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De Novo Asymmetric Synthesis of Anamarine and Its Analogues

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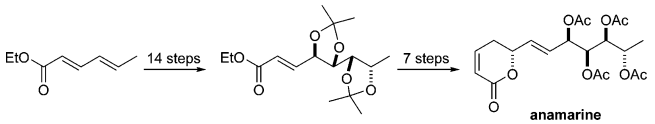

The enantioselective synthesis of anamarine has been achieved in 21 steps. The route relies on enantio- and regioselective Sharpless dihydroxylation of dienoate ester and zinc borohydride reduction to establish the C-8−C-11 stereochemistry. A diastereoselective Leighton allylation established the desired C-5 stereochemistry. The route has also been used to prepare two diastereoisomers of anamarine in 14 steps.

Introduction

For the last five years, we have been interested in a class of natural products with a skipped, 1,3-polyol/5,6-dihydro-2*H*-pyran-2-one structural motif which possess a wide range of biological properties.[1,2] This interest has met with some degree of success in terms of total synthesis.[3] As a result of these efforts, we became interested in the synthesis of natural products with a 1,2-polyol/5,6-dihydro-2*H*-pyran-2-one structural motif. Thus, we targeted the antitumor pyranone natural product anamarine for synthesis (**1a**, Figure 1).

The 5,6-dihydro-2*H*-pyran-2-one containing natural product, anamarine (**1a**), was isolated from the flowers and leaves of a Peruvian hyptis. Other members of this α,β-unsaturated lactone class of natural products include spicigerolide (**2**), hyptolide (**3**), and synrotolide (**4**) (Figure 1), which possess an array of properties ranging from cytotoxicity against human tumor cells to antibacterial and/or antifungal activity.[4]

Numerous synthetic approaches to this class of molecules have been reported.[5] In contrast to these previous syntheses, which derived their absolute and relative stereochemistry from carbohydrates,[5] we were interested in preparing several stereoisomers of anamarine via asymmetric catalysis.[6] Recently, we demonstrated the viability of this approach for the preparation of two epimers of anamarine.[5f] Key to this approach was the discovery of an expedient and practical synthesis of C-6-substituted *galacto*-sugars from simple achiral precursors with complete stereocontrol (**5**−**6**, Scheme 1).[7] Herein, we report the full account of this approach and detail the application for the synthesis of anamarine.

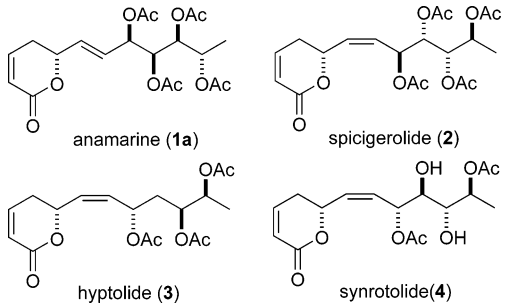

FIGURE 1. The anamarine-type α,β-unsaturated lactones.

(1) Jodynis-Liebert, J.; Murias, M.; Bloszyk, E. *Planta Med.* **2000**, *66*, 199.

(2) Drewes, S. E.; Schlapelo, B. M.; Horn, M. M.; Scott-Shaw, R.; Sandor, O. *Phytochemistry* **1995**, *38*, 1427.

(3) (a) Smith, C. M.; O'Doherty, G. A. *Org. Lett.* **2003**, *5*, 1959−1962. (b) Garaas, S. D.; Hunter, T. J.; O'Doherty, G. A. *J. Org. Chem.* **2002**, *67*, 2682−2685. (c) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777.

(4) (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.

(5) (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. (f) Gao, D.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 1069−1072.

(6) Miguel Carda and Alberto Marco noted that various stereoisomers of spicigerolide (**2**) have improved cytotoxicity against several cancer cell lines; see ref 5b.

(7) (a) Ahmed, Md. M.; Berry, B. P.; Hunter, T. J.; Tomcik, D. J.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 745−748. (b) Ahmed, Md. M.; O'Doherty, G. A. *Tetrahedron Lett.* **2005**, *46*, 3015−3019.

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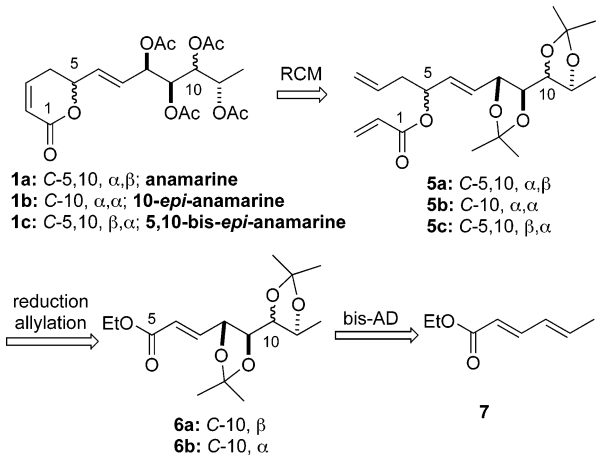
SCHEME 1. Retrosynthetic Analysis of Anamarine and Its Analogues

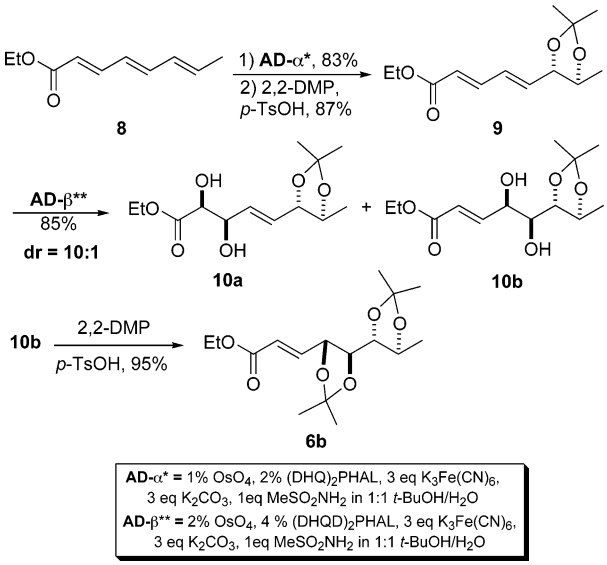


Results and Discussion

We envisioned that the lactone rings of anamarine **1a** could be prepared by a ring-closing metathesis reaction[8] of triene **5a** (Scheme 1), which could be obtained from **6a** by a reduction, a Leighton allylation,[9,10] and acylation. Finally, it was envisioned that the C-8 through C-11 tetrol stereochemistry of **6a** could be established by applying two Sharpless dihydroxylations followed by an inversion at C-10.[11] By simply skipping the inversion at C-10 and performing a diastereo−divergent allylation reaction, two diastereomers of anamarine (**1b** and **1c**) should be produced.

In our initial approach to 10-*epi*-anamarine (**1b**), we targeted the bis-acetonide **6b** as a key intermediate (Scheme 2). We envisioned preparing **6b** from trienoate **8**, which was easily prepared by a Wittig reaction of commercially available 2,4-hexadienal and ylide (EtO_2-CCH=PPh_3). Exposing trienoate **8** to the Sharpless dihydroxylation protocol yielded a diol, which was protected as the acetonide to give dienoate **9** in a good yield (72% for two steps) and enantiomeric excess (90% ee). A second Sharpless dihydroxylation on dienoate **9** was preformed using the stereochemically matched ligand system ($(DHQD)_2PHAL$). The desired diol **10b** was formed with excellent diastereocontrol; however, to our surprise, it was also formed with a significant amount of the undesired regioisomer **10a**. The two regioisomers **10a** and **10b** were obtained in a 1:1 ratio. To our delight,

SCHEME 2. Initial Synthesis of Ester 6b

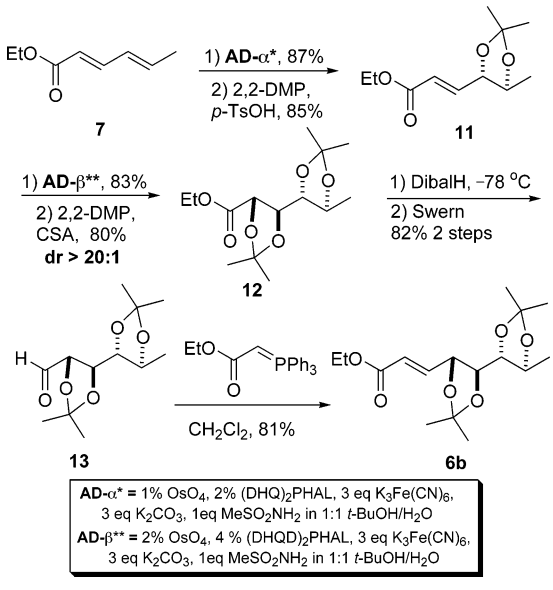


the desired regioisomer **10b** was separated by chromatography and protected as bis-acetonide **6b**.

Unfortunately, removing the acetonide protecting group had no positive effect on the regioselectivity of the second dihydroxylation.[12] This loss of regiocontrol is not solely due to the ligand. It also occurred when **9** was dihydroxylated under ligandless conditions (i.e., when **9** was exposed to OsO_4/NMO, four diastereomeric tetrol products were produced).

In a search for better regioselectivity in the synthesis of ester **6b**, we investigated the bis-dihydroxylation of the commercially available ethyl sorbate (**7**) (Scheme 3). Thus, ethyl sorbate (**7**) was enantioselectively dihydroxylated (1 mol % OsO_4 and 2 mol % $(DHQ)_2PHAL$) and

SCHEME 3. Improved Synthesis of Ester 6b



(8) For a review on ring-closing metathesis reactions, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238. For other uses of this pyranone formation in synthesis, see ref 3 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. (e) Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem.* **2001**, *66*, 2512. (f) Wang, Y.-G.; Kobayashi, Y. *Org. Lett.* **2002**, *4*, 4615. (g) Mizutani, H.; Watanabe, M.; Honda, T. *Tetrahedron* **2002**, *58*, 8929. (h) Trost, B. M.; Yeh, V. S. C. *Org. Lett.* **2002**, *4*, 3513. (i) Falomir, E.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, *44*, 539.

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

(10) We initially considered the use of the catalytic asymmetric allylation reagent developed by Keck but were dissuaded by its use of stoichiometric tin. See: (a) Keck, G. E.; Krishnamurthy, D. *Org. Synth.* **1997**, *75*, 12. (b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467−8468.

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

(12) In contrast to our results for acetonide **14** and its corresponding diol, Smith observed excellent regiocontrol (>10:1) in the dihydroxylation of related substituted epoxytrienoates. Similarly, they observed no significant loss of stereocontrol in the mismatched (slower) case. See: Smith, A. B., III; Walsh, S. P.; Frohn, M.; Duffey, M. O. *Org. Lett.* **2005**, *7*, 139−142.

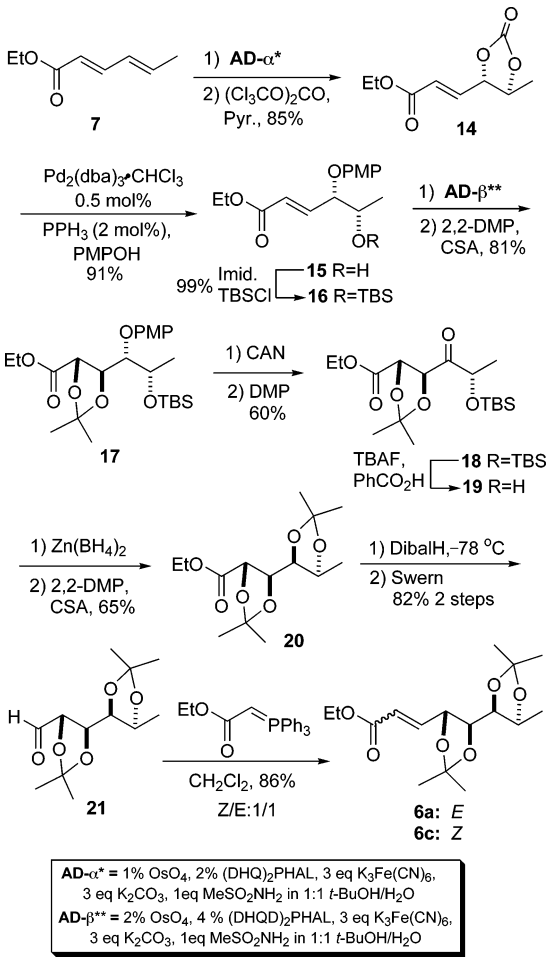
the corresponding diol was protected to give acetonide **11** in good yield (74% for two steps) and enantiomeric excess (80% ee).[7a] Once again, the α,β-unsaturated ester **11** was dihydroxylated in a diastereomerically matched sense,[5f] with the pseudoenantiomeric reagent (2 mol % OsO_4, 4 mol % $(DHQD)_2PHAL$, 3 equiv of $K_3Fe(CN)_6$, 3 equiv of K_2CO_3, and 1 equiv of $MeSO_2NH_2$). This diastereoselectively matched reaction gave a diol (diastereomeric ratio = 10:1), which was protected as the acetonide **12** (66% yield for two steps). It is worth noting that as a result of performing the second dihydroxylation (**11**−**12**) with a diastereomerically matched chiral reagent system, the bis-acetonide **12** was isolated with greater enantiomeric purity (>96% ee) than the initial acetonide **11**.[13]

Having established the relative and absolute stereochemistry of 10-*epi*-anamarine **1b** in **12**, we looked to convert ester **12** into α,β-unsaturated ester **6b**. This was accomplished by an exhaustive reduction of ester **12** with DIBALH (3.0 equiv, 93%) followed by a Swern oxidation, providing aldehyde **13** (82% yield, two steps). Finally, a Wittig reaction of aldehyde **13** with $EtO_2CCH{=}PPh_3$ provided the desired ester **6b** in 81% yield.

To approach the correct diastereomer **6a**, we returned to the asymmetric synthesis of the diastereomeric aldehyde **21** from the ethyl sorbate **7** (Scheme 4). As we previously described, ethyl sorbate was enantioselectively dihydroxylated and the corresponding diol was converted into cyclic carbonate **14** in good yield (74% for two steps) and enantiomeric excess (80% ee).[7b] Treatment of carbonate **14** with a catalytic amount of palladium(0) (0.5 mol %/2 mol % PPh_3) and *p*-methoxyphenol as the nucleophile provided the protected alcohol **15** in 91% yield. The other hydroxyl group was protected as silyl ether to give **16**. Enoate **16** was then dihydroxylated in a diastereomerically matched sense,[7b] with the matched 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 which was protected as the acetonide **17** (66% yield for two steps). As a result of performing the second dihydroxylation (**16**−**17**) with a diastereomerically matched chiral reagent system, the acetonide **17** was isolated with greater enantiomeric purity (>96% ee) than the initial diol.

We next looked into the inversion of the stereochemistry at C-10. Because our initial efforts to accomplish this with Mitsunobu chemistry met with little success, we turned to an oxidation/reduction strategy. Selective deprotection of the *p*-methoxyphenoxy ether (CAN) followed by Dess−Martin periodinane oxidation provided ketone **18**. Cleavage of the silyl ether with benzoic acid and TBAF gave alcohol **19**. Sodium borohydride reduction of the TBS-protected ketone **18** gave two diastereomers in a 4:1 ratio. Unfortunately, the major diastereomer was the undesired *syn*-diol. So, we turned to a chelation-controlled reduction. Treating the deprotected ketone **19** with zinc borohydride gave the *anti*-diol as the major product in a 5:1 ratio. The *anti*-diol was then treated with 2,2-dimethoxypropane and CSA, providing bis-acetonide

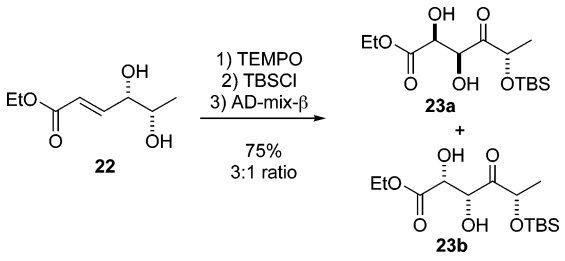
SCHEME 4. Synthesis of Epimeric Ester 6a



20 in good yield. With the relative and absolute tetrol stereochemistry established in **20**, we next looked to homologate ester **20** into enaote **6a**. Exhaustive reduction of ester **20** with DIBALH (3.0 equiv, 93%) followed by a Swern oxidation (88%) provided aldehyde **21** in 82% yield for two steps. A Wittig reaction of aldehyde **21** with corresponding ylide ($EtO_2CCH{=}PPh_3$) provided a 1:1 ratio of *Z*/*E* isomers of acetonide **6a,c** in 86% yield, which were inseparable.[14]

In an attempt to shorten the route to ester **6a**, we tried oxidizing the C-10 alcohol before the asymmetric dihy-

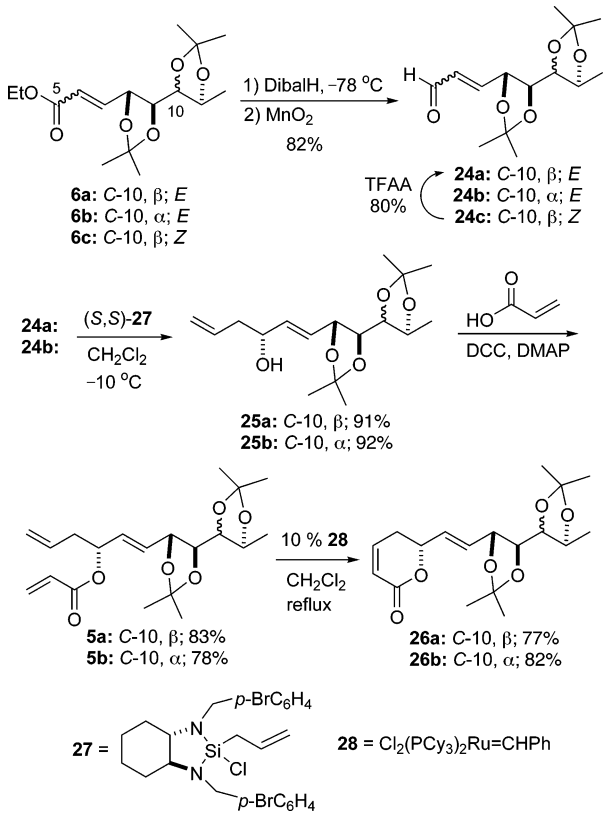
SCHEME 5. Alternative Approach to Ester 6a



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

(14) The lack of *E*/*Z* selectivity (1:1) in the Wittig reaction with aldehyde **21** is quite surprising when compared to the nearly identical Wittig reaction with the C-5 diastereomeric aldehyde **13**, where the *E* isomer **6b** was formed with almost 10:1 selectivity. Although we cannot offer an explanation for this result, we did find this result to be reproducible.

SCHEME 6. Installation of the Pyranone Ring in 26a,b

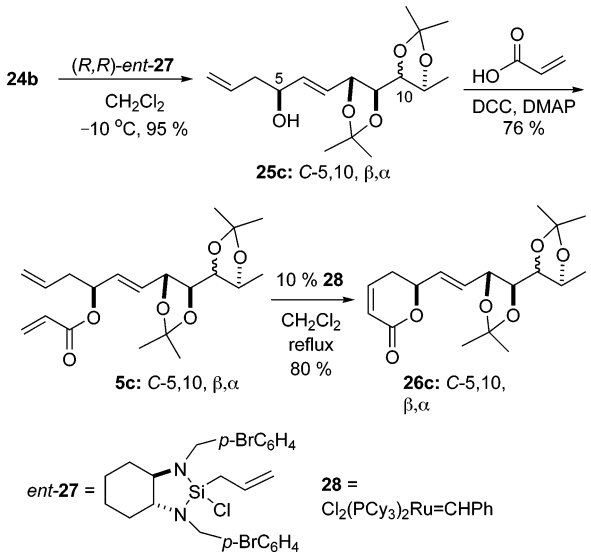


droxylation (Scheme 5). The oxidation of the allylic alcohol in **22** with TEMPO was accomplished after initial TBS protection of the C-5 alcohol (67% for two steps). To our surprise, the dihydroxylation reaction only gave a 3:1 mixture of diastereomers **23a** and **23b**, respectively (75% yield for the two isomers). Although this is a shorter sequence, because of the difficulty in separating the diastereomers **23a** and **23b**, we found it easier to prepare material by the previous route (Scheme 4).

The problem associated with inseparable double-bond isomers **6a** and **6c** was solved when the esters were converted into aldehydes **24a** and **24c**. This was accomplished by a reduction/oxidation sequence. Exposure of a THF solution of two isomers, **6a,c**, with 3.0 equiv of DIBALH at −78 °C provided allylic alcohol (Scheme 6), which without purification was oxidized with MnO_2 to give aldehyde **24a,c** in good yield (82% for two steps). At the aldehyde stage, the two isomers were separable. More importantly, the undesired isomer **24c** was converted back to the desired isomer upon treatment with 10 mol % TFA in CH_2Cl_2 (80% of a 10:1 ratio). By an identical sequence, the C-10 diastereomer **6b** was converted into aldehyde **24b** (82%).

With the two desired aldehydes **24a,b** in hand, we turned to the installation of the pyranone portion of the natural product. We envisioned that a diastereoselective allylation of aldehydes **24a,b** could be achieved by using either enantiomer of the easily prepared Leighton allyl silane reagents (*S*,*S*)-**27**[9] (Schemes 6 and 7). This was accomplished by simply adding a solution of either aldehyde **24a** or **24b** to the allylsilane reagent (*S*,*S*)-**27** (0.2 M in CH_2Cl_2) at −10 °C to give allylic alcohols **25a,b** in 91% and 92% yields with near complete stereocontrol

SCHEME 7. Installation of the Pyranone Ring in 26c

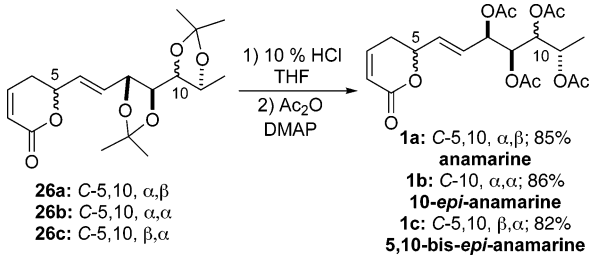


(>99% ee and dr).[15,16] The allylic alcohols **24a,b** were coupled with DCC (4 equiv) and acrylic acid (4 equiv) in CH_2Cl_2, providing trienes **5a** and **5b** in 83% and 78% yields, respectively. We next turned to the use of a ring-closing metathesis reaction to form the lactone ring. This was easily implemented by exposure of a refluxing CH_2Cl_2 solution of the trienes **5a,b** to the Grubbs catalyst **28** (10 mol %), resulting in a clean cyclization to dihydropyrans **26a** and **26b** in 77% and 82% yields, respectively.

The other diastereomeric series can be made by simply switching to the enantiomeric Leighton reagent ((*R*,*R*)-*ent*-**27**, Scheme 7). Thus, exposing aldehyde **24b** to the enantiomeric Leighton reagent, (*R*,*R*)-*ent*-**27**, yielded a diastereomerically pure allylic alcohol **25c** (95%), which, as before, could be converted into lactone **26c** via an acylation and metathesis sequence (61% yield for the two steps).

To complete the synthesis of anamarine **1a** and its two epimers, **1b,c** (Scheme 8), all that remains is to deprotect the acetonides and acylate the resulting tetrols. We found that this was most easily accomplished by heating the

SCHEME 8. Synthesis of Anamarine 1a and Epimers 1b,c



(15) Previous approaches to this class of pyranone natural products used the Brown AllylBIpc$_2$ reagent for this transformation; see ref 5a–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 ^{1}H NMR of the corresponding Mosher esters. See: Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.

three diastereomeric lactones **26a**−**c** in 10% aqueous hydrochloric acid in THF for 10 min at 65 °C. Because of the high polarity, the crude tetrol products were directly acylated by removal of solvent and addition of pyridine, acetic anhydride, and DMAP. This two-step/one-pot protocol provided excellent yields of anamarine **1a** (85% for two steps) and its two diastereomers **1b,c** (86% and 82% yields).

Conclusion

In summary, an enantioselective synthesis of anamarine has been developed. This highly enantio- and diastereocontrolled route illustrates the utility of an iterative Sharpless Asymmetric Dihydroxylation reaction and a Leighton allylation sequence. Although this approach to anamarine is rather long (21 steps), this route provides diastereomers of anamarine in significantly less steps (14 steps). This approach provided anamarine in 8% overall yield and provided its two diastereomers in 14% and 13% yields. It is also worth noting that these new routes start from achiral sources. Further application of this approach to other members of this class of natural products is ongoing.

Experimental Section[17]

(*E*,4*S*,5*S*)-Ethyl-4-(4-methoxyphenoxy)-5-(*tert*-butyldimethylsiloxy)-2-enoate (16). To a solution of alcohol **15** (13.2 g, 47.1 mmol) in 10 mL of dry DMF was added imidazole (9.6 g, 141.3 mmol) and TBSCl (10.2 g, 68.3 mmol) at room temperature. The reaction was stirred for 2 h, and then the reaction mixture was directly purified by flash chromatography on silica gel (7:3 (v/v) hexane/EtOAc) to provide compound **16** (18.5 g, 100% yield) as a colorless oil: R_f = 0.60 (7:3 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 2930, 1720; $[\alpha]^{25}_D$ −15° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.02 (dd, J = 4.5, 15.8 Hz, 1H), 6.78 (s, 2H), 6.77 (s, 2H), 6.06 (dd, J = 1.5, 15.8 Hz, 1H), 4.58 (ddd, J = 1.5, 4.2, 4.2 Hz, 1H), 4.14 (dq, J = 1.0, 7.2 Hz, 1H), 4.07 (q, J = 7.2 Hz, 1H), 4.05 (q, J = 7.2 Hz, 1H), 3.69 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H), 1.16 (d, J = 6.2 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 165.7, 154.0, 151.7, 144.0, 123.0, 116.5, 116.5, 114.3, 114.3, 81.3, 69.5, 60.1, 55.2, 25.6, 25.6, 25.6, 18.8, 17.8, 14.0, −4.91, −4.95; HRMS (CI) calcd for $[C_{21}H_{34}O_5Si + Na]^+$ 417.2068, found 417.2086.

(2*S*,3*S*,4*S*,5*S*)-Ethyl-4-(4-methoxyphenoxy)-5-(*tert*-butyldimethylsiloxy)-2,3-dihydroxyhexanoate (A).[18] Into a 250 mL round-bottom flask was added 50 mL of *t*-BuOH, 50 mL of water, $K_3Fe(CN)_6$ (19.7 g, 60.0 mmol), K_2CO_3 (8.3 g, 60.0 mmol), $MeSO_2NH_2$ (1.9 g, 20.0 mmol), $(DHQD)_2PHAL$ (321 mg, 0.4 mmol, 2 mol %), and OsO_4 (51 mg, 0.2 mmol, 1 mol %). The mixture was stirred at room temperature for about 15 min and then cooled to 0 °C. To this solution was added a solution of **16** (7.8 g, 20.0 mmol) in 5 mL of CH_2Cl_2, and the reaction was stirred vigorously at 0 °C for 20 h. The reaction was quenched with solid sodium sulfite at room temperature. Then the mixture was filtered through a pad of Celite/florisil and eluted with (2 × 80 mL) ethyl acetate. The combined organic layers were washed with 2 N KOH and brine and dried over anhydrous sodium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (7:3 (v/v) hexane/EtOAc) yielding compound **A** (7.3 g, 85% yield) as a viscous oil: R_f = 0.39 (7:3 (v/v) hexane/EtOAc); $[\alpha]^{25}_D$ −18° (*c* 1, $CHCl_3$); IR (neat, cm^{-1}) 3474, 2931, 1736, 1506; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.93 (d, J = 9.2 Hz, 2H), 6.78 (d, J = 9.2 Hz, 2H), 4.35−4.19 (m, 6H), 4.08 (s, 1H), 3.71 (s, 3H), 3.28 (d, J = 8.7 Hz, 1H), 1.32 (d, J = 6.4 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 173.3, 154.3, 151.5, 117.4, 117.4, 114.5, 114.5, 76.6, 71.9, 70.2, 68.3, 61.5, 55.3, 25.5, 25.5, 25.5, 17.6, 17.0, 14.0, −5.05, −5.40; HRMS (CI) calcd for $[C_{21}H_{36}O_7Si + Na]^+$ 451.2123, found 451.2142.

(4*S*,5*R*)-Ethyl-5-(1*R*,2*S*)-(2-methoxyphenoxy-1-*tert*-butyldimethylsiloxy)-2,2-dimethyl-1,3-dioxolane-4-carboxyate (17). To a solution of **A** (6.28 g, 14.7 mmol) in 20 mL of CH_2Cl_2 was added 2,2-dimethoxypropane (9.09 mL, 73.35 mmol) and CSA (137 mg, 4 mol %, 0.59 mmol) at room temperature. In 36 h, the reaction was quenched by adding saturated $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford the crude product. Flash chromatography on silica gel (8:2 (v/v) hexane/EtOAc) provided compound **17** (5.57 g, 81% yield) as a colorless oil: R_f = 0.39 (7:3 (v/v) hexane/EtOAc); $[\alpha]^{25}_D$ +6° (*c* 1, $CHCl_3$); IR (neat, cm^{-1}) 2932, 1749, 1506; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.91 (d, J = 9.2 Hz, 2H), 6.76 (d, J = 8.9 Hz, 2H), 4.65 (d, J = 5.9 Hz, 1H), 4.56 (dd, J = 3.9, 6.2 Hz, 1H), 4.27−4.15 (m, 3H), 4.05 (dd, J = 6.5, 6.2 Hz, 1H), 3.72 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.23 (d, J = 5.9 Hz, 3H), 0.83 (s, 9H), 0.05 (s, 3H), −0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 171.3, 153.8, 153.5, 117.2, 117.2, 114.1, 114.1, 111.2, 82.8, 78.6, 75.6, 68.2, 61.3, 55.5, 26.7, 25.7, 25.7, 25.7, 25.6, 20.1, 17.9, 14.0, -4.82, −4.82; HRMS (CI) calcd for $[C_{24}H_{40}O_7Si + Na]^+$ 491.2436, found 491.2453.

(4*S*,5*R*)-Ethyl-5-(1*R*,2*S*)-(2-hydroxy-1-*tert*-butyldimethylsiloxy)-2,2-dimethyl-1,3-dioxolane-4-carboxyate (B).[18] To a solution of ether **17** (2.70 g, 5.77 mmol) in 60 mL of CH_3CN/H_2O (4:1) was added CAN (6.32 g, 11.53 mmol) at 0 °C. After 10 min, the mixture was partitioned between EtOAc and brine. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated to afford the crude product. Flash chromatography on silica gel (8:2 (v/v) hexane/EtOAc) provided compound **B** (1.3 g, 61% yield) as a yellow oil: R_f = 0.29 (8:2 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 3442, 2932, 1749; $[\alpha]^{25}_D$ +12° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 4.48 (d, J = 5.9 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 4.18 (d, J = 5.9 Hz, 1H), 4.05 (dq, J = 1.5, 6.2 Hz, 1H), 3.26 (ddd, J = 1.7, 9.2, 9.2 Hz, 1H), 2.41 (d, J = 9.6 Hz, 1H), 1.42 (s, 3H), 1.38 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.21 (d, J = 6.2 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 171.2, 111.5, 78.3, 77.8, 76.2, 67.1, 61.3, 27.2, 25.8, 25.7, 25.7, 25.7, 20.3, 17.9, 14.1, −4.32, −5.07; HRMS (CI) calcd for $[C_{17}H_{34}O_6Si + Na]^+$ 385.2017, found 385.2006.

(4*S*,5*R*)-Ethyl-5-(1*R*)-(2-oxo-1-*tert*-butyldimethylsiloxy)-2,2-dimethyl-1,3-dioxolane-4-carboxyate (18). To a solution of alcohol **B** (1.22 g, 3.36 mmol) in 25 mL of CH_2Cl_2 was added Dess−Martin periodinane (1.85 g, 4.40 mmol) at room temperature. After 3 h, the mixture was diluted with hexanes and stirred with a solution of NaS_2O_3 for 30 min. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford the crude product. Flash chromatography on silica gel (8:2 (v/v) hexane/EtOAc) provided compound **18** (1.20 g, 99% yield) as a colorless oil: R_f = 0.40 (8:2 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 2989, 1748; $[\alpha]^{25}_D$ +14° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.10 (d, J = 5.7 Hz, 1H), 4.81 (d, J = 5.7 Hz, 1H), 4.50 (q, J = 6.7 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 1.45 (s, 3H), 1.44 (s, 3H), 1.35 (d, J = 6.9 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 207.2, 170.2, 112.9, 78.6, 75.5, 72.4, 61.6, 26.5, 26.0, 25.7, 25.7, 25.7, 19.9, 18.1, 14.0, −4.89, −5.08; HRMS (CI) calcd for $[C_{17}H_{32}O_6Si + Na]^+$ 383.1860, found 383.1872.

(17) Experimental procedures for the synthesis of anamarine are presented in the Experimental Section. Complete experimental procedures and spectral data for all compounds are presented in the Supporting Information.

(18) These structures are not shown in the text.

(4*S*,5*R*)-Ethyl-5-(1*R*)-(2-oxo-1-hydroxy)-2,2-dimethyl-1,3-dioxolane-4-carboxyate (19). To a solution of silyl ester **18** (298 mg, 0.83 mmol) in 4 mL of THF was added benzonic acid (202 mg, 1.65 mmol) and TBAF (1.65 mL of a 1.0 M solution in THF) at room temperature. After 2 h, the mixture was diluted with EtOAc and quenched with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford the crude product. Flash chromatography on silica gel (8:2 (v/v) hexane/EtOAc) provided compound **19** (151 mg, 90% yield) as a colorless oil: $R_f = 0.25$ (8:2 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 3453, 2986, 1744; $[\alpha]^{25}_D$ +32° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 4.93 (d, $J = 6.5$ Hz, 1H), 4.62 (d, $J = 6.4$ Hz, 1H), 4.56 (q, $J = 6.8$ Hz, 1H), 4.26 (q, $J = 7.2$ Hz, 2H), 1.49 (s, 3H), 1.45 (s, 3H), 1.42 (d, $J = 6.9$ Hz, 3H), 1.29 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 209.3, 169.8, 113.4, 79.9, 76.2, 71.5, 62.1, 26.3, 25.7, 19.3, 14.0; HRMS (CI) calcd for $[C_{11}H_{18}O_6 + Na]^+$ 269.0996, found 269.1007.

(4*S*,5*R*)-Ethyl-5-(1*S*,2*S*)-(1,2-dihydoxypropyl)-2,2-dimethyl-1,3-dioxolane-4-carboxyate (C).[18] **(4*S*,5*R*)-Ethyl-5-(1*R*,-2*S*)-(1,2-dihydoxypropyl)-2,2-dimethyl-1,3-dioxolane-4-carboxyate (D).**[18] To a solution of alcohol **19** (99 mg, 0.40 mmol) in 5 mL of ether was added $Zn(BH_4)_2$ (4 mL, 0.39 mmol) at −10 °C. After 2.5 h, the mixture was quenched with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford the crude mixture of regioisomers (**C**/**D** = 5/1 determined by ^1H NMR). Flash chromatography on silica gel (8:2 (v/v) hexane/EtOAc) provided two pure regioisomers (75 mg, 75% combined yield), **C** (62 mg, 63% yield) as a colorless oil and **D** (12 mg, 12%) as a colorless oil.

C: $R_f = 0.20$ (5:5 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 3465, 2988, 1453, 1375; ^1H NMR ($CDCl_3$, 600 MHz) δ 4.60 (d, $J =$ 7.8 Hz, 1H), 4.37 (dd, $J = 2.4$, 7.8 Hz, 1H), 4.24 (q, $J = 7.2$ Hz, 1H), 4.23 (q, $J = 7.2$ Hz, 1H), 3.86 (d, $J = 6.0$ Hz, 1H), 3.50 (ddd, $J = 1.8$, 7.5, 7.5 Hz, 1H), 2.60 (d, $J = 10.2$ Hz, 1H), 2.23 (d, $J = 7.2$ Hz, 1H), 1.47 (s, 3H), 1.42 (s, 3H), 1.29 (d, $J = 6.0$ Hz, 3H), 1.28 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 130 MHz) δ 170.8, 111.5, 78.3, 75.4, 72.7, 69.5, 61.5, 26.6, 25.7, 19.8, 14.1; HRMS (CI) calcd for $[C_{11}H_{20}O_6 + Na]^+$ 271.1152, found 271.1154.

D: $R_f = 0.25$ (5:5 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 3464, 2986, 1451, 1378; ^1H NMR ($CDCl_3$, 270 MHz) δ 4.52 (d, $J =$ 6.4 Hz, 1H), 4.30 (dd, $J = 5.2$, 6.7 Hz, 1H), 4.24 (q, $J = 7.2$ Hz, 1H), 4.23 (q, $J = 6.9$ Hz, 1H), 3.91 (dq, $J = 3.7$, 6.4 Hz, 1H), 3.54 (dd, $J = 3.7$, 5.2 Hz, 1H), 3.04 (bs, 2H), 1.46 (s, 3H), 1.38 (s, 3H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.24 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 171.8, 111.1, 79.4, 75.8, 74.9, 66.7, 61.8, 26.8, 25.4, 19.4, 14.0; HRMS (CI) calcd for $[C_{11}H_{20}O_6 + Na]^+$ 271.1152, found 271.1162.

(2*S*,3*R*)-Ethyl-2,2-dimethyl-5-((4*S*,5*S*)-2′,2′,5-trimethyl-1′,3′-dioxolan-4′-yl)-1,3-dioxolane-4-carboxyate (20). To a solution of diol **C** (120 mg, 0.49 mmol) in 4 mL of CH_2Cl_2 was added 2,2-dimethoxypropane (0.61 mL, 4.9 mmol) and CSA (18 mg, 10 mol %, 0.074 mmol) at room temperature. After 24 h, the reaction was quenched by adding saturated $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford the crude product. Flash chromatography on silica gel (8:2 (v/v) hexane/EtOAc) provided compound **20** (92 mg, 65% yield) as a colorless oil: $R_f = 0.65$ (7:3 (v/v) hexane/EtOAc); $[\alpha]^{25}_D$ +72° (*c* 1, $CHCl_3$); IR (neat, cm^{-1}) 2931, 1746; ^1H NMR ($CDCl_3$, 270 MHz) δ 4.47 (d, $J = 8.2$ Hz, 1H), 4.43 (dq, $J = 6.4$, 6.4 Hz, 1H), 4.24 (q, $J = 6.9$ Hz, 1H), 4.23 (q, $J = 7.2$ Hz, 1H), 4.19 (dd, $J = 2.0$, 6.7 Hz, 1H), 4.01 (dd, $J = 1.7$, 8.2 Hz, 1H), 1.51 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H), 1.39 (d, $J = 6.4$ Hz, 3H), 1.37 (s, 3H), 1.29 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 170.7, 111.5, 108.5, 77.6, 75.8, 75.6, 72.6, 61.4, 26.7, 26.7, 25.8, 25.5, 14.8, 14.2; HRMS (CI) calcd for $[C_{14}H_{24}O_6 + Na]^+$ 311.1465, found 311.1459.

(2*S*,3*R*)-2,2-Dimethyl-5-((4′*S*,5′*S*)-2′,2′,5-trimethyl-1′,3′-dioxolan-4′-yl)-1,3-dioxolane-4-carboxyate (E).[18] To a solution of ester **20** (100 mg, 0.35 mmol) in 1 mL of THF was added DIBAL-H (1.0 mL, 1.0 M in hexanes, 1.0 mmol) dropwise at -78 °C. After 1 h, the reaction was quenched by adding 1 mL of acetone and 3 mL of 20% sodium potassium tartrate solution. The mixture was stirred for 30 min. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford the crude product. Flash chromatography on silica gel (7:3 (v/v) hexane/EtOAc) provided compound **E** (75 mg, 89% yield) as a colorless oil: $R_f = 0.21$ (7:3 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 3369, 2989, 1456; $[\alpha]^{25}_D$ +60° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 4.38 (dq, $J = 6.5$, 6.5 Hz, 1H), 4.04 (ddd, $J = 3.5$, 3.5, 8.7 Hz, 1H), 3.96 (dd, $J = 1.5$, 6.5 Hz, 1H), 3.83 (dd, $J = 1.5$, 8.7 Hz, 1H), 3.58 (ddd, $J = 3.5$, 7.4, 11.4 Hz, 1H), 2.37 (bs, 1H), 1.48 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 1.36 (d, $J = 6.5$ Hz, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 109.3, 108.2, 77.5, 75.3, 75.2, 72.8, 60.8, 27.1, 27.0, 26.6, 25.4, 15.0; HRMS (CI) calcd for $[C_{12}H_{22}O_5 + Na]^+$ 269.1359, found 269.1353.

(2*S*,3*R*)-2,2-Dimethyl-5-((4′*S*,5′*S*)-2′,2′,5-trimethyl-1′,3′-dioxolan-4′-yl)-1,3-dioxolane-4-carbaldehyde (21). To a solution of oxalyl chloride (50 mg, 0.37 mmol) in 1 mL of CH_2Cl_2 was added DMSO (36 mg, 0.47 mmol) at −78 °C. After stirring for 10 min, alcohol **E** (75 mg, 0.31 mmol) in 0.5 mL of CH_2Cl_2 was added dropwise. The mixture was stirred for another 10 min, and then Et_3N (104 mg, 1.02 mmol) was added. After 20 min, the dry ice was removed and the solution was stirred for 30 min and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford the crude product. Flash chromatography on silica gel (7:3 (v/v) hexane/EtOAc) provided compound **21** (58 mg, 76% yield) as a colorless oil: $R_f = 0.23$ (7:3 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 2986, 1743; $[\alpha]^{25}_D$ = +33° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 9.79 (dd, $J = 1.5$, 1.7 Hz, 1H), 4.39 (dq, $J = 6.4$, 6.4 Hz, 1H), 4.31 (ddd, $J = 1.7$, 1.7, 7.9 Hz, 1H), 4.08 (dd, $J = 1.7$, 6.7 Hz, 1H), 3.94 (ddd, $J = 1.7$, 1.7, 7.9 Hz, 1H), 1.50 (s, 6H), 1.40 (s, 3H), 1.36 (d, $J = 6.7$ Hz, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 201.7, 111.7, 108.5, 81.2, 75.8, 75.7, 72.6, 26.7, 26.6, 26.2, 25.4, 14.9; HRMS (CI) calcd for $[C_{12}H_{20}O_5 + Na]^+$ 267.1203, found: 267.1206.

(*E*)-Ethyl-3-((2′*R*,3′*S*)-2′,2′-dimethyl-5′-((4″*S*,5″*S*)-2″,2″,5″-trimethyl-1″,3″-dioxolan-4″-yl)-1,3-dioxolane-4′yl)acrylate (6a). (*Z*)-Ethyl-3-((2′*R*,3′*S*)-2′,2′-dimethyl-5′-((4″*S*,5″*S*)-2″,2″,5″-trimethyl-1″,3″-dioxolan-4″-yl)-1,3-dioxolane-4′yl)acrylate (6c). To a solution of aldehyde **21** (50 mg, 0.21 mmol) in 1 mL of CH_2Cl_2 was added ylide (143 mg, 0.42 mmol) at room temperature. After 3 h, the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (8:2 (v/v) hexane/EtOAc) providing a mixture of *E*/*Z*-isomeric acetonides **6a,c** in a 1.1:1 ratio (63 mg, 98% yield) as a colorless oil: $R_f = 0.38$ (8:2 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 2989, 1714; ^1H NMR (mixture) ($CDCl_3$, 270 MHz) δ 6.99 (dd, $J = 15.6$, 4.3 Hz, 1H), 6.14 (dd, $J = 15.8$, 1.8 Hz, 1H), 4.56 (ddd, $J = 7.5$, 4.3, 1.8 Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 4.01 (dd, $J = 7.5$, 6.2 Hz, 1H), 3.68 (dd, $J = 7.9$, 7.5 Hz, 1H), 3.54 (dd, $J = 7.7$, 7.7 Hz, 1H), 1.40 (s, 3H), 1.39 (s, 6H), 1.34 (d, $J = 5.9$ Hz, 3H), 1.33 (s, 3H), 1.27 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 166.3, 145.0, 121.4, 110.4, 109.1, 83.1, 81.5, 79.3, 76.6, 60.5, 27.4, 27.0, 26.9, 26.8, 18.5, 14.3; HRMS (CI) calcd for $[C_{16}H_{26}O_4 + Na]^+$ 337.1622, found 337.1618.

(*E*)-3-((4′*R*,5′*S*)-2′,2′-Dimethyl-5′-((4″*S*,5″*S*)-2″,2″,5″-trimethyl-1″,3″-dioxolan-4″-yl)-1′,3′-dioxolane-4′-yl)prop-2-en-1-ol (F). [18] **(*Z*)-3-((4′*R*,5′*S*)-2′,2′-Dimethyl-5′-((4″*S*,5″*S*)-2″,2″,5″-trimethyl-1″,3″-dioxolan-4″-yl)-1′,3′-dioxolane-4′-yl)prop-2-en-1-ol (G).**[18] To a solution of ester **6a,c** (1.1:1 ratio

of *E*/*Z* isomers) (65 mg, 0.20 mmol) in 1 mL of THF was added DIBAL-H (0.60 mL, 1.0 M in hexanes, 4.0 mmol) dropwise at −78 °C. After 30 min, the reaction was quenched by adding 1 mL of acetone and 3 mL of 20% sodium potassium tartrate solution. The mixture was stirred for 30 min. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford the crude product. Flash chromatography on silica gel (7:3 (v/v) hexane/EtOAc) provided allylic alcohol **F** (26 mg, 46% yield) and **G** (25 mg, 45% yield) (91% combined yield) as a colorless oil.

F: $R_f = 0.20$ (7:3 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 3428, 2986; ^1H NMR ($CDCl_3$, 270 MHz) δ 6.06 (ddd, J = 5.0, 5.0, 15.6 Hz, 1H), 5.70 (dddd, J = 1.7, 1.7, 7.9, 15.5 Hz, 1H), 4.43−4.33 (m, 2H), 4.19 (d, J = 3.7 Hz, 2H), 3.94 (dd, J = 1.8, 6.5 Hz, 1H), 3.59 (dd, J = 2.0, 8.6 Hz, 1H), 1.53 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H), 1.37 (d, J = 6.4 Hz, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 135.2, 127.2, 109.4, 108.6, 79.3, 78.1, 74.8, 72.7, 62.7, 27.2, 26.9, 26.8, 25.6, 15.1; HRMS (CI) calcd for $[C_{14}H_{24}O_5 + Na]^+$ 295.1516, found 295.1513.

G: $R_f = 0.25$ (7:3 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 3423, 2986; $[\alpha]^{25}_D$ +59° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 5.94 (ddd, J = 1.0, 6.7, 11.1 Hz, 1H), 5.53 (dddd, J = 1.0, 1.0, 8.9, 9.9 Hz, 1H), 4.74 (ddd, J = 1.0, 8.6, 8.6 Hz, 1H), 4.37 (dq, J = 6.4, 6.4 Hz, 1H), 4.25 (dd, J = 6.9, 6.7 Hz, 2H), 3.89 (dd, J = 1.7, 6.7 Hz, 1H), 3.52 (dd, J = 1.8, 8.7 Hz, 1H), 1.52 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H), 1.37 (d, J = 6.5 Hz, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 134.7, 128.1, 109.5, 108.5, 79.4, 74.5, 73.2, 72.7, 58.4, 27.2, 26.9, 26.7, 25.5, 14.9; HRMS (CI) calcd for $[C_{14}H_{24}O_5 + Na]^+$ 295.1516, found 295.1513.

(*E*)-3-((4′*R*,5′*S*)-2′,2′-Dimethyl-5′-((4″*S*,5″*S*)-2″,2″,5″-trimethyl-1″,3″-dioxolan-4″-yl)-1′,3′-dioxolane-4′-yl)acrylaldehyde (24a). To a solution of alcohol **F** (40 mg, 0.15 mmol) in 3 mL of CH_2Cl_2 was added MnO_2 (127 mg, 1.5 mmol) at room temperature. After 4 h, the reaction mixture was filtered through a pad of Celite and washed with EtOAc. The organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford the crude product. Flash chromatography on silica gel (8:2 (v/v) hexane/EtOAc) provided aldehyde **24a** (37 mg, 93% yield) as a white solid: mp = 50−52 °C; $R_f = 0.51$ (7:3 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 2989, 1682; $[\alpha]^{25}_D$ +59 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 9.59 (d, J = 7.7, Hz, 1H), 6.76 (dd, J = 5.7, 15.8 Hz, 1H), 6.42 (ddd, J = 1.2, 7.7, 15.6 Hz, 1H), 4.68 (ddd, J = 1.2, 5.7, 8.7, Hz, 1H), 4.42 (dq, J = 6.5, 6.5 Hz, 1H), 3.97 (dd, J = 1.2, 6.7 Hz, 1H), 3.66 (dd, J = 1.2, 8.6 Hz, 1H), 1.53 (s, 3H), 1.48 (s, 3H), 1.43 (s, 3H), 1.39 (d, J = 6.7 Hz, 3H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 192.8, 151.6, 133.1, 110.7, 108.7, 79.4, 76.5, 74.5, 72.7, 26.9, 26.8, 26.6, 25.4, 14.8; HRMS (CI) calcd for $[C_{14}H_{22}O_5 + Na]^+$ 293.1359, found 293.1368.

(*Z*)-3-((4′*R*,5′*S*)-2′,2′-Dimethyl-5′-((4″*S*,5″*S*)-2″,2″,5″-trimethyl-1″,3″-dioxolan-4″-yl)-1′,3′-dioxolane-4′-yl)acrylaldehyde (24c). To a solution of alcohol **G** (38 mg, 0.14 mmol) in 3 mL of CH_2Cl_2 was added MnO_2 (122 mg, 1.4 mmol) at room temperature. After 5 h, the reaction mixture was filtered through a pad of Celite and washed with EtOAc. The organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford the crude product. Flash chromatography on silica gel (8:2 (v/v) hexane/EtOAc) provided aldehyde **24c** (35 mg, 92% yield) as a colorless oil: $R_f = 0.45$ (7:3 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 2989, 1682; $[\alpha]^{25}_D$ +60° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 10.17 (d, J = 7.9 Hz, 1H), δ 6.52 (dd, J = 8.2, 11.4 Hz, 1H), 6.10 (ddd, J = 1.2, 7.9, 11.4 Hz, 1H), 5.26 (ddd, J = 1.2, 8.7, 8.7 Hz, 1H), 4.42 (dq, J = 6.4, 6.4 Hz, 1H), 3.92 (dd, J = 1.2, 6.7 Hz, 1H), 3.64 (dd, J = 1.2, 8.6 Hz, 1H), 1.53 (s, 3H), 1.49 (s, 3H), 1.46 (s, 3H), 1.40 (d, J = 6.2 Hz, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 191.5, 146.2, 133.0, 110.8, 108.8, 79.5, 73.9, 73.4, 72.7, 27.2, 27.0, 26.7, 25.5, 14.9; HRMS (CI) calcd for $[C_{14}H_{22}O_5 + Na]^+$ 293.1359, found 293.1368.

(3*R*,*E*)-1-((4′*R*,5′*S*)-2′,2′-Dimethyl-5′-((4″*S*,5″*S*)-2″,2″,5″-trimethyl-1″,3″-dioxolan-4″-yl)-1′,3′-dioxolan-4′-yl)hexa-1,5-dien-3-ol (25a). To a solution of (*S*,*S*)-**27** (127 mg, 0.22 mmol) in 0.5 mL of CH_2Cl_2 was added aldehyde **24a** (20 mg, 0.074 mmol) in 0.5 mL of CH_2Cl_2 dropwise at −10 °C. The reaction flask was put in a freezer (−10 °C). After 20 h, the reaction was diluted with EtOAc and quenched by adding 1 N HCl and the mixture was vigorously stirred at room temperature for 15 min. The mixture was filtered through a pad of Celite, and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, before being concentrated to afford the crude product. Flash chromatography on silica gel (9:1 (v/v) hexane/EtOAc) provided compound **25a** (21 mg, 91% yield) as a colorless oil: $R_f = 0.25$ (7:3 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 3453, 2989, 1637; $[\alpha]^{25}_D$ +48° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 5.93 (dd, J = 6.0, 15.6 Hz, 1H), 5.80 (ddd, J = 7.8, 9.6, 17.4 Hz, 1H), 5.69 (dd, J = 7.8, 15.6 Hz, 1H), 5.16 (bs, 1H), 5.14 (dd, J = 1.2, 3.0 Hz, 1H), 4.37 (dd, J = 8.4, 8.4, 1H), 4.36 (dd, J = 6.0, 6.0, 1H), 4.23 (dd, J = 5.4, 5.4 Hz, 1H), 3.93 (d, J = 6.0 Hz, 1H), 3.58 (d, J = 8.4 Hz, 1H), 2.37 (ddd, J = 1.2, 7.8, 13.8 Hz, 1H), 2.25 (ddd, J = 7.2, 7.8, 13.2 Hz, 1H), 1.52 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H), 1.35 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 137.7, 133.7, 127.0, 118.7, 109.5, 108.4, 79.4, 78.2, 74.9, 72.7, 70.5, 41.7, 27.2, 26.9, 26.8, 25.6, 15.1; HRMS (CI) calcd for $[C_{17}H_{28}O_5 + Na]^+$ 335.1829, found 335.1823.

(3*R*,*E*)-1-((4′*R*,5′*S*)-2′,2′-Dimethyl-5′-((4″*S*,5″*S*)-2″,2″,5″-trimethyl-1″,3″-dioxolan-4″-yl)-1′,3′-dioxolan-4′-yl)hexa-1,5-dien-3-yl Acrylate (5a). To a solution of alcohol **5a** (20 mg, 0.064 mmol) in 1 mL of CH_2Cl_2 was added acrylic acid (18 μL, 0.26 mmol), DCC (52 mg, 0.26 mmol), and DMAP (2 mg, catalytic amount). After 3 h, the reaction mixture was diluted with Et_2O, filtered through a pad of Celite, and washed with Et_2O. The organic layer was washed with saturated aqueous $NaHSO_4$, saturated aqueous $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4, before being concentrated to afford the crude product. Flash chromatography on silica gel (9:1 (v/v) hexane/EtOAc) provided ester **25a** (19 mg, 83% yield) as a colorless oil: $R_f = 0.50$ (7:3 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 2986, 1731; $[\alpha]^{25}_D$ +40° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 6.39 (dd, J = 1.2, 17.4 Hz, 1H), 6.10 (dd, J = 10.2, 17.4 Hz, 1H), 5.86 (dd, J = 6.6, 15.6 Hz, 1H), 5.82 (dd, J = 1.2, 7.2 Hz, 1H), 5.75 (ddd, J = 7.2, 7.2, 10.2 Hz, 1H), 5.70 (ddd, J = 1.2, 7.2, 7.2 Hz, 1H), 5.42 (dd, J = 6.0, 6.6 Hz, 1H), 5.11−5.07 (m, 2H), 4.36−4.33 (m, 2H), 3.89 (dd, J = 2.4, 6.6 Hz, 1H), 3.57 (dd, J = 2.4, 8.4 Hz, 1H), 3.21−3.17 (m, 1H), 2.44 (dd, J = 6.6, 6.0 Hz, 1H), 1.51 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 1.36 (s, 3H), 1.33 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.2, 132.8, 132.7, 130.8, 129.7, 128.5, 118.3, 109.6, 108.4, 79.4, 78.0, 75.0, 72.8, 72.8, 38.8, 27.1, 26.9, 26.8, 25.6, 15.1; HRMS (CI) calcd for $[C_{20}H_{30}O_6 + Na]^+$ 389.1935, found 389.1924.

(6*R*)-5,6-Dihydro-6-(*E*)-2′-((4′*R*,5′*S*)-2′,2′-dimethyl-5′-((4″*S*,5″*S*)-2″,2″,5″-trimethyl-1″,3″-dioxolan-4″-yl)-1′,3′-dioxolan-4′-yl)pyran-2-one (26a). To a solution of triene **5a** (18 mg, 0.051 mmol) in 3 mL of CH_2Cl_2 was added Grubbs catalyst (9 mg, 0.01 mmol, 10 mol %) in 2 mL of CH_2Cl_2. The reaction was heated at reflux for 2 h. Solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (7:3 (v/v) hexane/EtOAc) providing lactone **26a** (13 mg, 77% yield) as a colorless oil: $R_f = 0.14$ (7:3 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 2983, 1742; $[\alpha]^{25}_D$ +133° (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 6.89 (ddd, J = 1.2, 3.0, 9.6 Hz, 1H), 6.05 (ddd, J = 1.2, 1.2, 9.6 Hz, 1H), 5.98 (dd, J = 6.0, 15.6 Hz, 1H), 5.85 (dd, J = 7.2, 15.0 Hz, 1H), 4.95 (ddd, J = 4.8, 6.0, 6.0 Hz, 1H), 4.41 (dd, J = 7.8, 7.8 Hz, 1H), 4.39 (dd, J = 6.9, 6.9 Hz, 1H), 3.95 (d, J = 6.6 Hz, 1H), 3.57 (d, J = 8.4 Hz, 1H), 2.49 (ddd, J = 4.8, 5.4, 18.6 Hz, 1H), 2.43 (dddd, J = 2.4, 2.4, 10.8, 18.0 Hz, 1H), 1.52 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H), 1.37 (d, J = 7.8 Hz, 3H), 1.37 (s,

3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.5, 144.4, 131.5, 130.9, 121.6, 109.8, 108.4, 79.4, 77.6, 77.1, 74.5, 72.7, 29.6, 27.1, 26.9, 26.7, 25.5, 15.0; HRMS (CI) calcd for $[C_{18}H_{26}O_6 + Na]^+$ 361.1622, found 361.1621.

Anamarine (1a). A solution of 10% aqueous HCl and THF (1:1, 1.0 mL) was added to a flask containing acetonide **26a** (8 mg, 0.024 mmol). The mixture was heated at 65 °C for 20 min, and the solvent was removed at reduced pressure. The residue was dissolved in 1.0 mL of pyridine, and then Ac_2O (0.1 mL) and a catalytic amount of DMAP were added. After 20 h, solid $NaHCO_3$ was added, diluted with EtOAc, and then filtered through a pad of Celite. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (50:50 (v/v) hexane/EtOAc) providing anamarine (8 mg, 85% yield) as a white solid: mp = 109−111 °C; R_f = 0.15 (1:1 (v/v) hexane/EtOAc); IR (neat, cm^{-1}) 2986, 1742; $[\alpha]^{25}_D$ +17° (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.88 (ddd, J = 3.5, 5.2, 9.9 Hz, 1H), 6.05 (ddd, J = 1.7, 1.7, 9.9 Hz, 1H), 5.88−5.74 (m, 2H), 5.36 (dd, J = 5.2, 7.2 Hz, 1H), 5.30 (dd, J = 3.5, 7.2 Hz, 1H), 5.17 (dd, J = 3.5, 7.0 Hz, 1H), 4.99−4.90 (m, 1H), 4.91 (dq, J = 6.4, 6.4 Hz, 1H), 2.47−2.41 (m, 2H), 2.12 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.17 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 169.8, 169.7, 169.6, 163.4, 144.4, 133.0, 125.6, 121.5, 75.8, 71.9, 71.6, 70.5, 67.3, 29.1, 21.0, 20.9, 20.8, 20.6, 15.8; HRMS (CI) calcd for $[C_{20}H_{26}O_{10} + Na]^+$ 449.1419, found 449.1424.

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

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