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Stereoselective synthesis of anamarine

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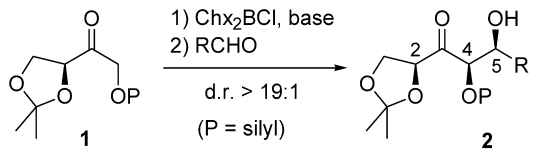
Abstract—A stereoselective synthesis of the naturally occurring, α,β-unsaturated lactone anamarine is described. The key step was a highly stereoselective aldol reaction of a protected erythrulose derivative with a chiral aldehyde. Another relevant step was an asymmetric aldehyde allylation with a chiral allylborane. The lactone ring was made by means of a ring-closing metathesis.

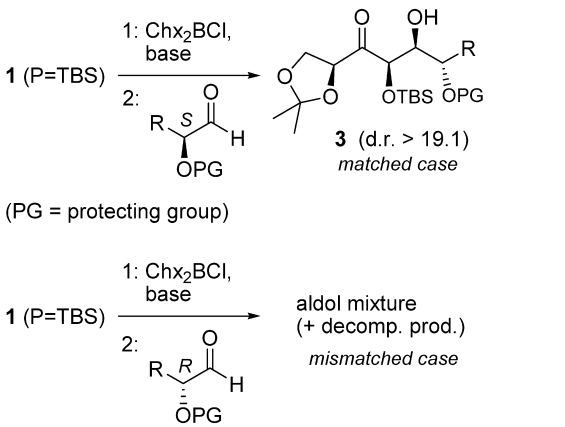
1. Introduction

The aldol reaction[1] has proven to be a powerful and general method for the stereocontrolled construction of carbon–carbon bonds and has relevant application in the synthesis of natural polyoxygenated molecules such as macrolide and polyether antibiotics.[2] Our current interest in the development of erythrulose[3] as a useful chiral building block for the stereocontrolled construction of polyfunctionalized structures has led us to investigate the enolization of protected derivatives thereof and the subsequent addition of the resulting enolates to aldehydes. We recently reported that L-erythrulose acetals with the general formula **1** (Scheme 1, protecting group P=silyl), readily prepared in two steps from L-erythrulose,[4] were transformed into boron enolates provided that chlorodicyclohexylborane (Chx_2BCl) was used as the enolization reagent.[5–7] The boron enolates were then allowed to react with a range of achiral aldehydes to yield aldol adducts of the general formula **2** with a high degree of *syn* 1,2- and 1,3-induction (the 2,4-*syn*/4,5-*syn* relationship in **2**, diastereomeric ratio, d.r.>19:1).



Scheme 1. Boron aldol reactions of erythrulose derivatives with achiral aldehydes.

Very recently, we have shown that such aldol reactions can be carried out with high stereoselectivity also in the case of α-chiral aldehydes. The sense of induction of these doubly diastereoselective processes was found to depend on the type of α-substituents (carbon vs heteroatom groups), matched and mismatched cases being observed. As a matter of fact, (*S*)-α-oxygenated aldehydes were found to react with ketones **1** to yield aldols **3** with a high degree of stereoselectivity, whereas those having the *R* configuration turned out to give sluggish and nonstereoselective reactions (Scheme 2). Mechanistic models were proposed to explain these diverging results.[8]



Scheme 2. Boron aldol reactions of erythrulose derivatives with chiral, α-oxygenated aldehydes.

In order to show the synthetic utility of these aldol reactions, we have now performed a total, stereoselective synthesis of the naturally occurring lactone anamarine (Fig. 1). This α,β-unsaturated lactone and several structural analogues thereof such as spicigerolide, hyptolide and synrotolide have been isolated from species of *Hyptis* and other botanically related genera (natural configurations depicted in Fig. 1).[9] These compounds contain a polyoxygenated chain connected with an α,β-unsaturated six-membered lactone and show a range of pharmacological properties,

Keywords: Erythrulose; Boron aldol reactions; Asymmetric allylboration; Stereoselectivity; Ring-closing metathesis; Anamarine.
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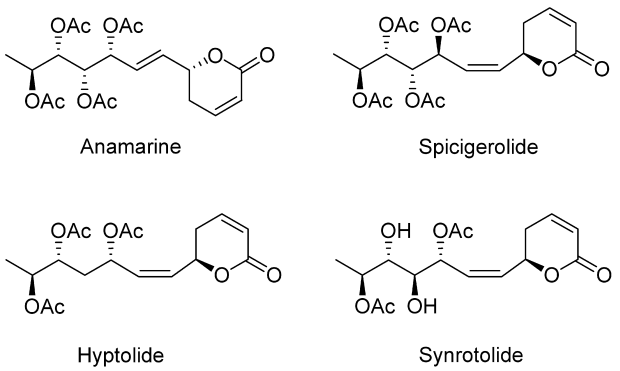
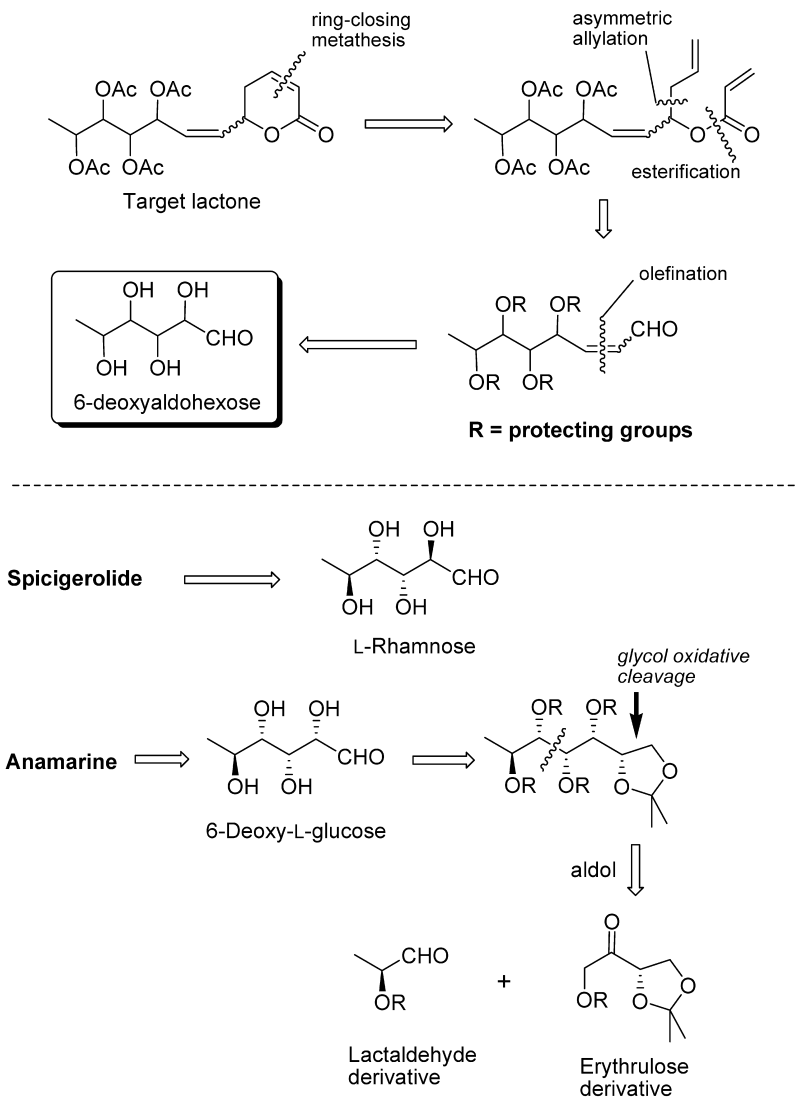


Figure 1. Naturally occurring γ-pyrones isolated from *Hyptis* spp. and related genera.

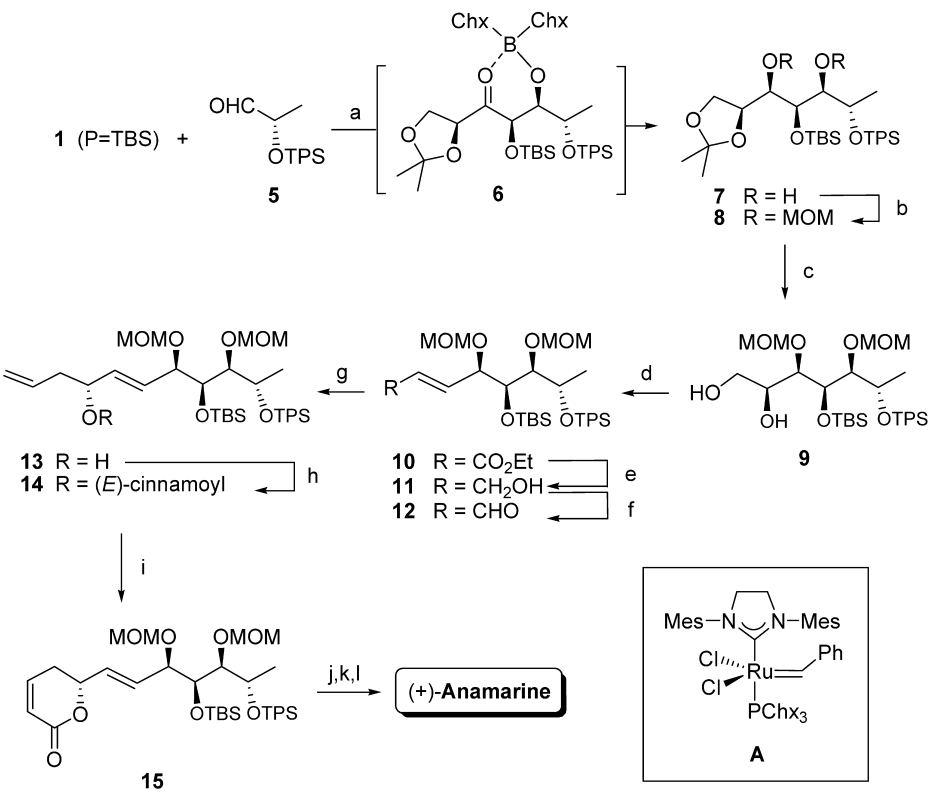
such as cytotoxicity against human tumor cells, antimicrobial or antifungal activity, etc. Pharmacological properties of these types make these compounds interesting synthetic goals. Efforts in this direction were limited for many years to the syntheses of natural (+)-anamarine (Fig. 1) and its nonnatural (−)-enantiomer.[10] Very recently, we have published stereoselective syntheses of the natural enantiomers of spicigerolide and hyptolide.[11]

2. Results and discussion

The previous syntheses of both enantiomers of anamarine were carbohydrate-based, with all stereogenic carbons being already present in the chiral starting materials.[10] Our synthesis relies upon the same general concept used in our recent syntheses of structurally similar lactones, where asymmetric allylations and ring-closing metatheses played a key role.[11] As shown in Scheme 3, the generic retrosynthetic analysis for such lactones points to a 6-deoxyaldohexose as the starting material. In our synthesis of spicigerolide, for instance,[11b] we used to advantage the fact that the polyoxygenated chain has the same absolute configuration as L-rhamnose (6-deoxy-L-mannose), a commercially available sugar. In the case of anamarine, however, the same analysis leads to the nonavailable sugar 6-deoxy-L-glucose. A synthesis for this compound in suitably protected



Scheme 3. Retrosynthetic analysis for anamarine and related polyoxygenated lactones.



Scheme 4. Synthesis of (+)-anamarine. Reaction conditions: (a) Chx_2BCl, Et_3N, Et_2O, 0 °C, then **5**, from −78 °C to 0 °C, 5 h, then $LiBH_4$, −78 °C, 2 h (75% of **7**); (b) MOMCl, DIPEA, 4 days, △ (72%); (c) PPTS, aq MeOH, rt, overnight (70%); (d) $Pb(OAc)_4$, CH_2Cl_2, rt, 1 h, then $(EtO)_2POCH_2COOEt$, LiCl, DIPEA, MeCN, rt, overnight (88% overall); (e) DIBAL, hexane–toluene, 0 °C, 4 h, (82%); (f) PCC, celite, CH_2Cl_2, rt, 1.5 h (90%); (g) allylBIpc$_2$ [from (+)-DIP-Cl and allylmagnesium bromide], Et_2O, −78 °C, 3 h (88:12 diastereoisomer mixture, 74% of pure **13** after chromatography); (h) cinnamoyl chloride, Et_3N, cat. DMAP, CH_2Cl_2, rt, 12 h (81%); (i) catalyst **A** (10%), CH_2Cl_2, reflux, 3 h (98%); (j) $BF_3{\cdot}Et_2O$, SMe_2, −10 °C, 30 min; (k) aq HF, rt, 7 h; (l) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, rt, overnight (62% overall for the three steps). Abbreviations: Chx, cyclohexyl; MOMCl, methoxymethyl chloride; DIPEA, ethyl *N*,*N*-di*iso*propylamine; PPTS, pyridinium *p*-toluenesulfonate; DIP-Cl, di*iso*pinocampheylboron chloride; PCC, pyridinium chlorochromate; DMAP, *N*,*N*-dimethylaminopyridine; DIBAL, di*iso*butylaluminum hydride.

form was then designed with reliance on our aldol methodology with erythrulose derivatives (Scheme 3).

As we have recently reported, the reaction between the boron enolate of ketone **1** (P=TBS) and the (*S*)-lactaldehyde derivative **5** generates with high diastereoselectivity the boron aldolate **6** which, by means of an oxidative hydrolytic work-up, gives rise to the corresponding aldol adduct (Scheme 4).[8] In the present case, however, aldolate **6** was reduced in situ with $LiBH_4$ to yield the *syn*-1,3-diol **7**.[12] After protection of the hydroxyl groups and hydrolytic cleavage of the acetonide ring,[13] diol **9** was oxidatively cleaved to an intermediate α-alkoxy aldehyde (not depicted) which, without purification, was olefinated by means of a modified Horner–Emmons reaction[14] to conjugated ester **10**. Standard functional group manipulations afforded conjugated aldehyde **12**, which was then subjected to asymmetric allylation[15] to alcohol **13**. Acylation of the latter with cinnamoyl chloride,[16] followed by ring-closing metathesis in the presence of the second-generation Grubbs ruthenium catalyst **A**,[17] provided conjugated lactone **15**. Finally, cleavage of all protecting groups and per-acetylation furnished synthetic (+)-anamarine, identical in its physical and spectral properties[9a] to the natural product (Scheme 4). The overall yield was about 8% (based on ketone **1**), a figure which compares well with the previous synthetic efforts.[10]

3. Conclusions

Erythrulose derivatives are able to give highly stereoselective aldol reactions with α-oxygenated aldehydes provided that the configurations of both chiral components are suitably matched (doubly diastereoselective process). The synthetic utility of these reactions has been shown here with the stereoselective synthesis of the naturally occurring, pharmacologically active lactone (+)-anamarine. Further applications of this methodology to the synthesis of natural products are being currently developed by our group and will be described in near future.

4. Experimental

4.1. General

NMR spectra were measured at 400 or 500 MHz in $CDCl_3$ solution at 25 °C. The signals of the deuterated solvent ($CDCl_3$) were taken as the reference (the singlet at δ 7.25 for ^{1}H NMR and the triplet centered at 77.00 ppm for ^{13}C NMR data). The multiplicities of the ^{13}C NMR signals were determined with the DEPT pulse sequence. Mass spectra were run by the electron impact (EIMS, 70 eV) or with the fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix) on a VG AutoSpec mass spectrometer. IR

data are given only for compounds with relevant functions (OH, C=O) and were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Optical rotations were measured at 25 °C. Reactions which required an inert atmosphere were carried out under N_2 with flame-dried glassware. Et_2O was freshly distilled from sodium-benzophenone ketyl. Dichloromethane was freshly distilled from CaH_2. Tertiary amines were freshly distilled from KOH. Toluene was freshly distilled from sodium wire. Commercially available reagents were used as received. Unless detailed otherwise, 'work-up' means pouring the reaction mixture into 5% aq $NaHCO_3$ (if acids had been utilized in the reaction) or into satd aq NH_4Cl (if bases had been utilized), then washing again the organic layer with brine, drying over anhydrous Na_2SO_4 or $MgSO_4$ and elimination of the solvent in vacuo. When solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent, and the washing liquids incorporated into the main organic layer. The obtained material was then chromatographed on a silica gel column (Süd-Chemie AG, 60–200 μ) with the indicated eluent. Reagent acronyms are explained in the caption of Scheme 4.

4.1.1. (1*R*,2*S*,3*S*,4*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldiphenylsilyloxy)-1-((4*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-pentane-1,3-diol (7). The aldol reaction of ketone **1** with aldehyde **5** promoted by Chx_2BCl, followed by in situ $LiBH_4$ reduction was performed as previously reported[8] to yield **7** in 75% overall yield: oil, IR ν_{max} (cm^{-1}) 3400 (br, OH); ^1H NMR (500 MHz) δ 7.75–7.65 (4H, m), 7.45–7.35 (6H, m), 4.25 (1H, br q, *J*=6.5 Hz), 4.10 (1H, dd, *J*=8, 4.5 Hz), 4.00–3.80 (3H, m), 3.55–3.45 (2H, m), 1.43 (3H, s), 1.36 (3H, s), 1.07 (9H, s), 1.07 (3H, d, *J*=6.5 Hz, overlapped), 0.86 (9H, s), 0.12 (3H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz) δ 134.0, 133.8, 109.2, 19.2, 19.1 (C), 135.9, 135.8, 129.7, 129.6, 127.7, 127.5, 76.0, 74.4, 72.5, 70.2, 68.2 (CH), 66.3 (CH_2), 27.1 (×3), 26.7, 26.0 (×3), 25.8, 18.2, −4.2, −4.5 (CH_3).

4.1.2. (4*S*)-4-[(1*R*,2*S*,3*S*,4*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldiphenylsilyloxy)-1,3-bis(methoxymethoxy)pentyl]-2,2-dimethyl-[1,3]dioxolane, 8. Diol **7** (2.355 g, 4 mmol) was dissolved in dry CH_2Cl_2 (100 mL) and treated dropwise with DIPEA (8 mL, 46 mmol) and MOM chloride (3 mL, ca. 40 mmol). The reaction was then stirred at reflux for 4 days. Work-up (extraction with CH_2Cl_2) and column chromatography on silica gel (hexanes–EtOAc, 95:5) afforded compound **8** (1.95 g, 72%): oil, $[\alpha]_D$=−25.5 (*c* 0.9; $CHCl_3$); ^1H NMR (500 MHz) δ 7.70–7.60 (4H, m), 7.40–7.30 (6H, m), 4.86 (2H, AB system, *J*=6.2 Hz), 4.60 (1H, d, *J*=6.7 Hz), 4.40 (1H, d, *J*=6.7 Hz), 4.20 (1H, br q, *J*=6.5 Hz), 3.95–3.90 (2H, m), 3.85 (1H, m), 3.77 (1H, br d, *J*=8 Hz), 3.56 (1H, dd, *J*=8, 3.6 Hz), 3.49 (1H, dd, *J*=8, 3.7 Hz), 3.48 (3H, s), 3.20 (3H, s), 1.31 (3H, s), 1.20 (3H, s), 1.07 (9H, s), 1.02 (3H, d, *J*=6.5 Hz), 0.87 (9H, s), 0.04 (3H, s), 0.00 (3H, s); ^{13}C NMR (125 MHz) δ 134.2, 134.1, 108.2, 19.1, 18.0 (C), 136.1, 135.9, 129.6, 129.5, 127.5, 127.4, 80.8, 80.1, 76.5, 73.7, 70.1 (CH), 97.7, 97.0, 65.8 (CH_2), 56.1, 55.6, 27.1 (×3), 26.8, 26.0 (×3), 25.7, 17.7, −4.7, −5.0 (CH_3). Anal. Calcd for $C_{36}H_{60}O_8Si_2$: C, 63.87; H, 8.93. Found, C, 64.01; H, 9.00.

4.1.3. (2*S*,3*R*,4*S*,5*S*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-3,5-bis(methoxymethoxy)-heptane-1,2-diol, 9. Acetonide **8** (1.354 g, 2 mmol) was dissolved in MeOH (20 mL) and treated with a solution of pyridinium *p*-toluenesulfonate (12 mg, 0.05 mmol) in water (1 mL). The solution was stirred overnight at room temperature and then carefully neutralized with aq Na_2CO_3. After removal of all volatiles in vacuo, the residue was subjected to column chromatography on silica gel (hexanes–EtOAc, 70:30) to furnish diol **9** (892 mg, 70%): oil, $[\alpha]_D$=+7.3 (*c* 0.9; $CHCl_3$); IR ν_{max} (cm^{-1}) 3400 (br, OH); ^1H NMR (500 MHz) δ 7.70–7.60 (4H, m), 7.40–7.30 (6H, m), 4.87 (2H, AB system, *J*=6 Hz), 4.48 (2H, AB system, *J*=6.5 Hz), 4.08 (1H, br q, *J*=6.5 Hz), 3.94 (1H, br d, *J*=6 Hz), 3.72 (2H, m), 3.55 (2H, m), 3.47 (3H, s), 3.44 (1H, t, *J*=5 Hz), 3.25 (3H, s), 2.60 (1H, d, *J*=5 Hz, OH), 2.50 (1H, t, *J*=6 Hz, OH), 1.08 (3H, d, *J*=6.5 Hz), 1.05 (9H, s), 0.84 (9H, s), 0.03 (3H, s), 0.02 (3H, s); ^{13}C NMR (125 MHz) δ 134.5, 133.9, 19.1, 18.4 (C), 136.1, 135.9, 129.6, 129.5, 127.6, 127.4, 81.5, 80.8, 73.0, 70.2, 69.9 (CH), 98.2, 97.7, 64.1 (CH_2), 56.1 (×2), 27.1 (×3), 26.0 (×3), 18.0, −4.6, −4.8 (CH_3). HR FABMS *m*/*z* 659.3393 $(M+Na)^+$, calcd for $C_{33}H_{56}NaO_8Si_2$, 659.3411. Anal. Calcd for $C_{33}H_{56}O_8Si_2$: C, 62.23; H, 8.86. Found, C, 62.03; H, 9.02.

4.1.4. Ethyl (2*E*,4*R*,5*S*,6*S*,7*S*)-5-(*tert*-butyldimethylsilyloxy)-7-(*tert*-butyldiphenylsilyloxy)-4,6-bis(methoxymethoxy)-oct-2-enoate, 10. Lead tetraacetate (488 mg, 1.1 mmol) was added to a solution of diol **9** (636 mg, ca. 1 mmol) in CH_2Cl_2 (10 mL). The solution was stirred for 1 h at room temperature, then filtered through a Celite pad and evaporated in vacuo. The residue was redissolved in Et_2O, cooled in an ice bath and stirred with powdered K_2CO_3 (1.38 g, 10 mmol) for 30 min. The mixture was then filtered and evaporated in vacuo. The oily residue was dissolved in dry acetonitrile (45 mL) and treated with DIPEA (610 μL, 3.5 mmol), LiCl (212 mg, 5 mmol) and $(EtO)_2POCH_2COOEt$ (790 μL, 4 mmol). The reaction mixture was then stirred overnight at room temperature and worked up (extraction with Et_2O). Solvent removal in vacuo and column chromatography of the residue on silica gel (hexanes–EtOAc, 90:10) provided ethyl ester **10** (594 mg, 88%): oil, $[\alpha]_D$=−22.5 (*c* 1; $CHCl_3$); IR ν_{max} (cm^{-1}) 1724 (C=O); ^1H NMR (500 MHz) δ 7.70–7.60 (4H, m), 7.40–7.30 (6H, m), 7.00 (1H, dd, *J*=16, 4.5 Hz), 5.86 (1H, dd, *J*=16, 1.7 Hz), 4.84 and 4.76 (2H, AB system, *J*=6 Hz), 4.35 (2H, AB system, *J*=6.6 Hz), 4.17 (3H, m), 3.98 (1H, dq, *J*=2, 6.5 Hz), 3.68 (1H, dd, *J*=7.7, 2 Hz), 3.60 (1H, dd, *J*=7.7, 4.5 Hz), 3.46 (3H, s), 3.20 (3H, s), 1.29 (3H, t, *J*=7 Hz), 1.04 (9H, s), 1.02 (3H, d, *J*=6.5 Hz), 0.88 (9H, s), 0.05 (6H, s); ^{13}C NMR (125 MHz) δ 165.9, 134.7, 133.8, 19.1, 18.0 (C), 144.5, 136.1, 136.0, 129.5, 129.4, 127.5, 127.4, 122.2, 81.5, 77.5, 74.1, 70.1 (CH), 97.8, 95.3, 60.3 (CH_2), 56.1, 55.8, 27.1 (×3), 25.9 (×3), 18.1, 14.2, −4.5, −5.0 (CH_3). HR FABMS *m*/*z* 697.3599 $(M+Na)^+$, calcd for $C_{36}H_{58}NaO_8Si_2$, 697.3562. Anal. Calcd for $C_{36}H_{58}O_8Si_2$: C, 64.06; H, 8.66. Found, C, 64.03; H, 8.88.

4.1.5. (2*E*,4*R*,5*S*,6*S*,7*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-(*tert*-butyldiphenylsilyloxy)-4,6-bis(methoxymethoxy)-oct-2-en-1-ol, 11. DIBAL (2.4 mL of a 1 M solution in toluene, 2.4 mmol) was added to an ice-cooled solution of ester **10** (540 mg, 0.8 mmol) in hexanes (10 mL). The solution was stirred for 4 h at 0 °C and quenched with satd

aq NH_4Cl. After filtering through a Celite pad, the solution was evaporated in vacuo. Column chromatography of the residue on silica gel (hexanes–EtOAc, 80:20) afforded alcohol **11** (415 mg, 82%): oil, $[\alpha]_D=-37.8$ (*c* 1.7; $CHCl_3$); IR ν_{max} (cm^{-1}) 3430 (br, OH); ^1H NMR (500 MHz) δ 7.70–7.60 (4H, m), 7.40–7.30 (6H, m), 5.70 (1H, dt, *J*=16, 5.2 Hz), 5.55 (1H, dd, *J*=16, 5.5 Hz), 4.86 and 4.73 (2H, AB system, *J*=6.2 Hz), 4.38 and 4.26 (2H, AB system, *J*=6.6 Hz), 4.02 (2H, m), 3.96 (2H, m), 3.78 (1H, dd, *J*=7.5, 2 Hz), 3.50 (1H, dd, *J*=7.5, 4 Hz), 3.46 (3H, s), 3.16 (3H, s), 1.04 (9H, s), 1.03 (3H, d, *J*=6.5 Hz), 0.87 (9H, s), 0.03 (6H, s); ^{13}C NMR (125 MHz) δ 134.4, 134.3, 19.1, 18.1 (C), 136.1, 136.0, 132.3, 129.5, 127.5, 127.4, 80.0, 77.8, 74.1, 70.4 (CH), 97.2, 94.4, 63.1 (CH_2), 55.9, 55.5, 27.1 (×3), 25.9 (×3), 17.7, −4.5, −4.9 (CH_3). HR FABMS *m/z* 655.3475 $(M+Na)^+$, calcd for $C_{34}H_{56}NaO_7Si_2$, 655.3462. Anal. Calcd for $C_{34}H_{56}O_7Si_2$: C, 64.51; H, 8.92. Found, C, 64.44; H, 8.80.

4.1.6. (4*R*,5*S*,6*S*,7*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-(*tert*-butyldiphenylsilyloxy)-4,6-bis(methoxymethoxy)-oct-2*E*-enal, 12. PCC (194 mg, 0.9 mmol) and Celite (180 mg) were added to a solution of alcohol **11** (380 mg, 0.6 mmol) in dry CH_2Cl_2 (6 mL). The solution was stirred for 1.5 h at room temperature, then filtered through a Celite pad and evaporated in vacuo. The oily residue was subjected to column chromatography on silica gel (hexanes–EtOAc, 90:10) to provide aldehyde **12** (341 mg, 90%): oil, $[\alpha]_D=-10.8$ (*c* 1.5; $CHCl_3$); IR ν_{max} (cm^{-1}) 1697 (C=O); ^1H NMR (500 MHz) δ 9.40 (1H, d, *J*=8 Hz), 7.70–7.60 (4H, m), 7.40–7.30 (6H, m), 6.82 (1H, dd, *J*=16, 4.3 Hz), 6.10 (1H, ddd, *J*=16, 8, 1 Hz), 4.80 and 4.76 (2H, AB system, *J*=6 Hz), 4.39 (2H, AB system, *J*=6.7 Hz), 4.28 (1H, m), 4.00 (1H, br q, *J*=6.5 Hz), 3.70–3.60 (2H, m), 3.43 (3H, s), 3.20 (3H, s), 1.06 (3H, d, *J*=6.5 Hz), 1.05 (9H, s), 0.87 (9H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz) δ 193.1, 134.5, 133.8, 18.1, 18.0 (C), 153.5, 136.0, 135.9, 132.3, 129.7, 129.5, 127.6, 127.4, 81.3, 77.6, 74.2, 70.2 (CH), 97.7, 95.7 (CH_2), 56.1, 55.9, 27.0 (×3), 25.9 (×3), 19.1, −4.6, −5.0 (CH_3). HR FABMS *m/z* 653.3325 $(M+Na)^+$, calcd for $C_{34}H_{54}NaO_7Si_2$, 653.3305.

4.1.7. (4*R*,7*R*,8*S*,9*S*,10*S*)-8-(*tert*-Butyldimethylsilyloxy)-10-(*tert*-butyldiphenylsilyloxy)-7,9-bis(methoxymethoxy)-undeca-1,5*E*-dien-4-ol, 13. Allylmagnesium bromide (commercial 1 M solution in Et_2O, 750 μL, 0.75 mmol) was added dropwise via syringe to a solution of (+)-di*iso*pinocampheylboron chloride (289 mg, 0.9 mmol) in dry Et_2O (5 mL) cooled in a dry ice–acetone bath. After replacing the latter by an ice bath, the mixture was stirred for 1 h. The solution was then allowed to stand, which caused precipitation of magnesium chloride. The supernatant solution was then carefully transferred to another flask via canula. After cooling this flask at −78 °C, a solution of aldehyde **12** (378 mg, 0.6 mmol) in dry Et_2O (5 mL) was added dropwise via syringe. The resulting solution was further stirred at the same temperature for 3 h. The reaction mixture was then quenched through addition of phosphate pH 7 buffer solution (2 mL), MeOH (3 mL) and 30% H_2O_2 (2 mL). After stirring for 30 min, the mixture was poured onto satd aq $NaHCO_3$ and worked up as usual (extraction with Et_2O). An NMR examination of the crude reaction product revealed that an 88:12 diastereoisomer mixture was present. A careful column chromatography on silica gel (hexanes–EtOAc, 90:10) afforded pure alcohol **13** (299 mg, 74%): oil, $[\alpha]_D=-47.6$ (*c* 1.8; $CHCl_3$); IR ν_{max} (cm^{-1}) 3450 (br, OH); ^1H NMR (400 MHz) δ 7.70–7.60 (4H, m), 7.40–7.30 (6H, m), 5.77 (1H, m), 5.62 (1H, ddd, *J*=15.7, 5.4, 1 Hz), 5.47 (1H, ddd, *J*=15.7, 6.6, 1 Hz), 5.15–5.10 (2H, m), 4.86 and 4.75 (2H, AB system, *J*=6.2 Hz), 4.37 and 4.22 (2H, AB system, *J*=6.6 Hz), 4.05 (1H, dq, *J*=2.2, 6.5 Hz), 4.00 (2H, m), 3.76 (1H, dd, *J*=7.5, 2.2 Hz), 3.53 (1H, dd, *J*=7.5, 4.3 Hz), 3.46 (3H, s), 3.17 (3H, s), 2.20 (2H, m), 1.70 (1H, br s, OH), 1.05 (3H, d, *J*=6.5 Hz), 1.04 (9H, s), 0.86 (9H, s), 0.03 (3H, s), 0.02 (3H, s); ^{13}C NMR (100 MHz) δ 134.5, 134.3, 19.1, 18.1 (C), 136.5, 136.1 (×2), 134.3, 129.6, 129.5, 127.6, 127.5, 126.1, 80.6, 78.2, 74.4, 70.8, 70.4 (CH), 118.2, 97.5, 94.1, 41.7 (CH_2), 56.0, 55.5, 27.1 (×3), 26.0 (×3), 18.0, −4.5, −4.8 (CH_3). HR FABMS *m/z* 695.3757 $(M+Na)^+$, calcd for $C_{37}H_{60}NaO_7Si_2$, 695.3775. Anal. Calcd for $C_{37}H_{60}O_7Si_2$: C, 66.03; H, 8.99. Found, C, 65.93; H, 9.08.

4.1.8. (4*R*,7*R*,8*S*,9*S*,10*S*)-8-(*tert*-Butyldimethylsilyloxy)-10-(*tert*-butyldiphenylsilyloxy)-7,9-bis(methoxymethoxy)-undeca-1,5*E*-dien-4-yl (*E*)-3-phenylacrylate, 14. Alcohol **13** (270 mg, 0.4 mmol) was dissolved in dry CH_2Cl_2 (8 mL) and treated with triethyl amine (140 μL, 1 mmol), (*E*)-cinnamoyl chloride (133 mg, 0.8 mmol) and DMAP (5 mg, ca. 0.04 mmol). The mixture was then stirred overnight at room temperature and worked up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexanes–EtOAc, 95:5) provided ester **14** (260 mg, 81%): oil, $[\alpha]_D=-60.4$ (*c* 3; $CHCl_3$); IR ν_{max} (cm^{-1}) 1716 (C=O); ^1H NMR (500 MHz) δ 7.70–7.60 (5H, m), 7.50 (3H, m), 7.40–7.30 (8H, m), 6.42 (1H, d, *J*=16 Hz), 5.78 (1H, m), 5.66 (1H, dd, *J*=15.7, 5.1 Hz), 5.62 (1H, dd, *J*=15.7, 6.5 Hz), 5.45 (1H, m), 5.15–5.10 (2H, m), 4.84 and 4.76 (2H, AB system, *J*=6.2 Hz), 4.43 and 4.28 (2H, AB system, *J*=6.6 Hz), 4.07 (1H, dq, *J*=2.2, 6.5 Hz), 4.03 (1H, m), 3.79 (1H, dd, *J*=7.2, 2.5 Hz), 3.58 (1H, dd, *J*=7.5, 4.7 Hz), 3.45 (3H, s), 3.20 (3H, s), 2.22 (2H, m), 1.06 (9H, s), 1.05 (3H, d, *J*=6.5 Hz), 0.86 (9H, s), 0.04 (3H, s), 0.02 (3H, s); ^{13}C NMR (125 MHz) δ 165.9, 134.8, 134.5, 134.1, 18.3, 18.1 (C), 144.8, 136.0, 135.9, 133.3, 132.2, 130.2, 129.6, 129.4, 128.8, 128.4, 128.1, 127.6, 127.4, 118.4, 80.8, 78.2, 74.2, 72.8, 70.6 (CH), 118.0, 97.6, 94.2, 39.0 (CH_2), 56.0, 55.5, 27.1 (×3), 26.0 (×3), 19.1, −4.4, −4.8 (CH_3). Anal. Calcd for $C_{46}H_{66}O_8Si_2$: C, 68.79; H, 8.28. Found, C, 68.93; H, 8.10.

4.1.9. (6*R*)-6-[(3*R*,4*S*,5*S*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-3,5-bis(methoxymethoxy)-hept-1-enyl]-5,6-dihydropyran-2-one, 15. Ester **14** (240 mg, 0.3 mmol) and ruthenium catalyst **A** (26 mg, 0.03 mmol) were dissolved in dry, degassed CH_2Cl_2 (42 mL) and heated under N_2 at reflux until consumption of the starting material (3–4 h, TLC monitoring!). Solvent removal under reduced pressure was followed by column chromatography on silica gel (hexanes–EtOAc, 4:1) to yield α,β-unsaturated lactone **15** (206 mg, 98%): oil, $[\alpha]_D=-15.2$ (*c* 1.5; $CHCl_3$); IR ν_{max} (cm^{-1}) 1733 (C=O); ^1H NMR (500 MHz) δ 7.75–7.65 (4H, m), 7.40–7.30 (6H, m), 6.74 (1H, m), 6.00 (1H, br d, *J*=10 Hz), 5.74 (1H, dd, *J*=16, 5.1 Hz), 5.64 (1H, dd, *J*=16, 5.5 Hz), 4.83 and 4.76 (2H, AB system, *J*=6.2 Hz), 4.70 (1H, m), 4.36 and 4.26

(2H, AB system, J=6.5 Hz), 4.04 (2H, m), 3.70 (1H, dd, J=7.7, 1.5 Hz), 3.53 (1H, dd, J=7.5, 4.5 Hz), 3.46 (3H, s), 3.16 (3H, s), 2.15 (2H, m), 1.06 (3H, d, J=6.5 Hz), 1.04 (9H, s), 0.86 (9H, s), 0.03 (6H, s); ^{13}C NMR (125 MHz) δ 163.8, 134.4, 134.3, 19.1, 18.1 (C), 144.6, 136.0, 135.9, 130.3, 129.6, 129.5, 129.3, 127.5, 127.4, 121.5, 80.7, 77.6, 77.4, 74.0, 70.2 (CH), 97.5, 94.7, 29.5 (CH_2), 55.9, 55.5, 27.0 (×3), 25.9 (×3), 17.9, −4.5, −5.0 (CH_3). FABMS m/z 721 $(M+Na)^+$, calcd for $C_{38}H_{58}NaO_8Si_2$, 721. Anal. Calcd for $C_{38}H_{58}O_8Si_2$: C, 65.29; H, 8.36. Found, C, 65.23; H, 8.16.

4.1.10. (6*R*)-6-[(3*R*,4*S*,5*S*,6*S*)-3,4,5,6-Tetraacetoxyhept-1-enyl]-5,6-dihydropyran-2-one, Anamarine. Lactone **15** (196 mg, 0.28 mmol) was dissolved in SMe_2 (3 mL) and cooled to −10 °C. Then, $BF_3{\cdot}Et_2O$ (710 μL, 5.6 mmol) was added to the solution, which was stirred at the same temperature for 30 min. Work-up (extraction with CH_2Cl_2) and solvent removal under reduced pressure gave an oily material which was dissolved in MeCN (5 mL) and treated at room temperature with 48% aq HF (115 μL, 2.8 mmol). After stirring at room temperature for 7 h, the reaction mixture was worked up (extraction with CH_2Cl_2) and evaporated in vacuo. The oily residue was then dissolved in dry CH_2Cl_2 (10 mL) and treated with Et_3N (310 μL, 2.2 mmol), acetic anhydride (190 μL, 2 mmol) and DMAP (4 mg, 0.03 mmol). After stirring overnight, the reaction mixture was worked up (extraction with CH_2Cl_2) and chromatographed on a silica gel column (hexanes–EtOAc, 1:1) to give (+)-anamarine (74 mg, 62% overall): white crystals, mp 110–111 °C (from Et_2O), lit.[9a] for natural anamarine, mp 110–112 °C; $[\alpha]_D$=+14.5 (c 0.06; $CHCl_3$); lit.[9a] for natural anamarine, $[\alpha]_D$=+28.2 (c 0.52; $CHCl_3$), value later revised to +18.8; lit.[10b] for synthetic (+)-anamarine, $[\alpha]_D$=+15.9 (c 0.8; $CHCl_3$); lit.[10c] for synthetic (−)-anamarine, $[\alpha]_D$=−15 (c 0.02; $CHCl_3$); IR ν_{max} (cm^{-1}) 1738 (C=O); ^{1}H NMR (500 MHz) δ 6.88 (1H, ddd, J=10, 5.2, 3 Hz), 6.04 (1H, dt, J=10, 1.5 Hz), 5.85–5.75 (2H, m), 5.36 (1H, dd, J=7, 6.5 Hz), 5.30 (1H, dd, J=7, 3.5 Hz), 5.17 (1H, dd, J=7, 3.5 Hz), 4.95 (1H, m), 4.90 (1H, quint, J=6.5 Hz), 2.45 (2H, m), 2.12 (3H, s), 2.07 (3H, s), 2.06 (3H, s), 2.02 (3H, s), 1.17 (3H, d, J=6.5 Hz); ^{13}C NMR (125 MHz) δ 170.0, 169.8, 169.7, 169.6, 163.4 (C), 144.5, 133.0, 125.7, 121.6, 75.9, 71.9, 71.7, 70.5, 67.4 (CH), 29.2 (CH_2), 21.0, 20.9, 20.8, 20.6, 15.8 (CH_3).

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