduction of **6** gave the pseudoglycal (+)-**8** as a single diastereomer (Scheme 3). We^{8a} and others¹⁴ have reported that the reaction of glycols with trialkylaluminum reagents is useful for the preparation of C-alkyl glycosides. To this end, treatment of pseudoglycal **8** with the weak nucleophile triethylaluminum, 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



Scheme 3.

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

Acknowledgements

Partial financial support for this research was provided by the Department of Education (P200A000228), and the Marquette University Graduate School Committee on Research. High resolution mass spectral data were obtained at the Washington University Resource for Mass Spectrometry.

References and notes

- 1 D.T. Connor, R.C. Greenough, M. von Strandtmann, *J. Org. Chem.*, 42 (1977), pp. 3664-3669
- 2 K. Gerth, P. Washausen, G. Höftle, H. Irschik, H. Reichenbach, *J. Antibiot.*, 49 (1996), pp. 71-75
- 3 (a) For other synthetic studies of ambruticin, see:
N.J. Barnes, A.H. Davidson, L.R. Hughes, G. Procter, V. Rajcoomar, *Tetrahedron Lett.*, 22 (1981), pp. 1751-1754 (b) N.J. Barnes, A.H. Davidson, L.R. Hughes, G. Procter, *J. Chem. Soc., Chem. Commun.* (1985), pp. 1292-1294 (c) G. Procter, A.T. Russell, P.J. Murphy, P.J. Tan, A.N. Mather, *Tetrahedron*, 44 (1988), pp. 3953-3973 (d) A.H. Davidson, N. Eggleton, I.H. Wallace, *J. Chem. Soc., Chem. Commun.* (1991), pp. 378-380 (e) I.E. Marko, D.J. Bayston, *Tetrahedron*, 50 (1994), pp. 7141-7156 (f) I.E. Marko, D.J. Bayston, *Synthesis* (1996), pp. 297-304 (g) H. Wakamatsu, N. Isono, M. Mori, *J. Org. Chem.*, 62 (1997), pp. 8917-8922 (h) P. Varelis, B.L. Johnson, *Aust. J. Chem.*, 59 (1997), pp. 43-51 (i) V. Michelet, K. Adiey, B. Bulic, J.-P. Genet, G. Dujardin, S. Rossignol, E. Brown, L. Toupet, *Eur. J. Org. Chem.* (1999), pp. 2885-2892 (j) J. Yin, I. Llorente, L.A. Villanueva, L.S. Liebeskind, *J. Am. Chem. Soc.*, 122 (2000), pp. 10458-10459 (k) I.E. Marko, T. Kumamoto, T. Giard, *Adv. Synth. Catal.* (2002), pp. 1063-1067 (l) V. Michelet, K. Adiey, S. Tanier, G. Dujardin, J.-P. Genet, *Eur. J. Org. Chem.* (2003), pp. 2947-2958
- 4 (a) A.S. Kende, J.S. Mendoza, Y. Fujii, *J. Am. Chem. Soc.*, 112 (1990), pp. 9645-9646 (b) A.S. Kende, J.S. Mendoza, Y. Fujii, *Tetrahedron*, 49 (1993), pp. 8015-8038
- 5 (a) T.A. Kirkland, J. Colucci, L.S. Geraci, M.A. Marx, M. Schneider, D.E. Kaelin Jr., S.F. Martin, *J. Am. Chem. Soc.*, 123 (2001), p. 12432 (b) S.M. Beberich, R.J. Cherney, J. Colucci, C. Courillon, L.S. Geraci, T.A. Kirkland, M.A. Marx, M. Schneider, S. F. Martin, *Tetrahedron*, 59 (2003), pp. 6819-6832
- 6 E. Lee, S.J. Choi, H. Kim, H.O. Han, Y.K. Kim, S.J. Min, S.H. Son, S.M. Lim, W.S. Jang, *Angew. Chem., Int. Ed.*, 41 (2002), pp. 176-177
- 7 P. Liu, E.N. Jacobsen, *J. Am. Chem. Soc.*, 123 (2001), pp. 10772-10773
- 8 (a) J.M. Lukesh, W.A. Donaldson, *Tetrahedron: Asymmetry*, 14 (2003), pp. 757-762 (b) P.B. Greer, W.A. Donaldson, *Tetrahedron*, 58 (2002), pp. 6009-6018 (c) L. Liu, W.A. Donaldson, *Synlett* (1996), pp. 103-104
- 9 (a) S. Danishefsky, M.T. Bilodeau, *Angew. Chem., Int. Ed. Engl.*, 35 (1996), pp. 1380-1419 (b) S.J. Danishefsky, *Aldrichim. Acta*, 19 (1986), pp. 59-69
- 10 D. Enders, S. von Berg, B. Jandeleit, *Org. Synth.*, 78 (2002), pp. 177-188
- 11 S. Danishefsky, C.F. Yan, R.K. Singh, R.B. Gammill, P.M. McCurry, N. Fritsh, J. Clardy, *J. Am. Chem. Soc.*, 101 (1979), pp. 7001-7008
- 12 Compound **6**: ^1H 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**: ^1H 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).
- 13 S.J. Danishefsky, W.H. Pearson, D.F. Harvey, C.J. Maring, J.P. Springer, *J. Am. Chem. Soc.*, 107 (1985), pp. 1256-1268
- 14 (a) K. Maruoka, K. Nonoshita, T. Itoh, H. Yamamoto, *Chem. Lett.* (1987), pp. 2215-2216 (b) P.P. Deshpande, K.N. Price, D.C. Baker, *J. Org. Chem.*, 61 (1996), pp. 455-458
- 15 Compound **11**: $[\alpha]_{\text{D}23}$ –129.2 (c 0.3320, CHCl_3); IR (neat): 2967, 2934, 2876, 1717, 1453, 1355, 1120, 1053, 924 cm^{-1} ; ^1H 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): $\delta = 209.6, 136.0, 118.1, 78.1, 73.3, 26.8, 26.2, 24.7, 20.1, 10.7$; EI-HRMS m/z 168.1150 (calcd for $\text{C}_{10}\text{H}_{16}\text{O}_2$ m/z 168.1136). Compound **3**: $[\alpha]_{\text{D}23} +172$ (c 0.248, CHCl_3); IR (neat): 2966, 2936, 2879, 1721, 1435, 1352, 1229, 1116, 1058, 927 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): $\delta = 5.60\text{--}5.33$ (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): $\delta = 210.0, 135.7, 119.7, 79.0, 78.5, 27.6, 26.1, 25.9, 19.2, 9.0$.

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**).