

Enantioselective Synthesis of 10-*epi*-Anamarine via an Iterative Dihydroxylation Sequence

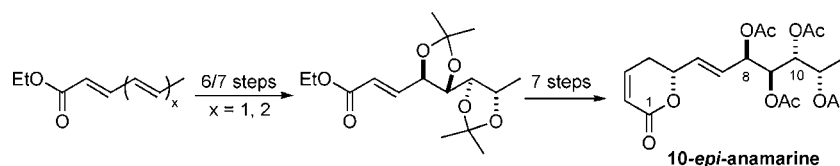
Dong Gao and George A. O'Doherty*

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506

george.odoherty@mail.wvu.edu

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ABSTRACT



The enantioselective syntheses of 10-*epi*-anamarine and 5,10-*epi,epi*-anamarine have been achieved in 13 to 14 steps. The route relies upon an enantio- and regioselective Sharpless dihydroxylation of either dienoates or trienoates to establish the C-8 to C-11 stereochemistry. A diastereoselective Leighton allylation established the desired C-5 stereochemistry. The route also relies upon a ring-closing metathesis to establish the α,β -unsaturated lactones.

Anamarine (**1**)¹ is a member of a growing class of polyacetate/pyranone-containing natural products, which display a broad spectrum of biological activity. Other examples of this class of natural products include spicigerolide (**2**),^{1b} hyptolide (**3**),^{1c} and synrotolide (**4**)^{1d} (Figure 1). All of these α,β -

shown significant medicinal properties.² This array of properties ranges from cytotoxicity against human tumor cells to antibacterial and/or antifungal activity.

Due to their interesting biological activities, several synthetic approaches to this class of molecules have been reported.³ All of the previous syntheses derived their absolute and relative stereochemistry from carbohydrate-based starting materials.³ In contrast, we were interested in the possibility of preparing various stereoisomers of anamarine via asymmetric catalysis.⁴ Recently, we⁵ and others⁶ have demonstrated that the selective oxidation/hydration of polyenoates

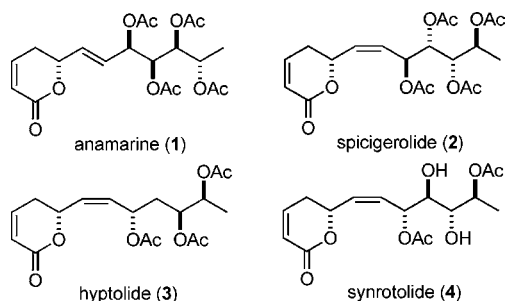


Figure 1. Anamarine-type pyranone polyacetates.

unsaturated lactones were isolated from the leaves and flowers of an unclassified *Hyptis* species and other botanically related genera. In addition, the common structural features of the members of this class of compounds have

(1) (a) Alemany, A.; Marquez, C.; Pascual, C.; Valverde, S.; Martinez-Ripoll, M.; Fayos, J.; Perales, A. *Tetrahedron Lett.* **1979**, 20, 3583–3586. (b) Pereda-Miranda, R.; Fragoso-Serrano, M.; Cerda-Garcia-Rojas, C. M. *Tetrahedron* **2001**, 57, 47–53. (c) Achmad, S. A.; Hoyer, T.; Kjaer, A.; Makmur, L.; Norrestam, R. *Acta Chem. Scand.* **1987**, 41B, 599–609. (d) Coleman, M. T. D.; English, R. B.; Rivett, D. E. A. *Phytochemistry* **1987**, 26, 1497–1499.

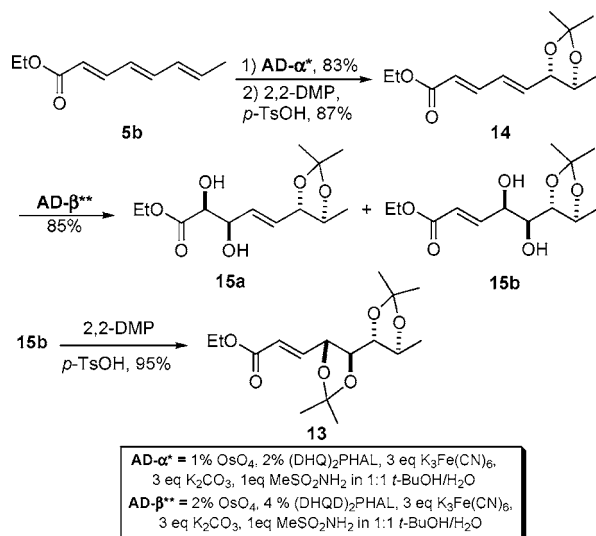
(2) (a) Pereda-Miranda, R.; Fragoso-Serrano, M.; Cerda-Garcia-Rojas, C. M. *Tetrahedron* **2001**, 57, 47–53. (b) Pereda-Miranda, R.; Hernandez, L.; Villavicencio, M. J.; Novelo, M.; Ibarra, P.; Chai, H.; Pezzuto, J. M. *J. Nat. Prod.* **1993**, 56, 583–593.

(3) (a) Diaz-Oltra, S.; Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2004**, 60, 2979–2985. (b) Falomir, E.; Murga, J.; Ruiz, P.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2003**, 68, 5672–5676. (c) Lorenz, K.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1987**, 28, 6437–6440. (d) Valverde, S.; Herradon, A.; Herradon, B.; Babanal, R. M.; Marrtin-Lomas, M. *Tetrahedron* **1987**, 43, 3499–3504. (e) Lichtenthaler, F. W.; Lorenz, K.; Ma, W. *Tetrahedron Lett.* **1987**, 28, 47–50.

with DIBALH (3.0 equiv; 93%) followed by a Swern oxidation (86%) provided aldehyde **12** in 82% yield for two steps. A Wittig reaction of aldehyde **12** with corresponding ylide ($\text{EtO}_2\text{CCH}=\text{PPh}_3$) provided the desired ester **13** in 81% yield.

In an effort to shorten the synthesis, as well as to further test the iterative dihydroxylation methodology, we decided to investigate a second approach to enoate **13** from trienoate **5b** (Scheme 4). The starting trienoate **5b** was easily prepared

Scheme 4. Alternative Synthesis of Acetonide **13**

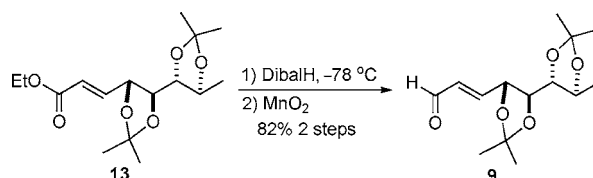


by a Wittig reaction of commercially available 2,4-hexadienal and ylide ($\text{EtO}_2\text{CCH}=\text{PPh}_3$). As with the dienoate **5a**, the trienoate **5b** was exposed to the Sharpless dihydroxylation protocol, and the resulting diol was protected as the acetonide to give dienoate **14** in a good yield (72% for two steps) and enantiomeric excesses (90% ee). Again, the second Sharpless AD reaction of dienoate **14** was preformed using the stereochemically matched ligand system $(\text{DHQD})_2\text{PHAL}$. While the desired diol **15b** was formed with excellent diastereocontrol, to our surprise it was also formed with a significant amount of the undesired regioisomer **15a**.¹² The two regioisomers **15a** and **15b** were obtained in a 1:1 ratio. Unfortunately, removing the acetonide protecting group had no positive effect on the regioselectivity.¹³ The desired regioisomer **15b** was separated by chromatography and protected as bis-acetonide **13** and proved to be spectroscopically identical to the bis-acetonide **13** prepared by the previous route (Scheme 3).¹⁴

To study the diastereoselective allylation reaction, ester **13** was converted into aldehyde **9**. This was accomplished

by a reduction/oxidation sequence. Exposure of a THF solution of ester **13** with 3.0 equiv of DIBALH at -78°C provided allylic alcohol (Scheme 5), which without purifica-

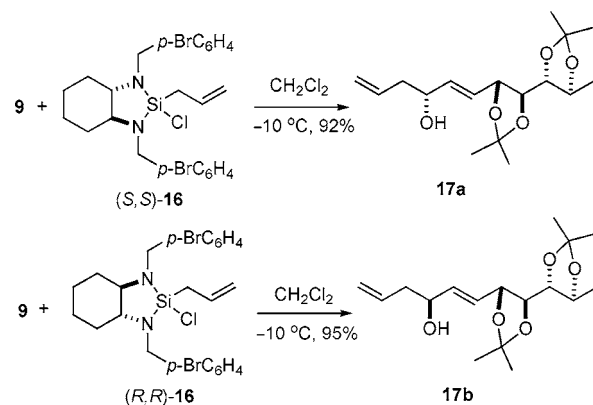
Scheme 5. Synthesis of Aldehyde **9**



tion was oxidized with MnO_2 to give aldehyde **9** in good yield (82% for two steps).

Diastereoselective allylation of aldehyde **9** was achieved by using either enantiomer of the easily prepared Leighton allyl silane reagents (*R,R*)-**16** and (*S,S*)-**16**⁹ (Scheme 6).

Scheme 6. Diastereoselective Leighton Allylation



Simply adding a solution of aldehyde **7** to the chiral allylsilane reagent (*S,S*)-**16** (0.2 M in CH_2Cl_2) at -10°C gave allylic alcohol **17a** in 92% with near complete stereocontrol ($>99\%$ ee and dr).^{15,16} Similarly exposing **9** to the enantiomeric reagent (*R,R*)-**16** provided a 95% yield of the diastereomeric allylic alcohol **17b** in equally high enantiomeric and diastereomeric purity ($>99\%$ ee and dr).¹⁶

We next prepared the metathesis precursor triene **8** (Scheme 7). A DCC-promoted coupling (4 equiv of acrylic acid/DCC in CH_2Cl_2) with allylic alcohol **17a** provided a triene **8** in a 78% yield. To address the formation of the lactone ring, we turned to the use of a ring-closing meth-

(12) To the best of knowledge, this loss of regiocontrol also occurs when **14** is dihydroxylated without $(\text{DHQD})_2\text{PHAL}$. When **14** was exposed to OsO_4/NMO in MeOH, four diastereotopic tetrol products were produced. This result is inconsistent with an initial regioselective formation of diol **15b**, because when diol **15b** is exposed to OsO_4/NMO in MeOH only a single tetrol is produced.

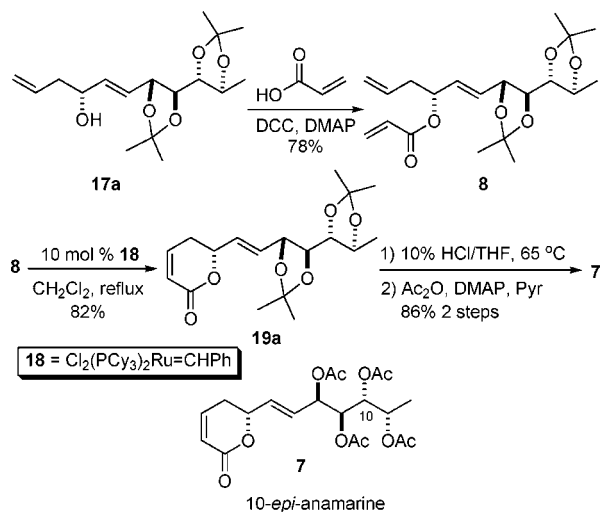
(13) In contrast to our results for acetonide **14** and its corresponding diol, Smith observed excellent regiocontrol ($>10:1$) in the dihydroxylation of related substituted epoxy-trienoates. Similarly, they observed no significant loss of stereocontrol in the mismatched (slower) case; see ref 6.

(14) While this second route (Scheme 4) is shorter, we preferred the first route (Scheme 3) because of the ease of isolation of all the intermediates and the greater overall yield (33 vs 26%).

(15) Previous approaches to this class of pyranone natural products use the Brown AllylBip₂ reagent for this transformation; see refs 3a–d. We have found that the Leighton reagent works equally well in terms of stereochemical outcome and allows for a significantly simpler product isolation procedure; see ref 9.

(16) All enantioexcesses were determined by examining the ^1H NMR of the corresponding Mosher esters, see: Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143–2147.

Scheme 7. Completion of the Synthesis of 10-*epi*-Anamarine **7**



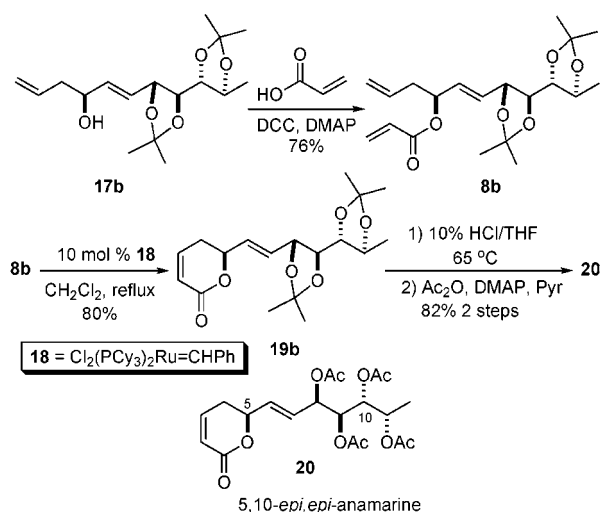
athesis reaction. This was easily implemented by exposure of a refluxing CH_2Cl_2 solution of the triene **8** to the Grubbs catalyst **18** (10 mol %), resulting in a clean cyclization to dihydropyran **19a** in 82% yield.

All that remained to complete the synthesis was to deprotect the acetonides and to acylate the resulting tetrol. After some experimentation, we found that this was most easily accomplished by heating **19a** in 10% aqueous hydrochloric acid for 20 min at 65 °C. The crude tetrol product was directly acylated by solvent removal and addition of pyridine, acetic anhydride, and DMAP. This two-step, one-pot protocol provided excellent yield of 10-*epi*-anamarine **7** (86% for two steps).

Similarly, the diastereomeric target molecule **20** was also prepared from **17b** by the same metathesis procedure (Scheme 8). Acylation of **17b** with DCC and acrylic acid provided triene **8b** in 76% yield, which similarly underwent a ring-closing metathesis reaction to give pyranone **19b** (80%). Finally a two-step, one-pot, acid-catalyzed deprotection/acylation reaction sequence provided 5,10-*epi, epi*-anamarine (**20**) in 82% yield for the two steps.

In conclusion, two short and enantioselective syntheses of 10-*epi*-anamarine (**7**) and 5,10-*epi, epi*-anamarine (**20**) have

Scheme 8. Completion of the Synthesis of 5,10-*epi, epi*-Anamarine **20**



been developed. This highly enantio- and diastereocontrolled route illustrates the utility of an iterative AD reaction and Leighton allylation sequence. This approach provided both 10-*epi*-anamarine and 5,10-*epi, epi*-anamarine in 14 and 13% overall yields, respectively. It is also worth noting that this route is significantly shorter than the previous carbohydrate-based approaches to the anamarines, yet this new route starts from achiral sources. Further application of this approach to other members of this class of natural product synthesis and biological testing is ongoing.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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