Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 4847–4850
Tetrahedron Letters

Synthesis of the C_1–C_{27} portion of the aplyronines

Michael A. Calter* and Jianguang Zhou

Department of Chemistry, University of Rochester, Rochester, NY 14627-0216, USA

Received 22 January 2004; accepted 28 April 2004

Abstract—This manuscript describes the use of the *anti*,*anti*-diastereoselective aldol reaction of an efficiently generated dipropionate equivalent to construct the C_5–C_{14}-portion of the aplyronines. This portion was then coupled with a compound corresponding to C_{15}–C_{20} of the targets. Further elaboration and an additional coupling led to an intermediate containing C_1–C_{27} with appropriate stereochemistry and functionalization for eventual conversion into the aplyronines.

The aplyronine family of polyketide natural products contains three members (Fig. 1).[1] These compounds share a common carbon skeleton, including a twenty-four-membered macrolactone, but differ in the position of various aminoesters. Aplyronine A exhibits sub-nanomolar activity toward a variety of cancer lines. This activity perhaps stems from the ability of these molecules to depolymerize actin filaments.[2]

One total synthesis of a member of the aplyronine family has appeared, [3] along with several subunit syntheses.[4] We recently reported the preparation of the aplyronine C_{21}–C_{34} subunit starting with methylketene dimer **1**.[5] As **1** is available from propionyl chloride in one step via asymmetric catalysis, we hoped to use this synthon in the synthesis of the remaining propionate portions of the aplyronine skeleton.[6] We recently discovered that ketoester **2**, derived from **1** in two simple steps, selectively affords the *anti*,*anti*-dipropionate aldol product under appropriate conditions (Scheme 1).[7] We realized that this aldol adduct possessed the stereochemical relationships necessary for the synthesis of the C_7–C_{10}-dipropionate portion of the aplyronine, and therefore we initiated a synthesis of a C_5–C_{14}-precursor. We report here the completion of this synthesis, along

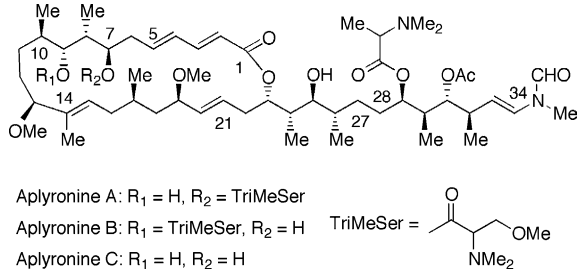
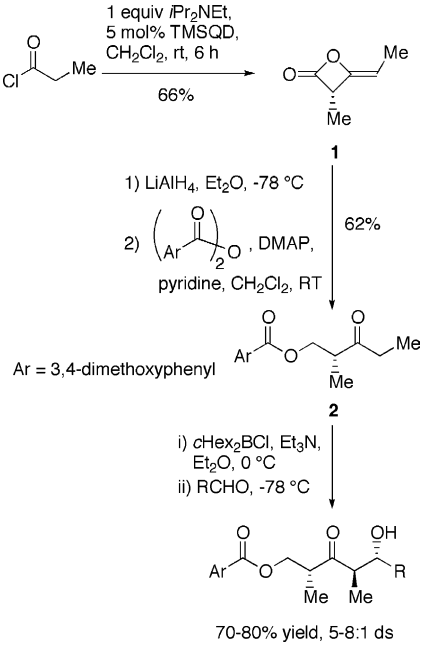


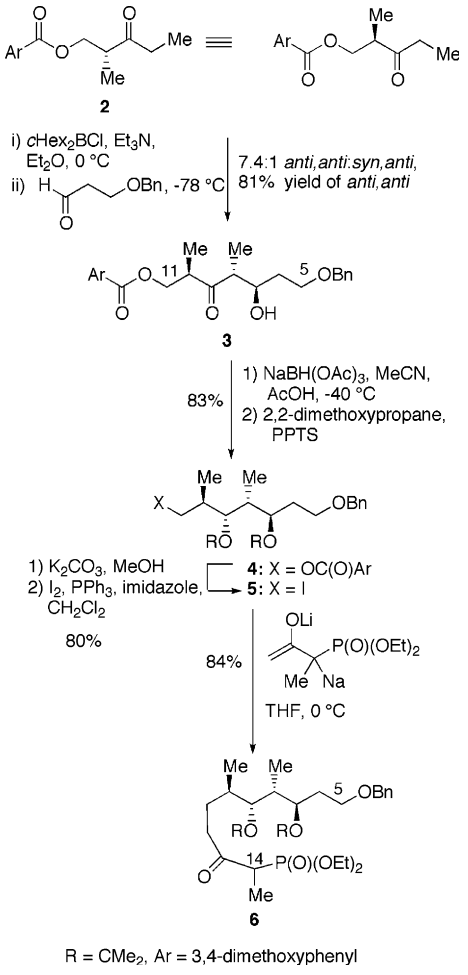
Figure 1. The aplyronines.



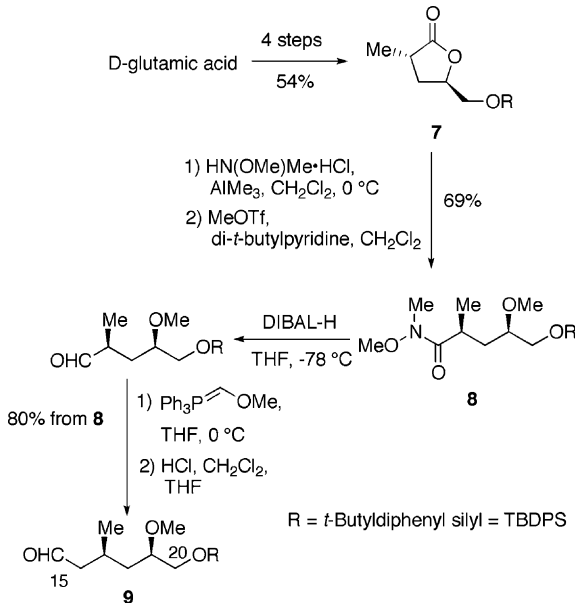
Scheme 1.

* Corresponding author. Tel.: +1-585-275-1626; fax: +1-585-506-0205;
e-mail: calter@chem.rochester.edu

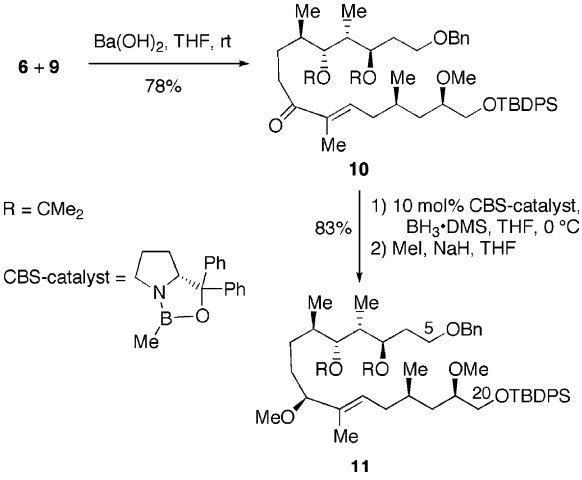
0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.04.159



Scheme 2.



Scheme 3.



Scheme 4.

with coupling of the newly synthesized precursor to other subunits to yield an intermediate containing C_1–C_{27} of the aplyronines.

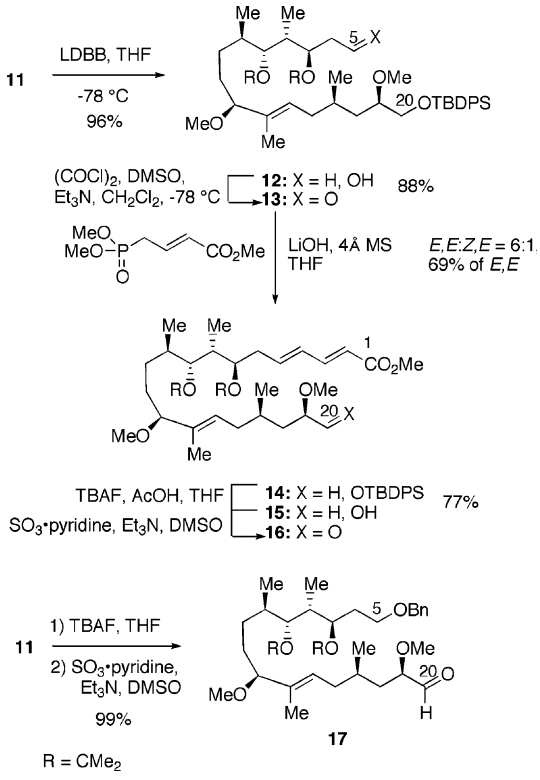
Our synthesis of the C_5–C_{14}-precursor began with the *anti*,*anti*-aldol adduct **3** (Scheme 2).[8] *anti*-Reduction of **3**, followed by ketalization, afforded acetonide **4**. Ester hydrolysis and iodination afforded iodide **5**.[9] Finally, the use of **5** to alkylate a phosphonate dianion yielded C_5–C_{14}-precursor **6**.[10]

We next prepared a C_{15}–C_{20}-precursor beginning with known lactone **7**, available in four steps and 54% overall yield from D-glutamic acid (Scheme 3).[11] Opening of the lactone to the Weinreb amide,[12] followed by methylation, gave methyl ether **8**.[13] Reduction of the amide, Wittig reaction of the resulting aldehyde, and hydrolysis gave aldehyde **9**.

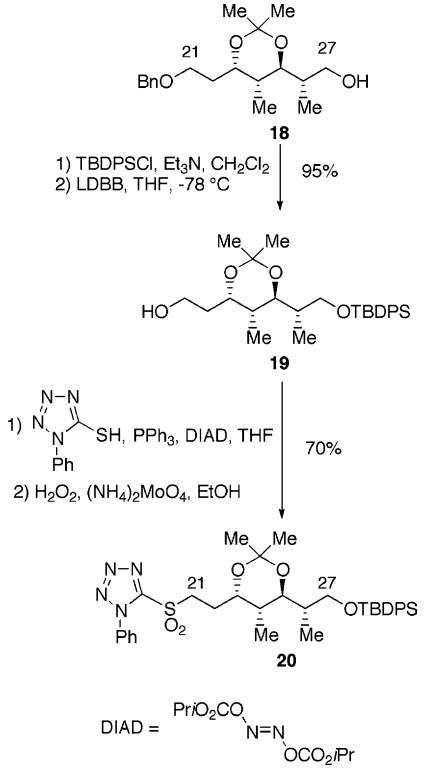
Our assembly of **6** and **9** into a C_5–C_{20}-precursor proceeded in a similar fashion to that used by Paterson et al. (Scheme 4).[4d] Horner–Wadsworth–Emmons reaction of **6** with **9** yielded enone **10**. Corey–Itsuno reduction[14] and methylation afforded the C_5–C_{20}-precursor **11**.

We next converted **11** into two electrophiles suitable for coupling to the remaining portion of the aplyronines (Scheme 5). Reduction of **11** with lithium 4,4′-di-*t*-butylbiphenylate (LDBB) accomplished deprotection of the C_5-hydroxyl.[15] Several hydrogenation-based conditions for benzyl ether removal either failed to afford any reaction or also led to significant hydrogenation of the alkene. Oxidation of primary alcohol **12**,[16] followed by reaction with an allylic phosphonate,[17] led to formation of *E*,*E*-dienoate **14** in moderate yield. Although removal of the silyl group under standard conditions led to extensive decomposition, the use of 'buffered' TBAF led to clean desilylation.[18] Oxidation of the resulting primary alcohol yielded aldehyde **16**,[19] corresponding to C_1–C_{20}. We also prepared C_5–C_{20} equivalent **17** by desilylation of **11**, followed by oxidation.

We next prepared a C_{21}–C_{27}-precursor, starting with primary alcohol **18** (Scheme 6). We had previously reported the preparation of **18** from the enantiomer of **1**

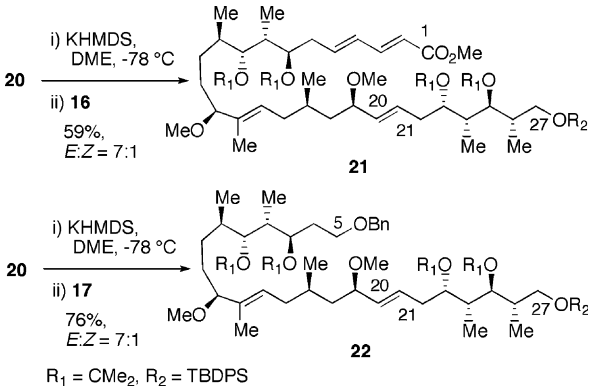


Scheme 5.



Scheme 6.

in four steps and 31% overall yield.[5] Silylation, debenzyla-tion, and installation of the tetrazole sulfone converted **18** into sulfone **20**.[20]



Scheme 7.

Sulfone **20** was then coupled to both **16** and **17** (Scheme 7). We confirmed the result of Kocienski and co-workers that the stereoselectivity of this type of reaction depended moderately on solvent, with the reaction in dimethoxyethane (DME) giving higher *E*-selectivity than the one in THF.[21] Compound **16** reacted in slightly lower yield **17**, perhaps reflecting some lability of the dienoate. However, the convergency gained by incorporation of the dienoate into the coupling partner more than outweighs the slightly lower yield.

In summary, we have prepared intermediate **21**, corresponding to C_1–C_{27} of the aplyronines. We assembled this compound in an efficient manner by coupling of C_1–C_{20}-aldehyde **16** with C_{21}–C_{27}-sulfone **20**. This synthesis benefited from the ready availability of dipropionate equivalents for the dimerization of methylketene. We are currently exploring removal of the acetonide and methyl ester protecting groups from **21** as a prelude to macrolactonization. We are also preparing a fully homologated sulfone for synthesis of the full carbon skeleton of the aplyronines.

Acknowledgements

We thank the NIH for support of this work.

References and notes

1. Yamada, K.; Ojika, M.; Ishigaki, T.; Yoshida, Y.; Ekimoto, H.; Arakawa, M. *J. Am. Chem. Soc.* **1993**, *115*, 11020–11021.
2. Saito, S.-y.; Watabe, S.; Ozaki, H.; Kigoshi, H.; Yamada, K.; Fusetani, N.; Karaki, H. *J. Biochem.* **1996**, *120*, 552–555.
3. Kigoshi, H.; Ojika, M.; Ishigaki, T.; Suenga, K.; Mutou, T.; Sakakura, A.; Ogawa, T.; Yamada, K. *J. Am. Chem. Soc.* **1994**, *116*, 7443–7444.
4. (a) Paterson, I.; Cowden, C. J.; Woodrow, M. D. *Tetrahedron Lett.* **1998**, *39*, 6037–6040; (b) Paterson, I.; Cowden, C. J.; Woodrow, M. D. *Tetrahedron Lett.* **1998**, *39*, 6041–6044; (c) Marshall, J. A.; Johns, B. A. *J. Org.*

Chem. **2000**, *65*, 1501–1510; (d) Paterson, I.; Blakely, S. B.; Cowden, C. J. *Tetrahedron Lett.* **2002**, *43*, 6005–6008.
5. Calter, M. A.; Guo, X. *Tetrahedron* **2002**, *58*, 7093–7100.
6. Calter, M. A.; Orr, R. K.; Song, W. *Org. Lett.* **2003**, *5*, 4745–4748.
7. Calter, M. A.; Song, W.; Zhou, J. *J. Org. Chem.*, **2004**, *69*, 1270–1275.
8. All new compounds gave satisfactory analytical and spectral data.
9. Hu, T.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 9229–9230.
10. Clark, R. D.; Kozar, L. G.; Heathcock, C. H. *Synthesis* **1975**, 635–636.
11. (a) Stone, K. J.; Little, D. R. *J. Am. Chem. Soc.* **1985**, *107*, 2495–2505; (b) Harmange, J.-C.; Figadere, B.; Hocquemiller, R. *Tetrahedron: Asymmetry* **1991**, *2*, 347–350; (c) Beach, J. W.; Kim, H. O.; Jeong, L. S.; Nampalli, S.; Islam, Q.; Ahn, S. K.; Babu, J. R.; Chu, C. K. *J. Org. Chem.* **1992**, *57*, 3887–3894; (d) Hanessian, S.; Roy, P. J.; Petrini, M.; Hodges, P. J.; Di Fabio, R.; Carganico, G. *J. Org. Chem.* **1990**, *55*, 5766–5777.
12. (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171–4172; (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989–993.
13. Ireland, R. E.; Gleason, J. L.; Gegnas, L. D.; Highsmith, T. K. *J. Org. Chem.* **1996**, *61*, 6856–6872.
14. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926.
15. Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924–1930.
16. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660.
17. Tufariello, J. J.; Dyszlewski, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, *15*, 1138–1140.
18. Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935–3948.
19. Parikh, J. R.; v. E. Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.
20. (a) Mitsunobu, O. *Synthesis* **1981**, 1–28; (b) Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963**, *28*, 1140–1142.
21. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28.