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

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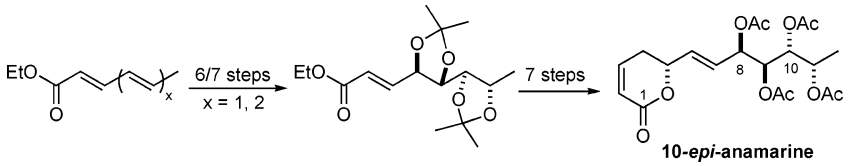
ABSTRACT



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

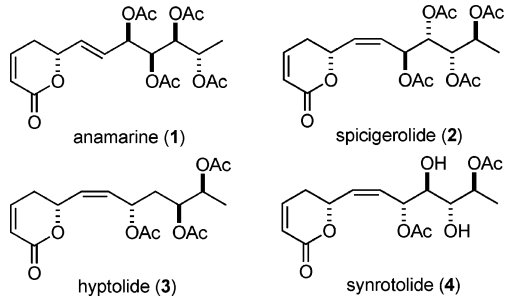


Figure 1. Anamarine-type pyranone polyacetates.

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, we[5] and others[6] have demonstrated that the selective oxidation/hydration of polyenoates

(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.

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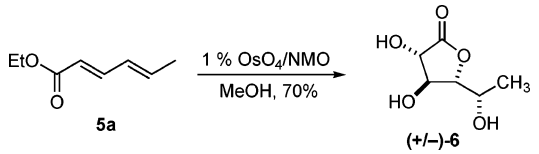
is a viable method for synthesis. In particular, we reported an expedient and practical synthesis of C-6-substituted *galacto*-sugars from simple achiral precursors with complete stereocontrol (**5a** to **6**, Scheme 1).[7] This approach relies on

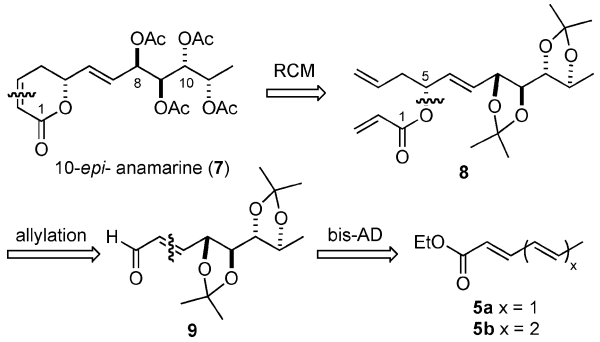
Scheme 1. One-Step Synthesis of *galacto*-γ-Lactone



the iterative use of an OsO_4-catalyzed dihydroxylation reaction on achiral dienoates such as **5a**. To test the utility of this methodology for natural product synthesis, we decided to apply it toward the synthesis of various anamarine analogues.[4] Reported herein is our approach to two unnatural analogues, 10-*epi*-anamarine and 5,10-*epi*,*epi*-anamarine, which both rely upon the enantio- and regioselective use of the Sharpless dihydroxylation,[8] as well as a Leighton asymmetric allylation[9] and Grubbs metathesis.[10]

Retrosynthetically, we envisioned that the lactone rings of 10-*epi*-anamarine and 5,10-*epi*,*epi*-anamarine could be synthesized by employing a selective metathesis reaction[10] of triene **8** (Scheme 2). The triene **8** could be prepared by

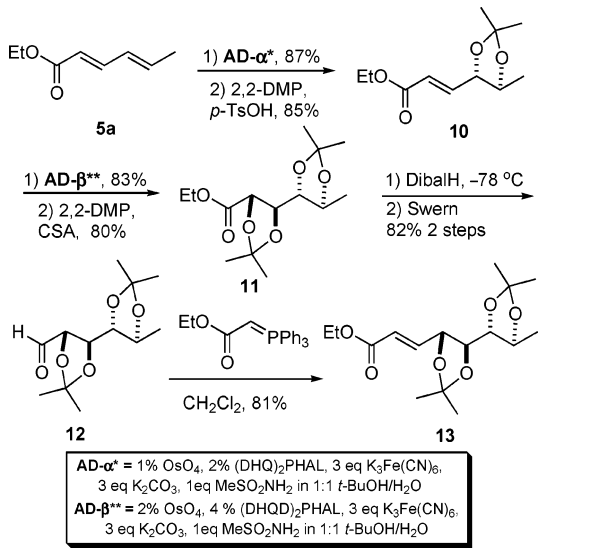
Scheme 2. Retrosynthetic Analysis of 10-*epi*-Anamarine



an asymmetric allylation[9] of aldehyde **9** followed by an acylation. Finally, it was envisioned that the C-8 through C-11 tetrol stereochemistry of **9** could be established by applying two Sharpless AD reactions on either dienoate **5a** or trienoate **5b**.[7]

We initially investigated the asymmetric synthesis of aldehyde **9** from the commercially available ethyl sorbate (**5a**) (Scheme 3). As we previously described, ethyl sorbate

Scheme 3. Synthesis of Ester **13**



(**5a**) was enantioselectively dihydroxylated and the corresponding diol was protected to give acetonide **10** in good yield (74% for two steps) and enantiomeric excess (80% ee).[7] Acetonide **10** was once again dihydroxylated in a diastereomerically matched sense,[7] with the pseudoenantiomeric reagent (2 mol % OsO_4, 4 mol % $(DHQD)_2PHAL$, 3 equiv of $K_3Fe(CN)_6$, 3 equiv of K_2CO_3, and 1 equiv of $MeSO_2NH_2$) to diastereoselectively give a diol (dr = 10:1), which was protected as the acetonide **11** (66% yield for two steps). As a result of performing the second dihydroxylation (**10** to **11**) with a diastereomerically matched chiral reagent system, the acetonide **11** was isolated with greater enantiomeric purity (>96% ee) than the initial acetonide **10**.[11]

With the relative and absolute tetrol stereochemistry established in **11**, we next looked to extend ester **11** into α,β-unsaturated ester **13**. Exhaustive reduction of ester **11**

(4) Migual Carda and Alberto Marco noted that various stereoisomers of spicigerolide (**2**) have improved cytotoxicity against several cancer cell lines; see ref 3b.

(5) (a) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 4447−4450. (b) Smith, C. M.; O'Doherty, G. A. *Org. Lett.* **2003**, *5*, 1959−1962. (c) Garaas, S. D.; Hunter, T. J.; O'Doherty, G. A. *J. Org. Chem.* **2002**, *67*, 2682−2685. (d) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777−2780. (e) Li, M.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 6407−6411.

(6) For a quite elegant use of this methodology in total synthesis, see: Smith, A. B., III; Walsh, S. P.; Frohn, M.; Duffey, M. O. *Org. Lett.* **2005**, *7*, 139−142.

(7) Ahmed, Md. M.; Berry, B. P.; Hunter, T. J.; Tomcik, D. J.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 745−748.

(8) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

(9) Kubota, K.; Leighton, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 946−948.

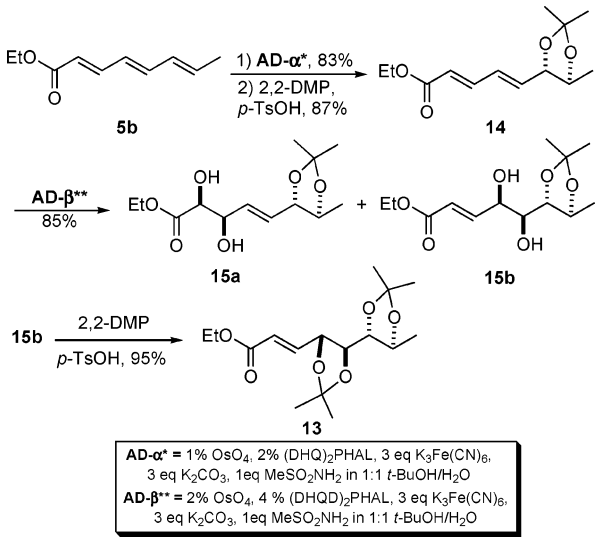
(10) For a review on ring-closing metathesis reactions, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238. For other uses of this pyranone formation in synthesis, see refs 5b−e and: (c) Pradaux, F.; Bouzbouz, S. *Org. Lett.* **2001**, *3*, 2233−2235. (d) Ghosh, A. K.; Wang, Y.; Kim, J. T. *J. Org. Chem.* **2001**, *66*, 8973−8982. (e) Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem.* **2001**, *66*, 2512−2514. (f) Wang, Y.-G.; Kobayashi, Y. *Org. Lett.* **2002**, *4*, 4615−4618. (g) Mizutani, H.; Watanabe, M.; Honda, T. *Tetrahedron* **2002**, *58*, 8929−8936. (h) Trost, B. M.; Yeh, V. S. C. *Org. Lett.* **2002**, *4*, 3513−3516. (i) Falomir, E.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, *44*, 539−541.

(11) While the conversion of **10** to **11** is a diastereoselective matched reaction with the $(DHQD)_2PHAL/OsO_4$ reagent system, the reaction occurs at a significantly slower rate and, as a result, a higher catalyst loading is required (2% OsO_4 and 4% $(DHQD)_2PHAL$, see Scheme 3).

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 ($EtO_2CCH{=}PPh_3$) 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

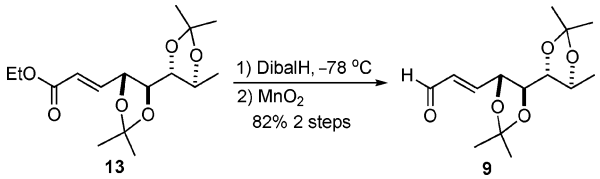
Scheme 4. Alterative Synthesis of Acetonide **13**



by a Wittig reaction of commercially available 2,4-hexadienal and ylide ($EtO_2CCH{=}PPh_3$). 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 ($(DHQD)_2PHAL$). 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]

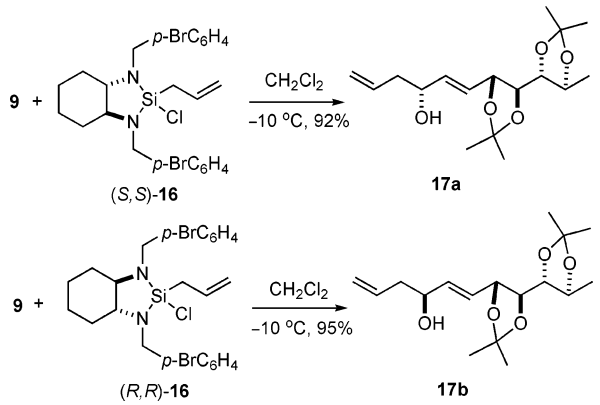
To study the diastereoselective allylation reaction, ester **13** was converted into aldehyde **9**. This was accomplished by a reduction/oxidation sequence. Exposure of a THF solution of ester **13** with 3.0 equiv of DIBALH at −78 °C provided allylic alcohol (Scheme 5), which without purification was oxidized with MnO_2 to give aldehyde **9** in good yield (82% for two steps).

Scheme 5. Synthesis of Aldehyde **9**



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 $(DHQD)_2PHAL$. 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.

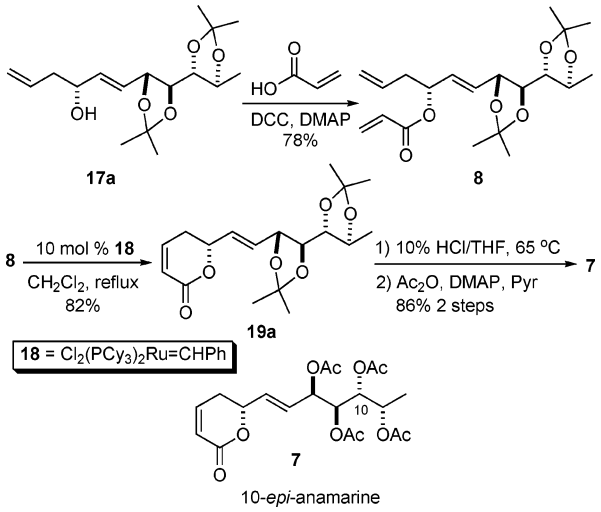
(13) In contrast to our results for acetonide **14** and its corresponding diol, Smith observed excellent regiocontrol (>10:1) in the dihydroxylation of related substituted epoxy-trienoates. Similarly, they observed no significant loss of stereocontrol in the mismatched (slower) case; see ref 6.

(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%).

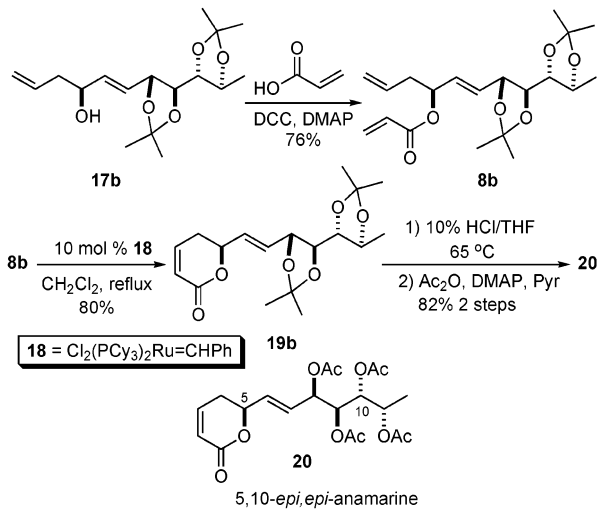
(15) Previous approaches to this class of pyranone natural products use the Brown $AllylBIpc_2$ reagent for this transformation; see refs 3a−d. We have found that the Leighton reagent works equally well in terms of stereochemical outcome and allows for a significantly simpler product isolation procedure; 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**



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



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 methathesis 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 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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