JOC The Journal of Organic Chemistry

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Total Synthesis of (−)-Anamarine

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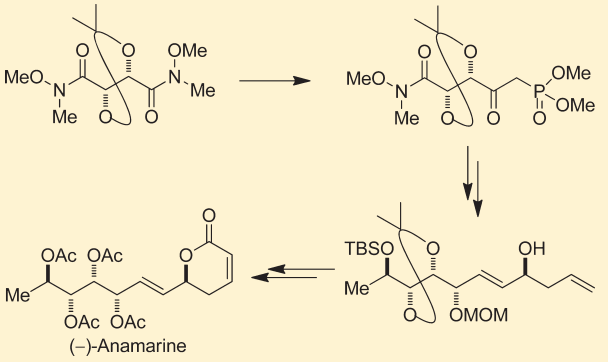
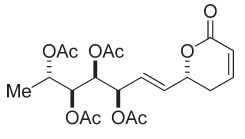
Supporting Information

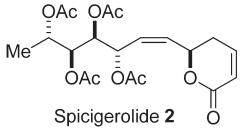
ABSTRACT: Total synthesis of polyhydroxy δ-pyranone natural product (−)-anamarine is accomplished from D-(−)-tartaric acid. The main feature of the synthesis is the utility of hitherto unexplored β-keto phosphonate derived from tartaric acid amide and further elaboration involving stereoselective reduction.



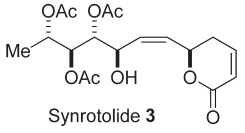
5,6-Dihydro-2*H*-pyran-2-one (δ-pyranone) is an ubiquitous structural unit found in a number of bioactive natural products of therapeutic significance. Natural products and analogues possessing this moiety have been shown to exhibit a number of biological activities including anticancer activity.[1] (+)-Anamarine (**1**), isolated from the flowers and leaves of an unclassified Peruvian *Hyptis* species, is such a δ-pyranone with a side chain comprising four contiguous hydroxy group substitutions.[2] (+)-Anamarine (**1**) is structurally similar to other members of the polyhydroxy δ-pyranone natural product family such as spicigerolide (**2**), synrotolide (**3**), synargentolide A (**4**), etc.



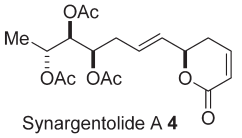
(+)-Anamarine **1**



Spicigerolide **2**



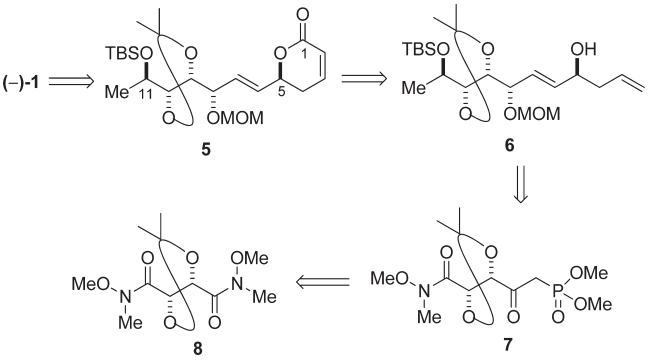
Synrotolide **3**



Synargentolide A **4**

Until now, five total syntheses were reported for (+)-anamarine in the literature. Early syntheses by Valverde et al.[3] and by Lorenz and Lichtenthaler[4] involved an arduous approach from carbohydrate precursors and suffered from low yields. A recent approach by Gao and O'Doherty[5] relied on Sharpless' asymmetric dihydroxylation of sorbic acid ester, while Sabitha et al.[6] disclosed a multistep sequence using asymmetric dihydroxylation and olefin cross-metathesis as the key steps in their synthesis of **1**. The synthesis by Marco's group[7] involved a boronate aldol reaction of lactic acid derived aldehyde with an appropriately protected erythrulose derivative. Our efforts in the use of tartaric acid as a four-carbon, four-hydroxy synthon culminated in the synthesis of a variety of natural products including bioactive lactones.[8] Herein, we report the synthesis of (−)-anamarine from D-(−)-tartaric acid based on a strategy of desymmetrization of tartaric acid amide.

Scheme 1. Retrosynthesis for (−)-Anamarine 1

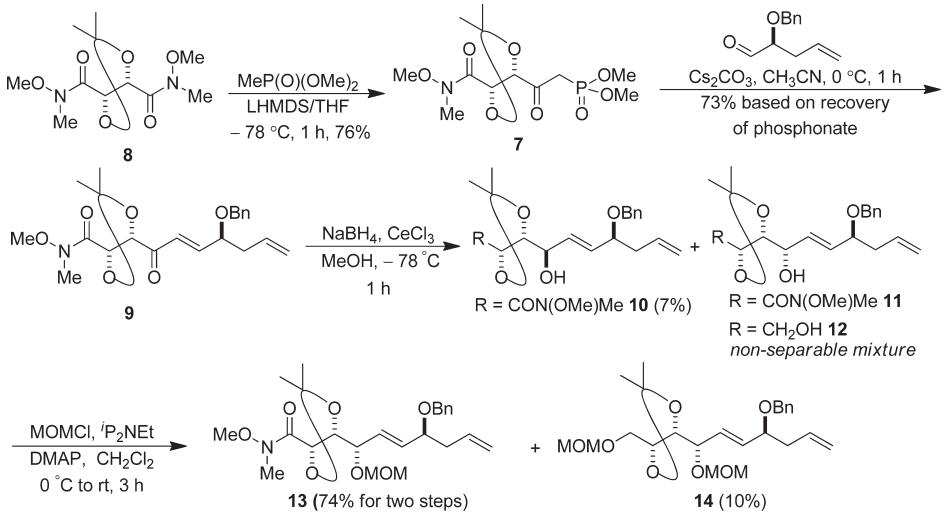


Our approach for the synthesis of (−)-anamarine is depicted in Scheme 1. Synthesis of **1** is anticipated by deprotection of the protecting groups in the lactone **5**, the synthesis of which is envisaged by ring-closing metathesis of the acryloyl ester derived from **6**. Formation of the 1,4-dienol unit in **6** is envisioned by elaboration of the hitherto unknown β-keto phsophonate **7** derived from tartaric acid amide, while Grignard reagent addition and stereoselective reduction is planned for the installation of the other hydroxy group at the C11 position (Scheme 1).

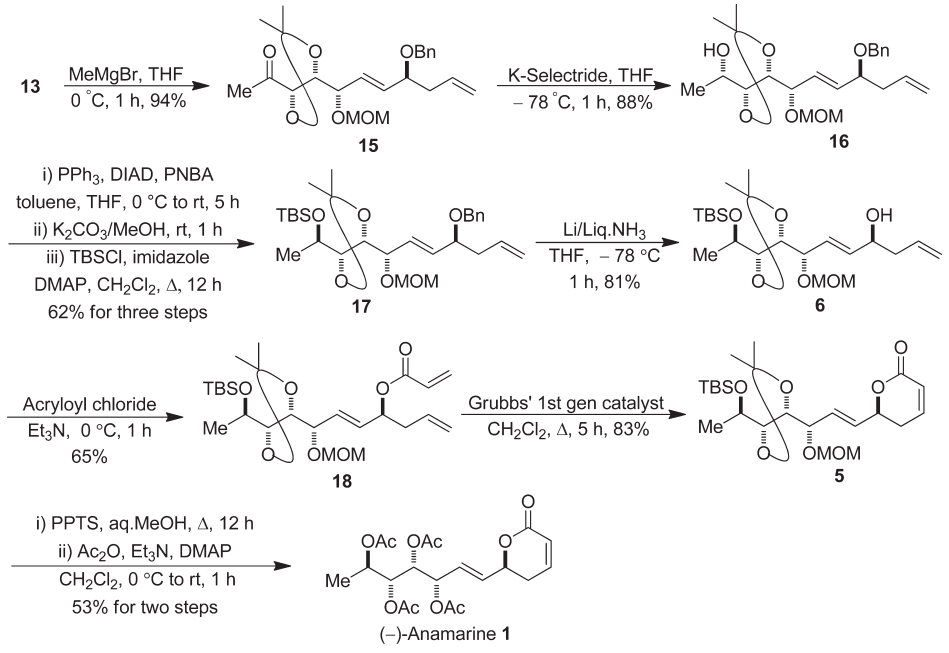
Received: May 26, 2011
Published: July 08, 2011

dx.doi.org/10.1021/jo2010389 | *J. Org. Chem.* 2011, 76, 6889–6893

Scheme 2. Synthesis of the 1,4-Dienol Unit 13



Scheme 3. Total Synthesis of (−)-Anamarine 1



Accordingly, the synthetic sequence commenced with the addition of 1.5 equiv of the lithium anion derived from dimethylmethyl phosphonate to the bis-Weinreb amide **8**[9] affording the mono keto phosphonate **7** in 76% yield.[10] Horner–Wadsworth–Emmons olefination of (*S*)-2-benzyloxypent-4-enal[11] with the phosphonate **7** yielded the α,β-unsaturated ketone **9** in 73% yield (based on 65% conversion). Reduction of the ketone under Luche reduction conditions furnished the diastereomeric alcohols **10** and **11** along with the diol **12** resulting from the competing reduction of the Weinreb amide. Minor diasteroemer **10** was separated by column chromatography, and the major diastereomer **11** which was nonseparable from **12** was purified as its MOM ether **13** (Scheme 2).

Addition of MeMgBr to **13** afforded the ketone **15** in almost quantitative yield. Reduction of **15** with K-Selectride yielded the alcohol **16** in 88% yield. Mitsunobu inversion of **16** furnished the required diastereomer, which was purified as the silyl ether **17** using standard conditions. Deprotection of the benzyl ether in **17** under Na/liqNH$_3$ conditions yielded the homoallylic alcohol **6** in 81% yield. Acryloylation of **6** furnished the ester **18**, which on ring-closing metathesis (RCM) reaction with Grubbs' first-generation catalyst[12] afforded the lactone **5** in 83% yield. Deprotection of the protecting groups in **5** with PPTS in aq MeOH yielded the polyol, which was acylated under standard conditions to afford (−)-anamarine **1** in 53% yield (Scheme 3). The spectral data and specific rotation of (−)-**1** are in complete agreement with that reported in literature.[2,3,7]

In conclusion, a linear strategy for the synthesis of polyol-containing δ-pyranone natural product (−)-anamarine is presented from D-(−)-tartaric acid. The synthetic sequence

dx.doi.org/10.1021/jo2010389 |*J. Org. Chem.* 2011, 76, 6889–6893

showcased the use of hitherto unknown β-keto phosphonate derived from tartaric acid amide in the construction of the 1,4-dienol unit. The synthesis depicted is useful for the synthesis of the other structurally similar natural products and their analogues.

EXPERIMENTAL SECTION

Preparation of 7. To a stirred solution of dimethyl methylphosphonate (0.77 mL, 7.19 mmol) in THF (5 mL) was added LHMDS (5.4 mL of 1 M solution in THF, 5.4 mmol) at −78 °C. The reaction mixture was stirred at the same temperature for 40 min. A solution of **8** (1.00 g, 3.6 mmol) in THF (10 mL) was added dropwise at −78 °C and stirred at the same temperature for 1 h. After completion of the reaction (monitored by TLC), it was cautiously quenched by the addition of saturated NH_4Cl (2 mL) and dried over Na_2SO_4. Evaporation of solvent followed by silica gel column chromatography of the resultant residue with EtOAc as eluent furnished **7** (0.93 g, 76%) as a yellow colored oil: $[\alpha]^{24}_D$ −31.5 (*c* 1.3, $CHCl_3$); IR (neat) 2939, 1721, 1670, 1261, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.11 (d, *J* = 4.5 Hz, 1H), 4.97 (d, *J* = 4.4 Hz, 1H), 3.81 (d, *J* = 5.4 Hz, 3H), 3.79 (d, *J* = 5.3 Hz, 3H), 3.72 (s, 3H), 3.53 (dd, *J* = 22.6, 14.3 Hz, 1H), 3.23 (s, 3H), 3.21 (dd, *J* = 22.6, 11.5 Hz, 1H), 1.50 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 200.1, 169.4, 113.0, 82.3, 73.8, 61.7, 53.1 (d, *J* = 7 Hz), 53.03 (d, *J* = 7 Hz), 36.9 (d, *J* = 130 Hz), 32.4, 26.6, 26.2; HRMS for $C_{12}H_{22}NO_8P$ + Na calcd 362.0981, found 362.0982.

Preparation of 9. To a solution of **7** (0.21 g, 0.62 mmol) in MeCN (2 mL) was added Cs_2CO_3 (0.38 g, 1.17 mmol), and the reaction mixture was stirred for 45 min at room temperature. It was cooled to 0 °C, and a freshly prepared solution of (*S*)-benzyloxypent-4-enal[11] (0.58 mmol) in MeCN (5 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h and was cautiously quenched by addition of saturated citric acid (5 mL). The reaction mixture was then poured into water (15 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. Evaporation of the solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether/EtOAc (3:2) as eluent to furnish **9** (0.12 g) in 48% yield as a colorless oil along with 0.073 g (35%) of the unreacted phosphonate **7**: $[\alpha]^{24}_D$ −18.3 (*c* 1.8, $CHCl_3$); IR (neat) 2983, 2936, 1721, 1668, 1207, 1091, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 6.95 (dd, *J* = 15.9, 6.0 Hz, 1H), 6.65 (d, *J* = 15.9 Hz, 1H), 5.76 (ddt, *J* = 17.2, 10.0, 7.0 Hz, 1H), 5.13 (brd, *J* = 4.2 Hz, 1H), 5.08 (dd, *J* = 18.6, 9.3 Hz, 2H), 5.0 (brd *J* = 4.6 Hz, 1H), 4.56, 4.41 (ABq, *J* = 11.7 Hz, 2H), 4.05 (q, *J* = 6.2 Hz, 1H), 3.69 (s, 3H), 3.21 (s, 3H), 2.53−2.27 (m, 2H), 1.50 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 196.3, 169.9, 148.5, 137.8, 133.3, 128.4, 127.8, 127.7, 125.9, 118.0, 113.0, 81.6, 77.9, 74.4, 71.2, 61.6, 39.2, 32.5, 26.7, 26.4; HRMS for $C_{22}H_{29}NO_6$ + Na calcd 426.1894, found 426.1894.

Preparation of 10−12. To a stirred solution of **9** (0.47 g, 1.15 mmol) in MeOH (1.5 mL) was added $CeCl_3 \cdot 7H_2O$ (0.65 g, 1.73 mmol), and the reaction mixture was stirred for 45 min at room temperature. It was cooled to −78 °C, and $NaBH_4$ (0.087 g, 2.3 mmol) was added portionwise for over 5 min. The reaction mixture was stirred at the same temperature for 1 h, and after completion of the reaction (monitored by TLC), it was quenched by addition of water (1 mL) at −78 °C, slowly warmed up to room temperature, and stirred at room temperature for 10 min. The mixture was then poured into water (10 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. Evaporation of the solvent gave the residue which was purified by silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluent to furnish **10** (0.032 g, 7%) as a colorless oil and a nonseparable mixture of **11** and **12** (0.42 g) which was used as such in the next step. Compound **10**: $[\alpha]^{24}_D$ −23.8 (*c* 2.0, $CHCl_3$); IR (neat) 3445, 2935, 1663, 1381, 1066, 990 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.20 (m, 5H), 5.89−5.72 (m, 2H), 5.67 (dd, *J* = 15.7, 4.8 Hz, 1H), 5.05 (dd, *J* = 15.6, 9.1 Hz, 2H), 4.75 (brs, 1H), 4.69 (brs, 1H), 4.52, 4.30 (ABq, *J* = 11.9 Hz, 2H), 4.48 (brs, 1H), 3.81 (q, *J* = 6.7 Hz, 1H), 3.71 (s, 3H), 3.14 (s, 3H), 2.48−2.34 (m, 2H), 2.33−2.20 (m, 1H), 1.49 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.2, 138.6, 134.4, 132.7, 130.1, 128.3, 127.7, 127.5, 117.0, 111.1, 79.9, 78.9, 78.8, 72.1, 70.4, 70.0, 61.3, 40.1, 32.3, 26.9, 26.0, 14.2; HRMS for $C_{22}H_{31}NO_6$ + Na calcd 428.2049, found 428.2043.

Preparation of 13 and 14. To a precooled (0 °C) solution of a mixture of **11** and **12** (0.42 g, obtained above) in DCM (5 mL) were added DMAP (0.025 g, 0.20 mmol) and $^iPr_2NEt$ (0.9 mL, 9.35 mmol) dropwise followed by MOMCl (0.3 mL, 4.13 mmol). The reaction mixture was slowly allowed to warm to room temperature and stirred at room temperature for 3 h. After completion of the reaction (TLC), it was poured into water (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. Evaporation of solvent gave the crude residue which was purified and separated by silica gel column chromatography using petroleum ether/EtOAc (4:1) as eluent to furnish **13** (0.34 g, 74% yield for two steps) as a colorless oil and **14** (0.046 g) in 10% yield. Compound **13**: $[\alpha]^{24}_D$ +16.2 (*c* 1.2, $CHCl_3$); IR (neat) 2987, 2935, 1669, 1381, 1070, 1030, 987 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.20 (m, 5H), 5.75 (ddt, *J* = 17.1, 10.4, 7.0 Hz, 1H), 5.70 (dd, *J* = 15.6, 7.4 Hz, 1H), 5.59 (dd, *J* = 15.7, 7.5 Hz, 1H), 5.04 (dd, *J* = 15.3, 8.4 Hz, 2H), 4.76−4.61 (brm, 2H), 4.67, 4.58 (ABq, *J* = 6.7 Hz, 2H), 4.50, 4.30 (ABq, *J* = 11.8 Hz, 2H), 4.23 (t, *J* = 6.5 Hz, 1H), 3.82 (q, *J* = 6.7 Hz, 1H), 3.70 (s, 3H), 3.36 (s, 3H), 3.14 (brs, 3H), 2.47−2.31 (m, 1H), 2.32−2.20 (m, 1H), 1.46 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.0, 138.4, 136.0, 134.2, 128.7, 128.3, 127.7, 127.5, 117.2, 111.5, 93.7, 79.1, 78.8, 76.1, 73.4, 70.1, 61.8, 55.5, 40.1, 32.3, 27.0, 26.1; HRMS for $C_{24}H_{35}NO_7$ + Na calcd 472.2311, found 472.2309. **Compound 14:** $[\alpha]^{24}_D$ +28.0 (*c* 4.6, $CHCl_3$); IR (neat) 2986, 2934, 2888, 1209, 1094, 1031, 917 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.21 (m, 5H), 5.79 (ddt, *J* = 16.6, 10.3, 6.6 Hz, 1H), 5.75 (dd, *J* = 15.5, 7.2 Hz, 1H), 5.60 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.07 (dd, *J* = 13.9, 8.7 Hz, 2H), 4.71, 4.65 (ABq, *J* = 6.7 Hz, 2H), 4.66, 4.59 (ABq, *J* = 6.3 Hz, 2H), 4.57, 4.39 (ABq, *J* = 11.9 Hz, 2H), 4.24 (t, *J* = 6.2 Hz, 1H), 4.14 (td, *J* = 7.6, 2.1 Hz, 1H), 3.98−3.82 (m, 2H), 3.71 (dd, *J* = 10.6, 2.3 Hz, 1H), 3.60 (dd, *J* = 10.6, 6.6 Hz, 1H), 3.39 (s, 3H), 3.35 (s, 3H), 2.54−2.39 (m, 1H), 2.38−2.30 (m, 1H), 1.45 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.4, 136.5, 134.2, 128.4, 128.0, 127.6, 127.5, 117.4, 109.8, 96.6, 93.5, 79.3, 78.8, 76.7, 75.9, 70.4, 68.3, 55.5, 55.3, 40.2, 27.2, 27.1; HRMS for $C_{24}H_{36}O_7$ + Na calcd 459.2359; found 459.2361.

Preparation of 15. To a precooled (0 °C) solution of **13** (0.293 g, 0.65 mmol) in THF (4 mL) was added a solution of methylmagnesium bromide (0.4 mL of 2.5 M solution in THF, 1.0 mmol) under argon atmosphere. The reaction mixture was stirred for 1 h at 0 °C, quenched with saturated NH_4Cl (3 mL), and extracted with ether (2 × 15 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was purified by column chromatography using petroleum ether/EtOAc (9:1) as eluent to yield **15** (0.25 g) in 94% yield as a colorless oil: $[\alpha]^{24}_D$ +22.0 (*c* 1.1, $CHCl_3$); IR (neat) 2989, 2935, 2893, 1716, 1211, 1152, 1086, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.20 (m, 5H), 5.76 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.70 (dd, *J* = 15.9, 7.3 Hz, 1H), 5.61 (dd, *J* = 15.6, 6.8 Hz, 1H), 4.05 (dd, *J* = 16.0, 8.9 Hz, 2H), 4.70, 4.58 (ABq, *J* = 6.7 Hz, 2H), 4.51, 4.35 (ABq, *J* = 12.0 Hz, 2H), 4.32−4.15 (m, 3H), 3.86 (q, *J* = 6.7 Hz, 1H), 3.37 (s, 3H), 2.51−2.37 (m, 1H), 2.35−2.23 (m, 1H), 2.25 (s, 3H), 1.47 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 208.3, 138.5, 136.3, 134.2, 128.6, 128.3, 127.5, 127.4, 117.2, 111.1, 93.6, 81.6, 79.4, 78.8, 75.8, 70.2, 55.6, 40.1, 26.73, 26.67, 26.1; HRMS for $C_{23}H_{32}O_6$ + Na calcd 427.2097, found 427.2093.

dx.doi.org/10.1021/jo2010389 |*J. Org. Chem.* 2011, 76, 6889–6893

Preparation of 16. To a stirred solution of the methyl ketone **15** (0.215 g, 0.53 mmol) in THF (5 mL) at −78 °C was added K-Selectride (0.8 mL of 1 M solution in THF, 0.79 mmol) dropwise over 5 min, under argon atmosphere. The reaction mixture was stirred for 1 h, quenched with 2 N NaOH (0.8 mL) followed by 30% H_2O_2 (0.4 mL) at −78 °C, and slowly allowed to warm to room temperature under stirring (∼3 h). The reaction mixture was diluted with water (15 mL) and extracted with ether (2 × 15 mL). The combined ethereal layers were washed with brine (5 mL) and dried over Na_2SO_4. Evaporation of solvent followed by purification of the resultant residue using petroleum ether/EtOAc (4:1) as eluent furnished the alcohol **16** (0.19 g) in 88% yield as a colorless oil: $[\alpha]^{24}_D$ +34.8 (*c* 3.5, $CHCl_3$); IR (neat) 3473, 2985, 2934, 1603, 1380, 1071, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.20 (m, 5H), 5.78 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.72 (dd, *J* = 15.8, 7.2 Hz, 1H), 5.60 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.14−5.0 (m, 2H), 4.70, 4.58 (ABq, *J* = 6.7 Hz, 2H), 4.56, 4.38 (ABq, *J* = 11.9 Hz, 2H), 4.21 (dd, *J* = 7.2, 5.9 Hz, 1H), 4.06 (t, *J* = 7.2 Hz, 1H), 3.89 (dd, *J* = 13.3, 6.6 Hz, 1H), 3.85−3.70 (m, 2H), 3.88 (s, 3H), 2.53−2.36 (m, 1H), 2.39−2.33 (m, 1H), 2.22 (d, *J* = 7.6 Hz, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 1.23 (d, *J* = 6.4 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) 138.3, 136.3, 134.1, 128.3, 128.2, 127.6, 127.5, 117.3, 109.5, 93.5, 81.0, 78.8, 76.0, 70.4, 66.8, 55.5, 40.1, 27.3, 27.2, 20.3; HRMS for $C_{23}H_{34}O_6$ + Na calcd 429.2253, found 429.2254.

Preparation of 17. To a precooled (0 °C) solution of alcohol **16** (0.189 g, 0.46 mmol), triphenylphosphine (0.366 g, 1.39 mmol), and *p*-nitrobenzoic acid (0.386 g, 2.32 mmol) in toluene (2 mL) was added a solution of DIAD (0.36 mL, 1.86 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 5 h. After completion of the reaction (TLC), most of the solvent was evaporated off and the residue thus obtained was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) to give *p*-nitrobenzoate as yellow colored oil along with DIAD impurity.

To a solution of the *p*-nitrobenzoate (obtained above) in MeOH (3 mL) was added K_2CO_3 (0.32 g, 2.36 mmol) and the mixture stirred at room temperature for 1 h. After completion of the reaction (monitored by TLC), it was filtered through a short pad of Celite, and the Celite pad was washed with ether (20 mL). Evaporation of the solvent gave the crude residue which was used in the next step without further purification.

To a precooled (0 °C) solution of the alcohol (obtained above) in CH_2Cl_2 (3 mL) were added DMAP (11 mg, 0.092 mmol) and imidazole (0.094 g, 1.38 mmol) followed by TBSCl (0.138 g, 0.92 mmol) under argon atmosphere. The reaction mixture was refluxed for 12 h. After completion of the reaction (TLC), it was poured into cold water (15 mL) and extracted with diethyl ether (2 × 15 mL). The ethereal layer was washed with brine (5 mL) and dried over Na_2SO_4. Evaporation of the solvent and purification of the resulting residue by column chromatography using petroleum ether/EtOAc (95:05) as eluent furnished **17** (0.148 g) in 62% yield for three steps as colorless oil: $[\alpha]^{24}_D$ +38.9 (*c* 0.8, $CHCl_3$); IR (neat) 2932, 2888, 1647, 1198, 1074, 1031, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.22 (m, 5H), 5.80 (ddt, *J* = 17.0, 9.8, 7.0 Hz, 1H), 5.70 (dd, *J* = 15.6, 5.4 Hz, 1H), 5.65 (dd, *J* = 15.6, 4.7 Hz, 1H), 5.07 (dd, *J* = 16.9, 9.8 Hz, 2H), 4.74, 4.58 (ABq, *J* = 6.7 Hz, 2H), 4.58, 4.38 (ABq, *J* = 11.8 Hz, 2H), 4.23 (dd, *J* = 7.1, 4.3 Hz, 1H), 4.07 (dd, *J* = 6.0, 3.9 Hz, 1H), 3.97−3.85 (m, 2H), 3.82 (dq, *J* = 12.7, 6.2 Hz, 1H), 3.40 (s, 3H), 2.56−2.40 (m, 1H), 2.39−2.24 (m, 1H), 1.47 (s, 3H), 1.41 (s, 3H), 1.25 (d, *J* = 6.0 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.5, 136.0, 134.3, 130.0, 128.3, 127.7, 127.5, 117.1, 109.6, 93.3, 82.1, 81.0, 79.2, 75.5, 70.5, 70.3, 55.7, 40.2, 27.9, 27.3, 25.9, 21.3, 18.0, −4.2, −4.4; HRMS for $C_{29}H_{48}O_6Si$ + Na calcd 543.3118, found 543.3113.

Preparation of 6. Lithium was added to precooled (−78 °C) liquid NH_3 followed by a THF (2 mL) solution of **17** (0.157 g, 0.3 mmol). The reaction mixture was stirred at the same temperature for 1 h, and solid NH_4Cl (0.05 mg) was added followed by cautious addition of water (15 mL). The reaction mixture was warmed up to room temperature and extracted with EtOAc (2 × 10 mL). The combined organic layer was washed with brine (5 mL) and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of the resulting residue using petroleum/EtoAc (3:2) as eluent furnished the homoallylic alcohol **6** (0.105 g) in 81% yield as colorless oil: $[\alpha]^{24}_D$ +73.0 (*c* 1.0, $CHCl_3$); IR (neat) 3420, 2932, 2888, 1640, 1105, 1032, 833 cm-^{1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85−5.70 (m, 2H), 5.66 (dd, *J* = 15.7, 8.3 Hz, 1H), 5.12 (dd, *J* = 17.1, 6.9 Hz, 2H), 4.70, 4.54 (ABq, *J* = 6.7 Hz, 2H), 4.21 (brs, 1H), 4.15 (dd, *J* = 8.1, 3.8 Hz, 1H), 3.99 (t, *J* = 4.0 Hz, 1H), 3.88 (t, *J* = 9.4 Hz, 1H), 3.79 (dq, *J* = 12.3, 5.9 Hz, 1H), 3.36 (s, 3H), 2.31−2.20 (m, 2H), 1.80 (brs, 1H), 1.42 (s, 3H), 1.37 (s, 3H), 1.21 (d, *J* = 5.9 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 137, 133.8, 127.4, 118.4, 109.6, 93.3, 81.8, 80.9, 75.6, 71.0, 70.5, 55.6, 41.7, 27.8, 27.2, 25.8, 21.2, 18.0, −4.3, −4.4; HRMS for $C_{22}H_{42}O_6Si$ + Na calcd 453.2648, found 453.2638.

Preparation of 18. To a precooled (0 °C) solution of **6** (0.064 g, 0.14 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (0.06 mL, 0.44 mmol) followed by acryloyl chloride (0.024 mL, 0.29 mmol) dropwise under argon atmosphere and the reaction mixture stirred at same temperature for 1 h. After completion of the reaction (TLC), it was poured into cold water and extracted with ether (2 × 10 mL). The combined ethereal layer was washed with brine (5 mL) and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of the resulting residue with petroleum ether/EtOAc (85:15) as eluent furnished the acrylate ester **18** (0.44 g) in 65% yield as colorless oil: $[\alpha]^{24}_D$ +57.1 (*c* 0.7, $CHCl_3$); IR (neat) 2902, 2894, 1729, 1188, 1093, 1072, 1031, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.38 (d, *J* = 17.2 Hz, 1H), 6.09 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.80 (d, *J* = 10.4 Hz, 1H), 5.78−5.55 (m, 3H), 5.41 (q, *J* = 6.1 Hz, 1H), 5.06 (dd, *J* = 17.3, 11.0 Hz, 2H), 4.67, 4.52 (ABq, *J* = 6.7 Hz, 2H), 4.15 (dd, *J* = 7.7, 3.7 Hz, 1H), 3.97 (dd, *J* = 6.0, 3.8 Hz, 1H), 3.83 (t, *J* = 6.6 Hz, 1H), 3.77 (dq, *J* = 12.3, 6.0 Hz, 1H), 3.32 (s, 3H), 2.53−2.31 (m, 2H), 1.40 (s, 3H), 1.36 (s, 3H), 1.19 (d, *J* = 5.8 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 165.1, 133.3, 132.8, 130.8, 128.6, 128.5, 118.2, 109.5, 93.3, 81.4, 80.1, 75.4, 72.7, 70.3, 55.6, 38.9, 27.7, 27.2, 25.8, 21.1, 17.9, −4.3, −4.5; HRMS for $C_{25}H_{44}O_7Si$ + Na calcd 507.2754, found 507.2755.

Preparation of 5. To a solution of the acrylate ester **18** (0.045 g, 0.092 mmol) in CH_2Cl_2 (10 mL) under stirring was added Grubbs first-generation catalyst (0.008 g, 0.0092 mmol) under argon atmosphere, and the reaction mixture was refluxed for 5 h. After completion of the reaction, most of the solvent was evaporated off and the residue thus obtained was purified by column chromatography using petroleum ether/EtOAc (3:2) as eluent to furnish the lactone **5** (0.035 g) in 83% yield as a brown oil: $[\alpha]^{24}_D$ +14.7 (*c* 3.5, $CHCl_3$); IR (neat) 2933, 2892, 1730, 1379, 1249, 1091, 1031, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (dt, *J* = 8.6, 3.8 Hz, 1H), 6.03 (d, *J* = 9.8 Hz, 1H), 5.87 (d, *J* = 15.5 Hz, 1H), 5.83 (d, *J* = 15.3 Hz, 1H), 4.95 (brs, 1H), 4.67, 4.56 (ABq, *J* = 6.7 Hz, 2H), 4.20 (brd, *J* = 2.3 Hz, 1H), 3.98 (dd, *J* = 6.3, 3.0 Hz, 1H), 3.86 (t, *J* = 6.8 Hz, 1H), 3.79 (dq, *J* = 12.2, 6.0 Hz, 1H), 3.36 (s, 3H), 2.54−2.34 (brm, 2H), 1.41 (s, 3H), 1.36 (s, 3H), 1.21 (d, *J* = 5.9 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 163.7, 144.5, 131.4, 130.7, 121.6, 109.5, 93.7, 81.6, 80.7, 77.1, 75.1, 70.5, 55.7, 29.6, 27.6, 27.1, 25.8, 21.3, 18.0, −4.25, −4.4; HRMS for $C_{23}H_{40}O_7Si$ + Na calcd 479.2441; found 479.2442.

Preparation of (−)-Anamarine (1). To a stirred solution of **5** (0.016 g, 0.035 mmol) in a mixture of MeOH/water (9:1, 2 mL) was added PPTS (0.005 g, 0.017 mmol) at room temperature, and the reaction mixture was refluxed for 12 h. After completion of the reaction (TLC), $NaHCO_3$ (0.1 g) was added and the mixture stirred for 5 min. The reaction mixture was filtered through a short pad of Celite, and the Celite pad was washed with $CHCl_3$ (15 mL). The residue obtained after evaporation of the solvent was purified by a short-path silica gel column chromatography using EtOAc/MeOH (4:1) as eluent to furnish the tetrol, which was used as such in the next step without characterization.

To a precooled (0 °C) solution of the tetrol obtained above in CH_2Cl_2 (1 mL) were added DMAP (0.001 g, 0.007 mmol) and Et_3N (0.047 mL, 0.35 mmol) followed by Ac_2O (0.026 mL, 0.028 mmol) under argon atmosphere. The reaction mixture was stirred at room temperature for 1 h. After completion of the reaction (TLC), it was poured into cold water and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of the resultant residue using petroleum ether/EtOAc (1:1) as eluent furnished (−)-anamarine (0.008 g) in 53% yield as a gummy mass: $[\alpha]^{24}_D$ −16.0 (*c* 0.5, $CHCl_3$); lit.[3] $[\alpha]^{24}_D$ −15.0 (*c* 0.02, $CHCl_3$); IR (neat) 2935, 1745, 1223, 1028 cm^{-1}; ^1H NMR[7] (400 MHz, $CDCl_3$) δ 6.89 (ddd, *J* = 9.3, 5.0, 3.5 Hz, 1H), 6.07 (d, *J* = 9.5 Hz, 1H), 5.90−5.75 (m, 2H), 5.36 (dd, *J* = 7.0, 6.0 Hz, 1H), 5.31 (dd, *J* = 7.3, 3.5 Hz, 1H), 5.18 (dd, *J* = 6.9, 3.5 Hz, 1H), 4.97 (td, *J* = 12.6, 7.7 Hz, 1H), 4.91 (quint, *J* = 6.5 Hz, 1H), 2.50−2.40 (m, 2H), 2.13 (s, 3H), 2.07 (s, 3H × 2), 2.03 (s, 3H), 1.18 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.0, 169.86, 169.83, 169.76, 163.5, 144.5, 133.0, 125.5, 121.5, 75.8, 71.9, 71.6, 70.4, 67.3, 29.1, 21.0, 20.91, 20.86, 20.6, 15.8; HRMS for $C_{20}H_{26}O_{10}$ + Na calcd 449.1424, found 449.1422.

■ ASSOCIATED CONTENT

Supporting Information. General experimental procedures and copies of ^1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

We thank the Department of Science and Technology (DST), New Delhi for funding. K.R.P is a swarnajayanthi fellow of DST, New Delhi. K.P. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, for a senior research fellowship.

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