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Sharpless AD strategy towards the γ-methyl butenolide unit of acetogenins: enantioselective synthesis of butenolide I and II with mosquito larvicidal activity

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Abstract—A novel synthetic strategy toward the γ-methyl butenolides has been established based on Sharpless asymmetric dihydroxylation in high yields and good enantiopurity. The route could be expanded to the synthesis of α,γ-disubstituted butenolide units of naturally occurring annonaceous acetogenins. Utilizing this strategy, three simple natural products with butenolide segments were synthesized enantioselectively.

1. Introduction

The butenolide unit is widespread in several natural products isolated from many sources including marine animals and territorial plants, amongst which annonaceous acetogenins are the most famous representative member of the butenolide family.[1] Usually, the butenolide segment of annonaceous acetogenins is a typical 3-substituted-5(*S*)-methyl-2(5*H*)-furanone, which is now believed to be one of the essential subunits for the cytotoxicity of these acetogenins (Fig. 1, corossolone and corossolin as examples). Other known butenolides also have interesting properties, e.g. **1** is a metabolite from *Streptomyses* griseas,[2] and **2** and **3** were recently isolated from the leaves of *Hortonia* (family Monimiaceae).[3] Both butenolides I (**2**) and II (**3**) exhibited mosquito larvicidal activity with LC_{50} values of 0.41 and 0.47 ppm, respectively. Accordingly, these butenolides have attracted a considerable amount of synthetic activity.[4–11] To the wealth of known syntheses of butenolides, we recently added a new straightforward access to these enantiopure or enantio-enriched α,γ-disubstituted butenolides. Its key steps are a deconjugative α-alkylation of ester dienolates[12] and a subsequent asymmetric Sharpless dihydroxylation[13,14] of the β,γ-unsaturated ester. In the

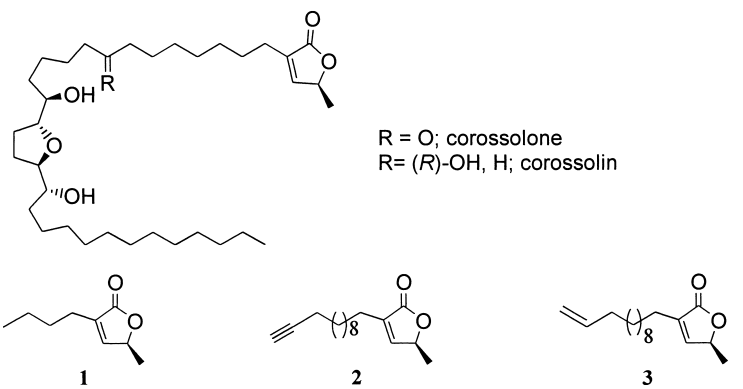

Figure 1. Several typical natural products with γ-methyl butenolide unit.

Keywords: Sharpless AD; acetogenin; butenolide.

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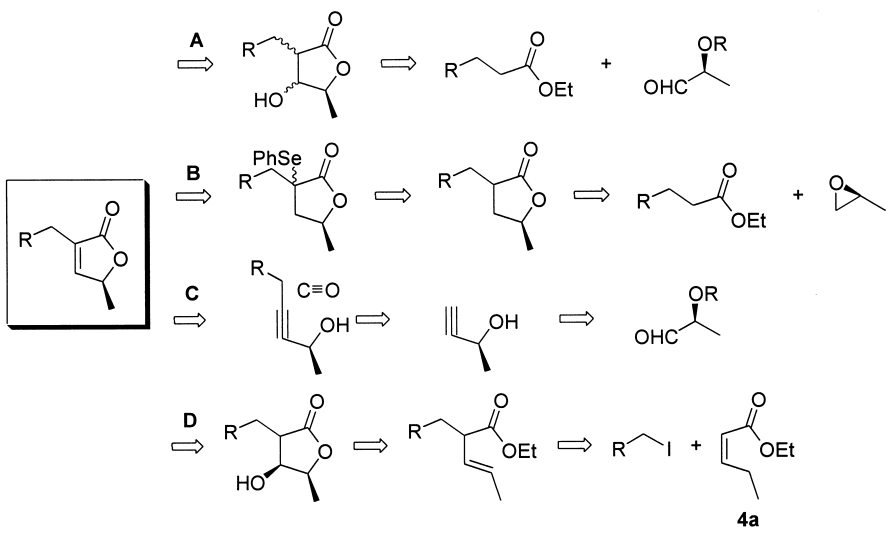
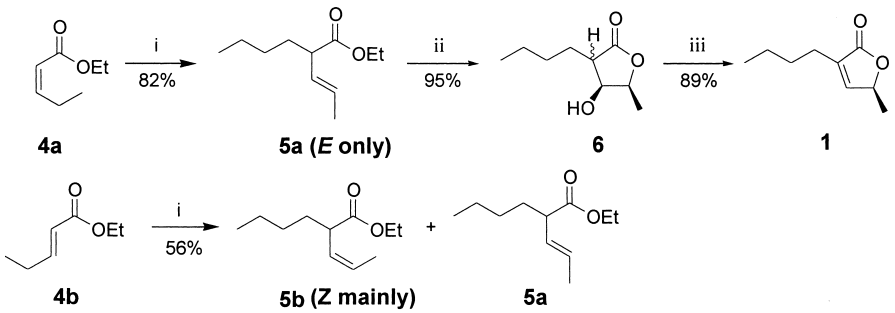


Figure 2. Major strategies toward the γ-methyl butenolides of acetogenins.



Scheme 1. *Reactions and conditions*: (i) LDA, HMPA, THF, then *n*-BuI (yields see Table 1). (ii) AD-mix-α, $MeSO_2NH_2$, 0°C, 95%; (iii) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 89%.

investigation presented herein, we successfully applied this strategy for preparing the optically active α,γ-disubstituted butenolides **1**–**3**.

2. Results and discussion

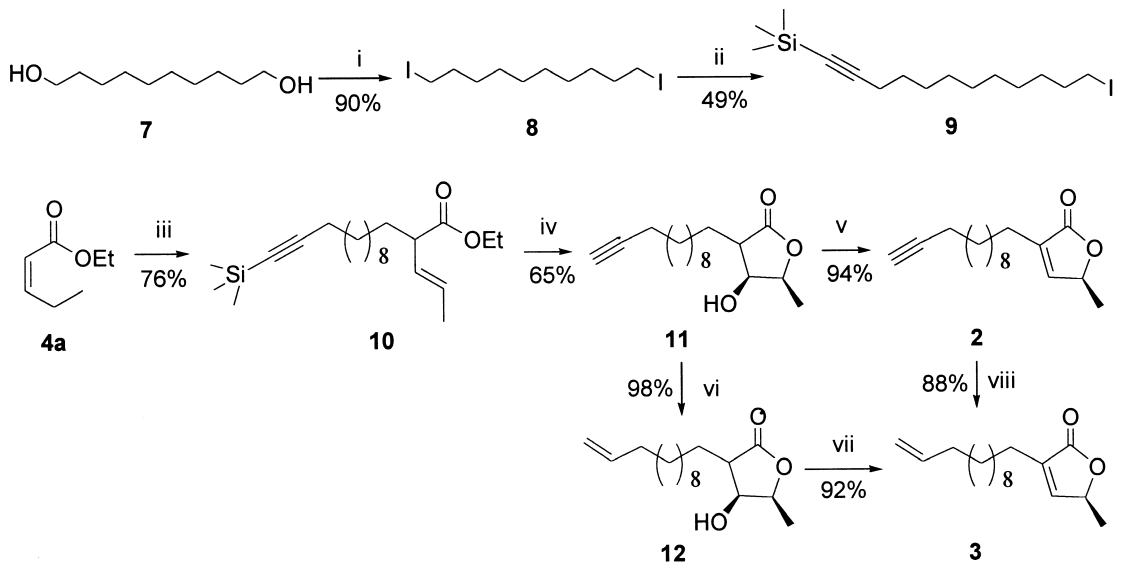
In previous work, the γ-methyl butenolide segment of annonaceous acetogenins has been constructed by three major different approaches. One, originally developed by us,[8,9] used an aldol reaction of an ester with protected L-lactaldehyde followed by sequential in situ lactonization and β-elimination (A in Fig. 2). The second[10] was to use regioselective epoxide opening of the enantiopure propylene oxide by an anion and then to introduce the unsaturated double bond by the PhSeSePh or PhSSPh-based oxidative elimination method (B in Fig. 2). The third method[11] used a palladium(II)-catalyzed lactonization of the chiral alkyne-alcohol with carbon monoxide (C in Fig. 2). As shown in Fig. 2, all of the above approaches have to start from the enantiopure compounds, originally prepared from L-lactic acid ester. Our presented work (D in Fig. 2), for the first time, uses the catalytic Sharpless asymmetric dihydroxylation of the *trans*-olefin as the key step to introduce the desired stereogenic centers. This strategy can be easily expanded to synthesize the related substructures of these naturally occurring annonaceous acetogenins.

The deconjugative alkylation of ester dienolates has been studied[12] and was applied in this work (Scheme 1). As reported, it was observed that deconjugative alkylations of the dienolates from (*Z*)-2-alkenoates gave the corresponding (*E*)-3-enoate products, whereas dienolates from (*E*)-2-enoates gave mainly the (*Z*)-3-enoate products (Table 1). On the other hand, in the subsequent asymmetric dihydroxylation step, the *trans*-olefins were dihydroxylated faster and with higher enantioselectivity than the corresponding *cis*-olefins.[15] As shown in Scheme 1, *cis*-pent-2-enoic acid ethyl ester (**4a**) was treated with LDA and then coupled to *n*-butyl iodide under the optimized reaction temperature (−70°C to −40°C) and reaction time (6 h) to give only the 3-*E*-product **5a** in medium to good yield (Table 1). The stereochemistry of the olefins **5** was assessed by its ^1H NMR spectra. Asymmetric dihydroxylation of the

Table 1. Conditions optimization of the deconjugative alkylation of dienolates

Entry	Reactant	Temperature (°C)	Time (h)	Product(s)	Yield (%)[a]
1	**4b**	−78	2	**5a/5b** (3/100)[b]	56
2	**4a**	−78	2	**5a**	59
3	**4a**	−78	6	**5a**	70
4	**4a**	−78 to −40	6	**5a**	82

[a] Isolated yields.
[b] Product ratio.



Scheme 2. *Reactions and conditions*: (i) Ph_3P, imidazole, I_2, THF. (ii) 0.5 equiv. *n*-BuLi, 0.5 equiv. TMSC≡CH, THF–HMPA. (iii) LDA, HMPA, THF, then 9. (iv) (a) AD-mix-α, *t*-BuOH–water; (b) H_2SO_4(cat.), THF; (c) TBAF, THF. (v) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2. (vi) H_2, Lindlar cat., EtOAc. (vii) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2. (viii) H_2, Lindlar cat., EtOAc.

enyne **5a** with AD-mix-α gave a mixture of diastereomers, (3*S*,4*S*, 5*S*)-3-butyl-4-hydroxy-5-methyltetrahydro-2-furanone (**6**) and (3*R*,4*S*, 5*S*)-3-butyl-4-hydroxy-5-methyltetrahydro-2-furanone (**6**). Dehydration of the β-hydroxyl lactone **6** with trifluoroacetic anhydride and triethylamine afforded **1** (82% ee by HPLC).[16]

Following the same strategy as the preparation of **1**, butenolides **2** and **3** were synthesized enantioselectively (Scheme 2). First of all, conversion of diol **7** to the diiodide **8** followed by treatment with TMSC≡CLi provided the desired the mono-iodide **9** (44% from **7**) (Scheme 2). The enolate of ethyl (*Z*)-2-pentenoate **4a** was now generated and reacted with iodide **9** followed by neutral workup to give **10**. Asymmetric dihydroxylation was readily accomplished and followed by acid-catalyzed cyclization of the crude AD product and then desilylation proceeded smoothly to afford a mixture of diastereomers **11**. Direct dehydration of β-hydroxyl lactone **11** with trifluoroacetic anhydride and triethylamine afforded **2** only in 70% ee as determined by chiral HPLC. Dehydration subsequent to three recrystallizations of **11** (yield 65%) from a cold DCM/hexane solution gave **2** in 91.3% ee. Butenolide **3** can be obtained directly by partial reduction of **2** (H_2, Lindlar catalyst) in 91.3% ee or obtained by partially reduction of **11** and dehydration of **12** in 93.9% ee.

3. Conclusions

In summary, a novel synthetic strategy toward the γ-methyl butenolides has been established based on Sharpless asymmetric dihydroxylation in high yields and good enantiopurity. It is worthy noting that the strategy could be easily expanded to the synthesis of α,γ-disubstituted butenolides units of naturally occurring annonaceous acetogenins. Utilizing this strategy, three simple natural products **1**, **2** and **3** with butenolide segments were synthesized enantioselectively.

4. Experimental

4.1. General

Mass spectrometry was conducted using the electron impact (EI) method. ^{1}H NMR spectra were recorded on a Varian 300 MHz instrument in $CDCl_3$ solution. Chemical shifts are given in δ (ppm) relative to TMS and coupling constants (*J*) are given in Hz, and ^{13}C NMR spectra were record at 75 MHz. Values of $[\alpha]_D^{20}$ are given in deg. cm^2 g^{-1}. HPLC conditions: chiral butenolides **1**–**3** were assayed on a chiralcel OD columm using hexane/Pr^{i}OH (100:1, v/v), flow rate at 0.7 mL min^{-1}; UV-detector: 214 nm. THF was distilled over Na, CH_2Cl_2 and HMPA were distilled over CaH_2 prior to use. All reactions requiring dry conditions were performed under an inert atmosphere (N_2). All reactions were monitored by TLC.

4.1.1. Ethyl 2-butyl-3(*E*)-pentenoate (5a). To a solution of diisopropylamine (5.0 mmol, 1.0 equiv.) in THF (10 mL) at 0°C was added *n*-BuLi (5.0 mmol, 2.5 mL, 2 M solution in hexanes, 1.0 equiv.). After stirring for 30 min, the reaction was cooled to −78°C and HMPA (5.0 mmol, 1.0 equiv.) was added. This mixture was stirred for 30 min before adding a solution of the unsaturated ester **4a** in THF (2 mL) via cannula. The dienolate was allowed to form for 30 min, and then a solution of butyl iodide in THF (2 mL) was added dropwise. After 2 h of stirring at −78°C, the solution was warmed to −40°C. After 4 h at −40°C, the reaction was quenched with saturated NH_4Cl solution and warmed to rt, the aqueous phase was extracted three times with ether, the combined organic phase were then washed with brine, dried with anhydrous Na_2SO_4, and filtered, and the solvent was removed in vacuo. The crude product was purified by column chromatography eluting with diethyl ether/pentane (1.5/100) to give **5a**[12] as a colorless oil (756 mg, 82%). IR (neat): 2962, 2927, 1737, 1261, 1097, 1020, 803 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 5.54 (dqd, *J*=15.6, 6.3, 0.6 Hz, 1H, CH=C*H*Me), 5.41 (ddq, *J*=15.6, 6.9, 1.2 Hz, 1H, C*H*=CHMe); 4.13 (q, *J*=6.9 Hz, 2H, COOCH_2CH$_3$), 2.91

(dt, J=8.1, 7.8 Hz, 1H, C*H*COOEt), 1.68 (dd, J=6.3, 1.2 Hz, 3H, CH=CH*Me*), 1.26 (t, J=6.9 Hz, 3H, $COOCH_2CH_3$), 1.23–1.73 (m, 6H, $CH_3CH_2CH_2CH_2CH$), 0.88 (t, J=6.9 Hz, 3H, $CH_3CH_2CH_2$) ppm. EIMS (*m/z*, %): 185 (M^++1, 6), 141 (22), 128 (17), 127 (25), 111 (21), 69 (100), 67 (17), 55 (85), 41 (32).

4.1.2. (4*S*,5*S*)-3-Butyl-4-hydroxyl-5-methyltetrahydro-2-furanone (6). A 50 mL round-bottomed flask, equipped with a magnetic stirrer, was charged with tert-butyl alcohol (10 mL), water (10 mL), and AD-mix-α (2.8 g). Stirring at rt, methanesulfonamide (190 mg, 2.0 mmol, 1 equiv.) was added. The mixture was cooled to 0°C, compound **5a** (368 mg, 2 mmol) was then added. The heterogeneous slurry was stirred vigorously at 0°C for 24 h. While the mixture was stirred at 0°C, solid sodium sulfite (3 g) was added and the mixture was allowed to warm to room temperature and stirred for 1 h. Ethyl acetate was added to the reaction mixture, the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with 2N KOH, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by flash chromatography eluting with hexane/diethyl ether (1/1) to afford known diastereoisomers **6**[20] as a colorless oil (327 mg, 95%). IR (neat): 3420, 2960, 2925, 2863, 1748, 1458, 1344, 997 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 4.64 (qd, J=6.6, 5.8 Hz, 0.4H, CH_2CHOC=O), 4.46 (qd, J=6.6, 3.3 Hz, 0.6H, CH_2CHOC=O), 4.32 (ddd, J=4.8, 3.3, 3.0 Hz, 0.6H, C*H*OH), 4.21 (ddd, J=5.1, 7.8, 1.5 Hz, 0.4H, C*H*OH), 2.57 (m, 1H, C*H*COO), 2.15 (d, J=4.8 Hz, 0.4H, CHO*H*), 1.88 (d, J=5.1 Hz, 0.6H, CHO*H*), 1.44 (d, J=6.6 Hz, 1.8H, CH*Me*), 1.41 (d, J=6.6 Hz, 1.2H, CH*Me*), 1.35–1.48 (m, 6H, $CH_3(CH_2)_3$), 0.94 (t, J=7.2 Hz, 1.2H, CH_2CH_3), 0.92 (t, J=6.9 Hz, 1.8H, CH_2CH_3) ppm. EIMS (*m/z*, %): 173 (M^++1, 46), 172 (M^+, 0.01), 116 (25), 99 (37), 82 (35), 57 (100), 55 (30), 43 (49), 41 (37).

4.1.3. (5*S*)-3-Butyl-5-methyl-2(5*H*)-furanone (1). To a mixture of β-hydroxylated lactone **6** (76 mg, 0.44 mmol) and Et_3N (0.184 mL, 1.32 mmol, 3 equiv.) in CH_2Cl_2 was added $(CF_3CO)_2O$ (0.093 mL, 0.66 mmol, 1.5 equiv.) at 0°C. The reaction mixture was stirred at 0°C for 10 h and then warmed to rt. After 2 h at rt, the reaction mixture was diluted with ether, washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with diethyl ether/hexane (1/5) to afford **1** as a colorless oil (60 mg, 89%). HPLC: 82% ee; retention time 22.19 min [(*S*)-**1**], (*R*)-isomer appeared at t_R 25.7 min; $[\alpha]_D$=+44.3 (*c* 1.24, $CHCl_3$) [lit.[17] $[\alpha]_D$=−53.7 ($CHCl_3$) for the (−)-(*R*) enantiomer; lit.[18] $[\alpha]_D$=+11.7 (*c* 0.16, $CHCl_3$); lit.[19] $[\alpha]_D$=+79.2 (c 1.18, $CHCl_3$)]. All other data consistent with the literature.[19]

4.1.4. 1,10-Diiododecane (8). To a THF (300 mL) solution of diol **7** (6.96 g, 40 mmol, 1 equiv.), imidazole (8.17 g, 120 mmol, 3.0 equiv.) and PPh_3 (31.44 g, 120 mmol, 3.0 equiv.) was added, at −10°C, iodine (30.48 g, 120 mmol, 3.0 equiv.). After stirring for 1 h at −10°C, the solution was warmed to rt for additional 5 h. The reaction was diluted with diethyl ether, washed with brine and sat. aq $Na_2S_2O_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product was then diluted petroleum ether to precipitate Ph_3PO. Compound **8**, white solid, was obtained in 90% yield (14.18 g) and could be used for the next step without further purification. mp 29–30°C (crystallized from hexanes) (lit.[21] 29–30°C); IR: 2926, 2853, 1462, 1426, 1263, 1199, 1171, 800, 720 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 3.19 (t, J=7.2 Hz, 4H, CH_2I), 1.81 (m, 4H, CH_2CH_2I), 1.38–1.29 (brm, 12H) ppm. EIMS (*m/z*, %): 395 (M^++1, 0.77), 394 (M^+, 3.94), 267 (M^+−I, 11.68), 140 (M^+−2I, 0.69), 97 (30), 83 (67), 71 (37), 69 (59), 57 (65), 55 (100), 43 (53), 41 (78).

4.1.5. 12-Iodo-1-(trimethylsilyl)-1-dodecyne (9). A 0.25 M solution of lithium trimethylsilyl acetylide was generated in situ by addition of *n*-BuLi (6.0 mmol, 3.0 mL, 2 M solution in hexanes) to trimethylsilylacetylene (6.0 mmol, 0.85 mL) in THF (20 mL) at −78°C and stirred 30 min at 0°C. This solution was transferred to a solution of diiodide **8** (2.37 g, 6.0 mmol, 1.0 equiv.) in HMPA (6 mL) and THF (12 mL) at 0°C. After 30 min, the dark solution was poured into ethyl ether and water. The aqueous phase was extracted with ethyl ether, the combined organic layers were washed with water and brine and dried (Na_2SO_4). Evaporation of solvent afforded a clear liquid, which was purified by flash chromatography eluting with hexane to afford **9** as a colorless oil (1.07 g, 49%). IR: 2955. 2929, 2856, 2175, 1464, 1428, 1249, 842, 760 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 3.19 (t, J=7.2 Hz, 2H, CH_2I), 2.21 (t, J=6.9 Hz, 2H, ≡CCH_2), 1.82 (m, 2H, CH_2CH_2I), 1.51 (m, 2H, ≡CCH_2CH_2), 1.29–1.38 (brm, 12H), 0.15 (s, 9H) ppm. EIMS (*m/z*, %): 349 (M^+-15, 1.86), 185 (100), 163 (23), 93 (17), 81 (16), 73 (91), 59 (26), 43 (20), 41 (21). Anal. calcd for $C_{15}H_{29}SiI$: C, 49.44; H, 8.02. Found: C, 49.72; H, 7.74.

4.1.6. Ethyl 2(12-Trimethylsilyl-11-dodecyne)-3(*E*)-pentenoate (10). The experimental procedure was followed as that of **5a**. For compound **10**: oil, 1.329 g, 76% yield. IR: 2929, 2857, 2175, 1737, 1465, 1370, 1249, 1174, 1158, 843, 760, 640 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 5.55 (dq, J=15.3, 6.0 Hz, 1H, CH=C*H*Me), 5.42 (ddq, J=15.3, 8.4, 1.2 Hz, 1H, C*H*=CHMe), 4.13 (q, J=7.2 Hz, 2H, $COOCH_2Me$), 2.92 (dt, J=7.8, 7.6 Hz, 1H, C*H*COOEt), 2.21 (t, J=6.9 Hz, 2H, ≡CCH_2), 1.68 (dd, J=6.3, 1.2 Hz, 3H, CH=CH*Me*), 1.50 (m, 4H, ≡CCH_2CH_2 and $CH_2CHCOOEt$), 1.26–1.42 (brm, 17H), 0.15 (s, 9H, SiMe_3) ppm. EIMS (*m/z*, %): 365 (M^++1, 5), 364 (M^+, 15), 349 (M^+-15, 32), 335 (M^+−29, 3.26), 199 (39), 141 (22), 127 (23), 103 (52), 81 (24), 73 (100), 55 (29). Anal. calcd for $C_{22}H_{40}SiO_2$: C, 72.46; H, 11.06. Found: C, 72.50; H, 10.88.

4.1.7. (4*S*,5*S*)-3(12-Dodecyne)-4-hydroxy-5-methyltetrahydro-2-furanone (11). The procedure of AD reaction was followed as that of compound **6**. Cyclization reaction: The crude product of the above AD reaction of **10** (300 mg, 0.82 mmol) was dissolved in THF (25 mL) with five drops of con. H_2SO_4. The mixture was stirred at rt for 24 h, then diluted with ethyl ether, washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product, which was directly used for next step without further purification. A solution of the above crude diastereomeric mixture in THF (10 mL) was treated with *n*-Bu_4NF in THF (1 M, 0.9 mL, 1.1 equiv.) at 0°C under N_2 for 30 min. The reaction mixture

was then diluted with water (10 mL), and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed to afford **11** as a white solid (209 mg, 91%). This material was further crystallized from CH_2Cl_2/hexanes to give a white crystalline solid (149 mg, 65%). mp 58–60°C. IR: 3493, 3427, 3296, 2936, 2919, 2850, 2118, 1732 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 4.62 (m, 0.5H, MeC*H*OC=O), 4.44 (m, 0.5H, MeC*H*OC=O), 4.31 (m, 0.5H, C*H*OH), 4.20 (m, 0.5H, C*H*OH), 2.55 (m, 1H, C*H*C=O), 2.18 (td, *J*=6.3, 2.4 Hz, 2H, ≡CC*H*$_2$), 1.93 (t, *J*=2.7 Hz, 1H, C*H*≡), 1.43 (d, *J*=6.0 Hz, 1.5H, CH*Me*), 1.42 (d, *J*=6.6 Hz, 1.5H, CH*Me*), 1.28–1.70 (m, 18H) ppm. EIMS (*m*/*z*, %): 281 (M^++1, 0.87), 264 (M^++1−15, 0.41), 116 (100), 111 (32), 99 (74), 81 (43), 67 (39), 57 (77), 55 (43), 41 (4). Anal. calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.07. Found: C, 72.61; H, 10.11.

4.1.8. (4*S*,5*S*)-3-(12-Dodecene)-4-hydroxy-5-methyltetrahydro-2-furanone (12). To a solution of alkyne **11** (100 mg, 0.357 mmol) in EtOAc (10 mL) were added Lindlar catalyst (10 mg) and one drop of quinoline. After being stirred under 1 atm of hydrogen at rt for 45 min (monitored by TLC), the mixture was filtered and concentrated in vacuo and chromatographed eluting with hexane/diethyl ether (1/1) to give **12** (99 mg, 98%) as a white solid. mp 43–44°C. IR: 3404, 2924, 2850, 1737, 1643, 1465, 1187 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 5.82 (ddt, *J*=16.5, 10.5, 6.6 Hz, 1H, =C*H*CH$_2$), 4.98 (m, 1H, C*H*$_2$=CHCH$_2$), 4.92 (m, 1H, C*H*$_2$=CHCH$_2$), 4.63 (qd, *J*=6.3, 5.0 Hz, 0.5H, MeC*H*OC=O), 4.45 (qd, *J*=6.6, 5.1 Hz, 0.5H, MeC*H*OC=O), 4.32 (dt, *J*=4.8, 5.0 Hz, 0.5H, C*H*OH), 4.19 (dt, *J*=4.8, 5.1 Hz, 0.5H, C*H*OH), 2.56 (m, 1H, C*H*C=O), 2.34 (d, *J*=4.8 Hz, 1H, CHO*H*), 2.04 (m, 2H, CH$_2$=CHC*H*$_2$), 1.44 (d, *J*=6.6 Hz, 1.5H, CH*Me*), 1.40 (d, *J*=6.3 Hz, 1.5H, CH*Me*), 1.27–1.50 (brm, 18H) ppm. EIMS (*m*/*z*, %): 282 (M^+, 1), 267 (0.4), 265 (2), 129 (33), 116 (82), 111 (35), 99 (56), 67 (26), 57 (100), 55 (54), 41 (56). Anal. calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.12; H, 10.42.

4.1.9. (+)-(5*S*)-3-(12-Dodecyne)-5-methyl-2(5*H*)-furanone (2). The procedure was followed as that of **1**. For compound **2** (59 mg, 94%): mp 24–25°C; HPLC: 91.9% ee (t_R 25.01 min for (*S*)-**2**, and t_R 30.18 min for (*R*)-**2**); $[\alpha]_D$=+30.3 ($CHCl_3$, *c* 0.46), [lit.[3] $[\alpha]_D$=+38 ($CHCl_3$, *c* 0.0026)]; IR: 3310, 2981, 2930, 2856, 2118, 1756, 1656, 1320 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 6.99 (dd, *J*=3.3, 1.8 Hz, 1H), 5.00 (qdd, *J*=6.6, 3.3, 1.8 Hz, 1H), 2.27 (tdd, *J*=6.9, 1.8, 1.8 Hz, 2H), 2.18 (td, *J*=6.9, 2.7 Hz, 2H), 1.94 (t, *J*=2.7 Hz, 1H), 1.48–1.57 (m, 4H), 1.41 (d, *J*=6.6 Hz, 3H), 1.26–1.43 (brm, 12H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): 171.91, 148.88, 134.58, 85.07, 77.53, 68.10, 29.59, 29.59, 29.43, 29.32, 29.20, 28.88, 28.64, 27.57, 25.32, 19.37, 18.55 ppm. EIMS (*m*/*z*, %): 262 (M^+, 1), 247 (M^+−15, 1.5), 217 (6), 167 (7), 149 (14), 135 (24), 112 (100), 95 (78), 79 (45), 67 (89), 55 (57). HRMS (EI, *m*/*z*) calcd for $C_{17}H_{26}O_2$ $(M)^+$: 262.1933. Found: 262.1922.

4.1.10. (+)-(5*S*)-3(12-Dodecene)-5-methyl-2(5*H*)-furanone (3). *Method A*: To a solution of 41 mg (0.156 mmol) of alkyne **2** in EtOAc (5 mL) were added Lindlar catalyst (3 mg) and one drop of quinoline. After being stirred under 1 atm of hydrogen at rt for 45 min, the mixture was filtered and the filtrate was concentrated in vacuo and chromatographed to give **3** as a white solid (36.3 mg, 88%). *Method B*: To a mixture of β-hydroxylated lactones **12** (20 mg, 0.071 mmol) and Et_3N (6 equiv.) in CH_2Cl_2 was added $(CF_3CO)_2O$ (3.0 equiv.) at 0°C. The reaction mixture was stirred at 0°C for 10 h and then warmed to rt for additional 2 h. The reaction mixture was diluted with ether, washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash column chromatography to afford **3** (17.2 mg, 92%) as a white solid. mp: 22–23°C. HPLC: 93.9% ee (t_R 16.54 min for (*S*)-**3**, and t_R 18.05 min for (*R*)-**3**); $[\alpha]_D$=+33.4 ($CHCl_3$, *c* 0.285) [lit.[3] $[\alpha]_D$=+80 ($CHCl_3$, 0.0028)]; IR: 2928, 2856, 1759, 1641 cm^{-1}. ^1H NMR ($CDCl_3$): 7.00 (dd, *J*=3.3, 1.5 Hz, 1H), 5.82 (ddt, *J*=16.5, 10.5, 6.8 Hz, 1H), 5.01 (m, 1H), 4.90–5.00 (m, 2H), 2.28 (tdd, *J*=7.8, 1.8, 1.5 Hz, 2H), 2.04 (tddd, *J*=7.2, 6.8, 1.2, 1.5 Hz, 2H), 1.55 (m, 2H), 1.41 (d, *J*=6.6 Hz, 3H), 1.28 (brm, 14H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): 172.96, 147.8, 138.21, 133.35, 113.08, 76.36, 32.79, 28.530, 28.49, 28.45, 28.29, 28.17, 28.11, 27.93, 26.41, 24.18, 18.20 ppm. EIMS (*m*/*z*, %): 265 (M^++1, 6), 264 (M^+, 5), 246 (1), 235 (3), 219 (2), 207 (4), 193 (5), 179 (7), 169 (6), 152 (9), 137 (13), 123 (17), 112 (37), 109 (25), 95 (42), 81 (43), 67 (44), 57 (100). HRMS (EI) *m*/*z* calcd for $C_{17}H_{28}O_2$ $(M)^+$: 264.2089. Found: 264.2092.

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