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Synthesis of β-Methoxyacrylate Natural Products Based on Box-Pd^{II}-Catalyzed Intermolecular Methoxycarbonylation of Alkynoles

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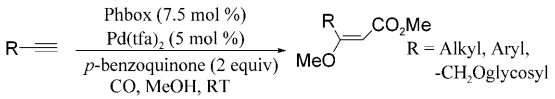
Abstract: Bis(oxazoline)-palladium(II) catalyzed carbonylation of homopropargyl alcohols afforded acyclic methoxyacrylate **2** and 6-membered lactone **3a–k** in good combined yield. In the case of propargyl alcohols, 5-membered lactones **3p**, **3q**, **16** were obtained in moderate yields. The one-pot synthesis of kawa lactones **3a**, **3r**, **3s** and formal synthesis of dihydroxycystothiazole A and dihydroxycystothiazole C are presented. To elucidate the stereochemistry of (+)-annularin G and (−)-annularin H, the first asymmetric syntheses of these natural products were achieved.

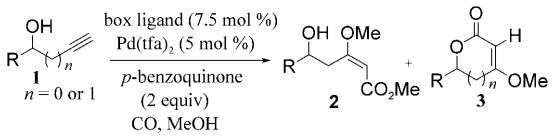
Keywords: annularin · bis(oxazoline) · carbonylation · kawa lactones · palladium

Introduction

The β-methoxyacrylate system is a common structural motif present in biologically active natural products, such as dihydrokawain[1a] (and related 6-membered lactones[1b–e,n,o]), tetronic acids[2a] (and related 5-membered lactones[2b–e]), and β-methoxyacrylate antibiotics.[3] Thus, the practical construction of the β-methoxyacrylate system is attractive for the synthesis of these natural products. Palladium-catalyzed carbonylation of alkynes has provided several kinds of transformations.[4] Although the intermolecular methoxycarbonylation of terminal alkynes is considered to be a useful method for the direct conversion of terminal alkyne units to β-methoxyacrylate units, the intermolecular addition of alcohols to alkynes is more difficult to accomplish than the intramolecular process,[5–7] requiring stronger π-Lewis acid catalysts.[8] In our preliminary communication, we reported the intermolecular methoxycarbonylation of terminal alkynes catalyzed by palladium(II) bisoxazoline (box) complexes (Scheme 1).[9] The box ligand enhances the π electrophilicity of Pd^{II} complexes,[7c,d,9,10] which leads to effective activation of the triple bond. Herein, we report the direct conversion of homopropargyl and propargyl alcohols to β-methoxyacrylates, and its application to the synthesis of natural products containing 4-methoxyfuran-2-one, acyclic β-methoxyacrylate, and 4-methoxy-2-pyrone structures (Scheme 2).



Scheme 1. Previous work.[9]



Scheme 2. This work.

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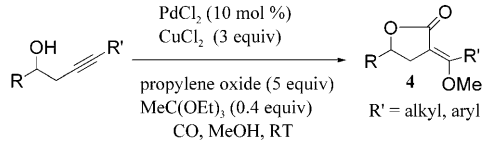
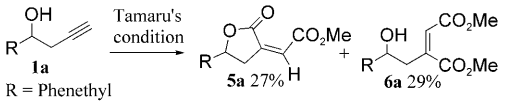
Results and Discussion

Tamaru et al. reported the palladium-catalyzed carbonylation of 4-alkyl (or 4-aryl)-3-butyne-1-ols for which MeOH attacked the C4 position of the alkyne to afford 5-membered lactones **4**, but the reaction of terminal alkynes was not described (Scheme 3).[4c]



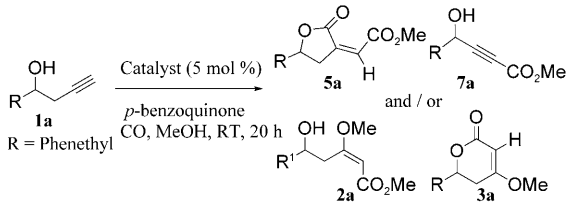
Scheme 3. Tamaru et al.[4c]

Therefore, initial experiments were carried out by the reaction of **1a** under the reported conditions (Scheme 4). However, maleate derivatives[4p] **5a** and **6a** were obtained together with an unidentified mixture instead of the desired β-methoxyacrylates **2a**, **3a**, and **4a**.



Scheme 4. Carbonylation of **1a** under the Tamaru's conditions.

The reaction conditions were then changed to those used for our previously reported Pd^{II}/*p*-benzoquinone catalytic system (Scheme 5).[5–7,9] The reaction of **1a** with $[Pd(tfa)_2]$



Scheme 5. Carbonylation of **1a** by using various catalysts.

(5 mol %) and *p*-benzoquinone (2 equiv) in the absence of the ligand in methanol under a carbon monoxide atmosphere (balloon) afforded acetylene carboxylate derivative[4d] **7a** (37 %) and maleate derivative **5a** (19 %) with a small amount of **2a** (8 %). Although the use of $[(CH_3CN)_2PdCl_2]$ resulted in increased yields of β-methoxyacrylate **2a** (12 %) and six-membered lactone **3a** (12 %), **5a** was also produced in 19 % yield. As mentioned previously,[7c,d,9,10] the phosphine ligand seemed to be ineffective for reactions of this type, that is, the $[Pd(tfa)_2]$ complex of (*S*)-BINAP gave **7a** (20 %), and $[(Ph_3P)_2PdCl_2]$ did not show catalytic activity. Bipyridine-$PdCl_2$ complex and (−)-sparteine-$[Pd(tfa)_2]$ complex also gave no reaction. Next, we used the box ligand depicted in Figure 1 according to our previous results.[7c,d,9]

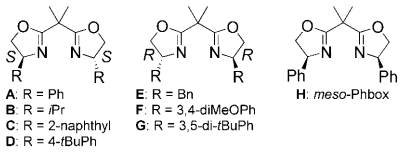


Figure 1. Box ligands for Table 1.

As expected, the reaction proceeded smoothly in the presence of (*S*)-Phbox **A**, (*S*)-*i*Prbox **B**, and (*R*)-Bnbox **E**, affording acyclic methoxyacrylate **2a** and six-membered lactone **3a** in 59–66 % combined yields (Scheme 1, Table 1, entries 1–3). Although effective kinetic resolution (or parallel kinetic resolution) was not observed, Phbox **A** seems to be more effective than alkyl substituted boxes **B** and **E**. Thus, we examined other kinds of aryl-boxes **C**, **D**, **F**, **G**, and **H** (entries 4–8). Among them, (±)-3,5,3′,5′-tBu$_4$Phbox **G** gave the best combined yield (entry 8). With the optimized conditions in hand, the reaction of different substrates was examined to explore the scope of the reaction (Table 2, Scheme 6).

Table 1. Intermolecular methoxycarbonylation of homopropargyl alcohol **1a** (R = Phenethyl, $n = 1$): screening of box ligands (Scheme 2).

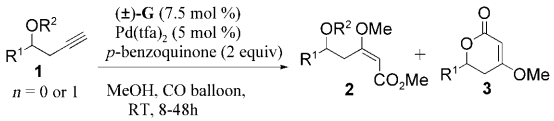
Entry	Ligand	Yield of **2a** [%] (*ee*)	Yield of **3a** [%] (*ee*)	Combined yield [%]
1	**(S)-A**	53 (4)	13 (12)	66
2	**(S)-B**	34 (2)	25 (4)	59
3	**(S)-E**	17 (4)	42 (4)	59
4	**H**	35	25	60
5	**(S)-C**	48 (6)	23 (5)	71
6	**(±)-F**	44	23	67
7	**(S)-D**	56 (0)	23 (6)	79
8	**(±)-G**	65	23	88

For substrates **1a–d** with alkyl substituents, the reaction proceeded well (Table 2, entries 1–4). The alkenyl and aryl series **1e–i** and furyl substituents **1j** and **1k** gave satisfactory results (entries 5–11). The reaction of protected homopropargyl alcohols **1l–o** provided acyclic β-methoxyacrylates **2l–o** in moderate yields (entries 12–15). In the case of propargyl alcohols **1p** and **1q**, ligands **(±)-A** and **(±)-E** gave better results, affording five-membered lactones **3p** and **3q** in 58 and 53 % yields, respectively (Scheme 7).

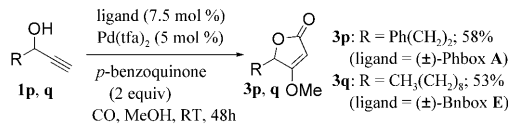
As an application of these reactions, we describe new syntheses of β-methoxyacrylate natural products. Kawa lactones are 2-pyrones and 5,6-dihydro-2-pyrones found in the roots, stem, and rhizomes of the kawa plant (*Piper mythisticum*), which grows in the Pacific Islands.[1] Extracts of the root and stem of this plant are utilized in folk medicine. Analgesic, anesthetic, antifungal, antithrombotic, anticonvulsive, and muscle-relaxing properties have been reported.[1f] The reaction of **1a**, **1r**, and **1s**, using the conditions depicted in

Table 2. Intermolecular methoxycarbonylation of homopropargyl alcohol **1** (Scheme 6).

Entry	R^1	R^2	Yield [%]	Yield [%]	Combined yield [%]
1	$Ph(CH_2)_2$	H	**2a**: 65	**3a**: 23	88
2	Bn	H	**2b**: 56	**3b**: 27	83
3	nonyl	H	**2c**: 52	**3c**: 31	83
4	cyclohexyl	H	**2d**: 47	**3d**: 35	82
5	(*E*)-PhCH=CH	H	**2e**: 62	**3e**: 15	77
6	Ph	H	**2f**: 58	**3f**: 29	87
7	4-MeO-Ph	H	**2g**: 60	**3g**: 34	94
8	4-Cl-Ph	H	**2h**: 54	**3h**: 26	80
9	2-naphthyl	H	**2i**: 58	**3i**: 26	84
10	2-furyl	H	**2j**: 43	**3j**: 30	73
11	3-furyl	H	**2k**: 45	**3k**: 35	80
12	$Ph(CH_2)_2$	Me	**2l**: 63	–	–
13	$Ph(CH_2)_2$	Ac	**2m**: 50	–	–
14	$Ph(CH_2)_2$	MOM	**2n**: 58	–	–
15	$Ph(CH_2)_2$	TBDMS	**2o**: 53	–	–

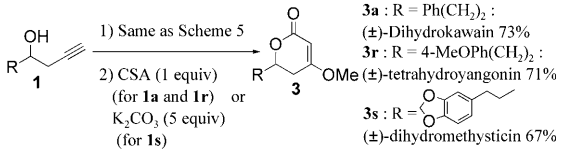


Scheme 6. Intermolecular methoxycarbonylation of homopropargyl alcohol **1**.



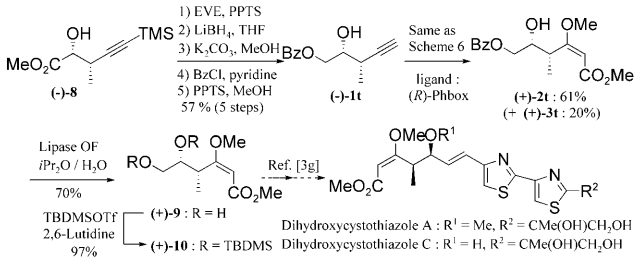
Scheme 7. Intermolecular methoxycarbonylation of propargyl alcohol **1**.

Scheme 5, followed by a one-pot treatment with (+)-10-camphorsulfonic acid (CSA) or K_2CO_3, afforded (±)-dihydrokawain **3a**, (±)-tetrahydroyangonin **3r**, and (±)-dihydromethysticin **3s** in 73, 71, and 67% yields, respectively (Scheme 8).[1h,i,m]



Scheme 8. One-pot synthesis of kawa lactones **3a**, **3r**, and **3s**.

Antifungal substances, myxothiazoles and cystothiazoles, were isolated from different strains of the myxobacteria *Cystobacter fuscus* and *Archangium gephyra*, respectively.[3] Dihydroxycystothiazole A and dihydroxycystothiazole C are known metabolites of cystothiazole A,[3h] and the synthesis of these compounds from the β-methoxyacrylate **(+)-10** was reported by our laboratory.[3g] The substrate **1t** was prepared from known hydroxyester **(−)-8** (Scheme 9).[3i] Protection of the secondary hydroxyl group of **(−)-8** followed by reduction and subsequent desilylation gave the primary alcohol. This was treated with benzoyl chloride followed by deprotection of the ethoxyethyl group to afford homopropargyl alcohol **(−)-1t**. The intermolecular methoxycarbonylation of **(−)-1t** (under the conditions depicted in Scheme 7), using (*R*)-Phbox ligand, afforded acyclic β-methoxyacrylate **(+)-2t** and 6-membered lactone **(+)-3t** in 61% and 20% yields, respectively. The use of (*S*)-Phbox resulted in slightly decreased



Scheme 9. Formal chiral synthesis of cystothiazoles.

yields [**(+)-2t**: 56% and **(+)-3t**: 17%]. Hydrolysis of **(+)-2t** with lipase OF to avoid lactonization followed by silylation gave **(+)-10**, which is a known precursor for the synthesis of cystothiazoles.

Annularin G and annularin H were isolated from the organic extracts of the freshwater fungus *Annulatascus triseptatus*.[2b] Although the stereochemistry at C-7 of annularin G was proposed to be the same as in annularin A, the stereochemistry at C-5 of annularins G and H was not determined (Figure 2). This prompted us to investigate the stereochemistry by asymmetric total synthesis.

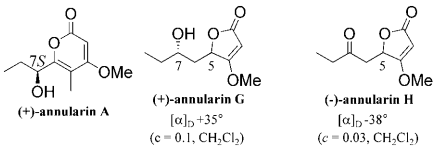
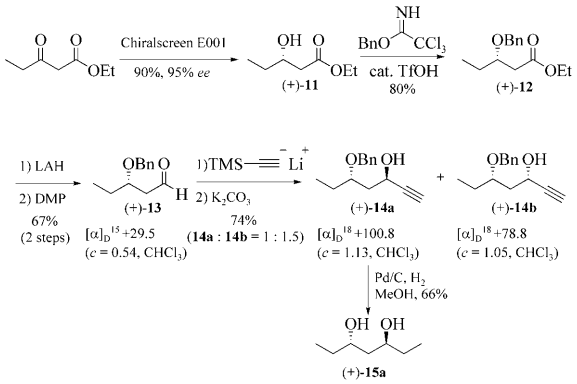


Figure 2. Annularins.

At first, the known secondary alcohol **(*S*)-11**[11] was prepared by enzymatic reduction based on the proposed stereochemistry (Scheme 10).[15]

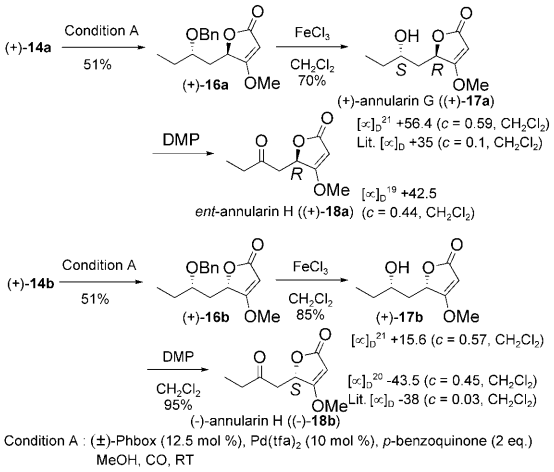
Protection[12] of **(+)-11**, followed by reduction of the ester group and subsequent oxidation, furnished aldehyde **(+)-13**.[13] Nucleophilic addition of TMS-acetylide, followed by desilylation, afforded a mixture of **(+)-14a** and **(+)-14b**



Scheme 10. Synthesis of **(+)-14a** and **(+)-14b**.

(ratio = 1:1.5) separable by column chromatography. The stereochemistry was determined by conversion to known diol **(+)-15a**.[14]

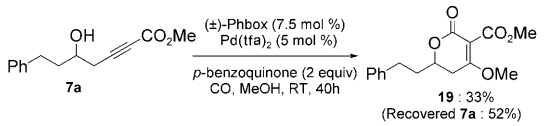
The intermolecular methoxycarbonylation of diastereomeric propargyl alcohols **(+)-14a** and **(+)-14b** under Conditions A afforded **(+)-16a** and **(+)-16b** in moderate yields, respectively (Scheme 11). The use of (*S*)-Phbox, (*R*)-Phbox,



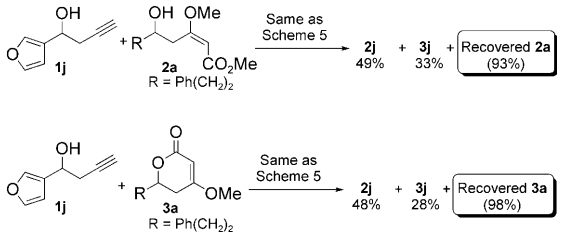
Scheme 11. Synthesis of annularin G and annularin H.

and cationic complex $[\{(S)\text{-Phbox}\}Pd(CH_3CN)_2](SbF_6)_2]$ gave similar results: **(+)-16a** was obtained in 55, 52, and 52% yields, respectively. (+)-Annularin G [**(+)-17a**] and its diastereomer **(+)-17b** were obtained by deprotection of the benzyl group. The absolute stereochemistry of (+)-annularin G was unequivocally determined to be in the (5*R*, 7*S*) configuration. Eventually, the natural (−)-annularin H [**(−)-18b**] was obtained by oxidation of the unnatural diastereomer **(+)-17b**, and its absolute configuration at C-5 was determined to be (*S*).

Next, to investigate the mechanism of the present reaction, some control reactions were performed (Schemes 12 and 13). Formation of acetylene carboxylate, as reported in the literature,[4d] and the ensuing 1,4-addition of MeOH



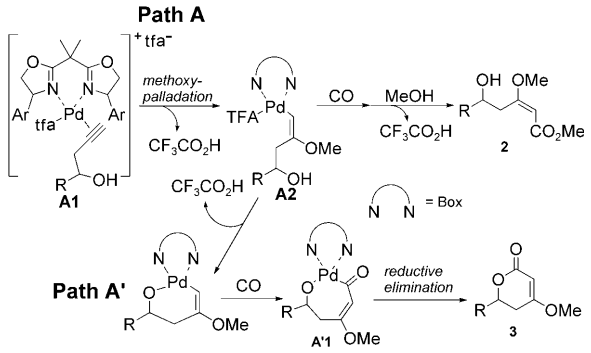
Scheme 12. Intermolecular methoxycarbonylation of acetylene carboxylates **7a**.



Scheme 13. Control experiments for interconversion between **2a** and **3a**.

were conceivable. However, the process was ruled out by experiments using acetylene carboxylates **7a**.

Intermolecular methoxycarbonylation of **7a** gave diesters **19** with recovery of the substrate. Next, the products **2a** and **3a** were treated under the previous reaction conditions (Scheme 13). Interconversion between **2a** and **3a** was not observed. These results indicated that these products **2a** and **3a** were produced by independent pathways. Based on these control experiments, a plausible mechanism for the reaction is shown in Scheme 14.



Scheme 14. Plausible mechanism.

The β-methoxyacrylate **2** should be produced via Path A, because the reaction of simple terminal alkynes without hydroxyl groups proceeded well.[9] The triple bond of **1** coordinates to box-Pd^{II}, and intermediate **A1** undergoes nucleophilic attack by MeOH to produce the vinyl palladium intermediate **A2**. This is followed by CO insertion and methanolysis to provide acyclic β-methoxyacrylate **2**. On the other hand, the assistance of the hydroxyl group is also important. The 6-membered lactone **3** should be produced by reductive elimination of the intermediates **A′1** through Path A′.

Conclusions

In conclusion, we have demonstrated the direct conversion of homopropargyl and propargyl alcohols to β-methoxyacrylates with the aid of the box ligand. The present reaction is considered to be a useful method for the construction of 4-methoxy-2-pyrone, acyclic β-methoxyacrylate, and 4-methoxyfuran-2-one structures. One-pot synthesis of kawa lactones **3a**, **3g**, and **3r**, chiral formal synthesis of dihydroxycystothiazoles and the first asymmetric synthesis of (+)-annularin G and (−)-annularin H[2b] were also achieved.

Experimental Section

General Remarks

See Supporting Information for general experimental details, as well as procedures for the preparation and characterization of all precursors and products.

General Procedure for the Intermolecular Methoxycarbonylation

A 30 mL two-necked round-bottom flask containing a magnetic-stirring bar, $[Pd(tfa)_2]$ (0.015 mmol), ligand (0.0225 mmol), *p*-benzoquinone (0.6 mmol), and MeOH (5 mL) was fitted with a rubber septum and a three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pump-filling through the three-way stopcock. A MeOH solution (1 mL) of substrate **1** (0.3 mmol) was added to the stirred solution by syringe. The remaining substrate was washed in MeOH (1 mL) twice. After stirring for 8–48 h, the mixture was diluted with CH_2Cl_2 (50 mL) and washed with 5% NaOH (40 mL). The aqueous layer was extracted with CH_2Cl_2 (25 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/EtOAc afforded methoxyacrylate **2** and lactone **3**.

*(2E)-5-Hydroxy-3-methoxy-7-phenyl-2-heptenoic Acid Methyl Ester (**2a**)*

Colorless oil; ^{1}H NMR ($CDCl_3$): δ = 1.79–1.85 (2H, m), 2.67–2.75 (1H, m), 2.79–2.87 (2H, m), 3.04 (1H, dd, J = 8.4, 13.6 Hz), 3.09 (1H, d, J = 5.6 Hz), 3.65 (3H, s), 3.69 (3H, s), 3.87–3.94 (1H, m), 5.15 (1H, s), 7.15–7.29 ppm (5H, m); ^{13}C NMR ($CDCl_3$): δ = 31.9, 39.6, 39.7, 51.2, 55.6, 70.1, 92.3, 125.7, 128.3 (2C), 128.5 (2C), 142.2, 169.5, 173.7 ppm; IR (neat): $\tilde{\nu}$ = 3437, 1709, 1617, 1133 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{15}H_{20}O_4$: 264.1362; found: 264.1360.

*(±)-Dihydrokawain (**3a**)[1h]*

Colorless needles; m.p.: 59–61 °C; ^{1}H NMR ($CDCl_3$): δ = 1.88–1.97 (1H, m), 2.09–2.18 (1H, m), 2.30 (1H, dd, J = 4.0 17.0 Hz), 2.51 (1H, ddd, J = 1.6, 12.0, 17.0 Hz), 2.74–2.92 (2H, m), 3.73 (3H, s), 4.36 (1H, octet, J = 4.0 Hz), 5.14 (1H, d, J = 1.6 Hz), 7.18–7.31 ppm (5H, m); ^{13}C NMR ($CDCl_3$): δ = 30.9, 33.0, 36.3, 56.0, 74.8, 90.3, 126.1, 128.4 (2C), 128.5 (2C), 140.8, 167.2, 172.7 ppm; IR (neat): $\tilde{\nu}$ = 3083, 2937, 1693, 1626, 1401 cm^{-1}; HRMS-EI:m/z: [M^+] calcd for $C_{14}H_{16}O_3$: 232.1099; found: 232.1094.

*(2E)-5-Hydroxy-3-methoxy-6-phenyl-2-hexenoic Acid Methyl Ester (**2b**)*

Colorless oil; ^{1}H NMR ($CDCl_3$): δ = 2.77–2.89 (3H, m), 3.00–3.05 (2H, m), 3.64 (3H, s), 3.67 (3H, s), 4.10–4.16 (1H, m), 5.15 (1H, s), 7.10–7.32 ppm (5H, m); ^{13}C NMR ($CDCl_3$): δ = 39.2, 44.3, 51.2, 55.7, 71.5, 92.4, 126.3, 128.4 (2C), 129.5 (2C), 138.4, 169.3, 173.7 ppm; IR (neat): $\tilde{\nu}$ = 3451, 2946, 1709, 1617, 1133 cm^{-1}; HRMS-APCI: m/z: [M+H]$^+$ calcd for $C_{14}H_{19}O_4$: 251.1278; found: 251.1282.

*5,6-Dihydro-4-methoxy-6-(phenylmethyl)-2H-pyran-2-one (**3b**)*

Colorless oil; ^{1}H NMR ($CDCl_3$): δ = 2.25 (1H, dd, J = 3.8, 17.1 Hz), 2.47 (1H, ddd, J = 1.6, 11.6, 17.1 Hz), 2.95 (1H, dd, J = 7.4, 13.8 Hz), 3.17 (1H, dd, J = 5.8, 13.8 Hz), 3.70 (3H, s), 4.56–4.64 (1H, m), 5.13 (1H, d, J = 1.6 Hz), 7.22–7.34 ppm (5H, m); ^{13}C NMR ($CDCl_3$): δ = 32.2, 40.9, 56.0, 76.4, 90.3, 127.0, 128.7 (2C), 129.6 (2C), 135.9, 167.1, 172.8 ppm; IR (neat): $\tilde{\nu}$ = 2945, 1702, 1620, 1389, 1212 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{13}H_{14}O_3$: 218.0943; found: 218.0941.

*(2E)-5-Hydroxy-3-methoxy-2-tetradecenoic Acid Methyl Ester (**2c**)*

Colorless oil; ^{1}H NMR ($CDCl_3$): δ = 0.88 (3H, t, J = 7.0 Hz), 1.26 (14H, br-s), 1.44–1.54 (2H, m), 2.77 (1H, dd, J = 3.4, 13.6 Hz), 2.91 (1H, d, J = 3.4 Hz), 2.99 (1H, dd, J = 8.8, 13.6 Hz), 3.67 (3H, s), 3.68 (3H, s), 3.85 (1H, br-s), 5.14 ppm (1H, s); ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 25.5, 29.3, 29.6, 29.6, 29.7, 31.9, 38.0, 39.8, 51.2, 55.7, 70.8, 92.2, 169.4, 174.1 ppm; IR (neat): $\tilde{\nu}$ = 3485, 2924, 2853, 1619, 1137 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{16}H_{30}O_4$: 286.2144; found: 286.2142.

*5,6-Dihydro-4-methoxy-6-nonyl-2H-pyran-2-one (**3c**)*

Colorless needles; m.p.: 60–62 °C (hexane); ^{1}H NMR ($CDCl_3$): δ = 0.88 (3H, t, J = 6.8 Hz), 1.26 (12H, br-s), 1.37–1.54 (2H, m), 1.59–1.67 (1H, m), 1.76–1.85 (1H, m), 2.32 (1H, dd, J = 3.8, 17.1 Hz), 2.47 (1H, ddd, J = 1.3, 11.8, 17.1 Hz), 3.74 (3H, s), 4.33–4.40 (1H, m), 5.14 ppm (1H, d, J = 1.3 Hz); ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.6, 24.8, 29.2, 29.3, 29.4, 29.5, 31.8, 33.0, 34.7, 55.9, 75.9, 90.3, 167.4, 172.8 ppm; IR (KBr): $\tilde{\nu}$ = 3388, 3083, 2915, 2847, 1713, 1627 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{15}H_{26}O_3$: 254.1882; found: 254.1876.

*(2E)-5-Cyclohexyl-5-hydroxy-3-methoxy-2-pentenoic Acid Methyl Ester (**2d**)*

Colorless oil; ^{1}H NMR ($CDCl_3$): δ = 1.01–1.30 (5H, m), 1.35–1.44 (1H, m), 1.65–1.89 (5H, m), 2.67 (1H, dd, J = 2.8, 13.4 Hz), 2.95 (1H, br-s), 3.07 (1H, dd, J = 10.0, 13.4 Hz), 3.61 (1H, br-s), 3.67 (3H, s), 3.68 (3H, s), 5.15 ppm (1H, s); ^{13}C NMR ($CDCl_3$): δ = 26.2, 26.3, 26.6, 27.9, 28.8, 37.0, 44.5, 51.2, 55.7, 74.9, 92.1, 169.6, 174.9 ppm; IR (neat): $\tilde{\nu}$ = 3464, 2924, 2851, 1617, 1133 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{13}H_{22}O_4$: 242.1518; found: 242.1519.

*6-Cyclohexyl-5,6-dihydro-4-methoxy-2H-pyran-2-one (**3d**)*

Colorless needles; m.p.: 80–81 °C; ^{1}H NMR ($CDCl_3$): δ = 1.02–1.32 (5H, m), 1.60–1.81 (5H, m), 1.95–1.98 (1H, m), 2.26 (1H, dd, J = 3.8, 17.0 Hz), 2.53 (1H, ddd, J = 1.6, 12.6, 17.0 Hz), 3.74 (3H, s), 4.11–4.17 (1H, m), 5.13 ppm (1H, d, J = 1.6 Hz); ^{13}C NMR ($CDCl_3$): δ = 25.8, 25.9, 26.3, 28.2, 28.3, 30.3, 41.5, 56.0, 80.0, 90.4, 167.6, 173.2 ppm; IR (KBr): $\tilde{\nu}$ = 3094, 2937, 2853, 1700, 1631 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{12}H_{18}O_3$: 210.1256; found: 210.1257.

*(2E,6E)-5-Hydroxy-3-methoxy-7-phenyl-2,6-heptedienoic Acid Methyl Ester (**2e**)*

Yellow oil; ^{1}H NMR ($CDCl_3$): δ = 2.91 (1H, dd, J = 4.0, 13.3 Hz), 3.18 (1H, dd, J = 8.6, 13.3 Hz), 3.38 (1H, br-s), 3.66 (3H, s), 3.69 (3H, s), 4.59 (1H, br-s), 5.17 (1H, s), 6.27 (1H, dd, J = 5.8, 15.7 Hz), 6.65 (1H, d, J = 15.7 Hz), 7.20–7.38 ppm (5H, m); ^{13}C NMR ($CDCl_3$): δ = 40.2, 51.2, 55.7, 71.2, 92.6, 126.5 (2C), 127.4, 128.4 (2C), 129.5, 131.9, 136.8, 169.4, 172.9 ppm; IR (neat): $\tilde{\nu}$ = 3421, 2947, 1708, 1617, 1135 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{15}H_{18}O_4$: 262.1205; found: 262.1203.

*(±)-Kawain (**3e**)[1h]*

Colorless needles; m.p.: 142–143 °C; ^{1}H NMR ($CDCl_3$): δ = 2.55 (1H, dd, J = 4.4, 17.2 Hz), 2.67 (1H, ddd, J = 1.2, 10.2, 17.2 Hz), 3.77 (3H, s), 5.04–5.09 (1H, m), 5.20 (1H, d, J = 1.2 Hz), 6.26 (1H, dd, J = 6.2, 16.1 Hz), 6.74 (1H, d, J = 16.1 Hz), 7.26–7.41 ppm (5H, m); ^{13}C NMR ($CDCl_3$): δ = 33.3, 56.1, 75.9, 90.6, 125.5, 126.7 (2C), 128.3, 128.7 (2C), 133.2, 135.7, 166.7, 172.3 ppm; IR (KBr): $\tilde{\nu}$ = 3076, 2920, 1703, 1625, 1230 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{14}H_{14}O_3$: 230.0943; found: 230.0947.

*(2E)-5-Hydroxy-3-methoxy-5-phenyl-2-pentenoic Acid Methyl Ester (**2f**)*

Colorless oil; ^{1}H NMR ($CDCl_3$): δ = 2.91 (1H, dd, J = 3.6, 13.6 Hz), 3.32 (1H, dd J = 9.6, 13.6 Hz), 3.65 (3H, s), 3.71 (3H, s), 3.74 (1H, br-s), 4.96–4.99 (1H, m), 5.18 (1H, s), 7.24–7.44 ppm (5H, m); ^{13}C NMR ($CDCl_3$): δ = 42.4, 51.3, 55.8, 72.9, 92.6, 125.5 (2C), 127.4, 128.3 (2C), 144.5, 169.6, 173.3 ppm; IR (neat): $\tilde{\nu}$ = 3431, 2947, 1706, 1616, 1133 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{13}H_{16}O_4$: 236.1049; found: 236.1048.

*5,6-Dihydro-4-methoxy-6-phenyl-2H-pyran-2-one (**3f**)*

Spectral data were identical with those reported in the literature.[1j]

(2E)-5-Hydroxy-3-methoxy-5-(4-mthoxyphenyl)-2-pentenoic Acid Methyl Ester (**2g**)

Colorless oil; ^{1}H NMR ($CDCl_3$): δ = 2.89 (1H, dd, J = 3.5, 13.6 Hz), 3.30 (1H, dd, J = 9.7, 13.6 Hz), 3.65 (3H, s), 3.71 (3H, s), 3.80 (3H, s), 4.93 (1H, dd, J = 3.5, 9.7 Hz), 5.17 (1H, s), 6.86–6.89 (2H, m), 7.33–7.36 ppm (2H, m); ^{13}C NMR ($CDCl_3$): δ = 42.3, 51.2, 55.2, 55.7, 72.4, 92.4, 113.7 (2C), 126.7 (2C), 136.6, 158.8, 169.5, 173.3 ppm; IR (neat): $\tilde{\nu}$ = 3436, 2948, 1707, 1611, 1133 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{14}H_{18}O_5$: 266.1154; found: 266.1157.

*5,6-Dihydro-4-methoxy-6-(4-methoxyphenyl)-2H-pyran-2-one (**3g**)*

Colorless needles; m.p.: 98–100 °C; ^{1}H NMR ($CDCl_3$): δ = 2.55 (1H, dd, J = 3.8, 17.1 Hz), 2.83 (1H. ddd, J = 1.4, 12.3, 17.1 Hz), 3.78 (3H, s), 3.81 (3H, s), 5.23 (1H, d, J = 1.4 Hz), 5.37 (1H, dd, J = 3.8, 12.3 Hz), 6.89–6.93 (2H, m), 7.32–7.35 ppm (2H, m); ^{13}C NMR ($CDCl_3$): δ = 34.9, 55.3, 56.1, 77.0, 90.5, 114.0 (2C), 127.5 (2C), 130.3, 159.8, 167.0, 172.7 ppm; IR (KBr): 3053, 2961, 2837, 1712, 1626 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{13}H_{14}O_4$: 234.0892; found: 234.0896.

*(2E)-5-(4-Chlorophenyl)-5-hydroxy-3-methoxy-2-pentenoic Acid Methyl Ester (**2h**)*

Colorless oil; ^{1}H NMR ($CDCl_3$): δ = 2.91 (1H, dd, J = 3.6, 13.6 Hz), 3.23 (1H, dd, J = 9.4, 13.6 Hz), 3.64 (3H, s), 3.71 (3H, s), 3.91 (1H, d, J = 3.6 Hz), 4.95 (1H, d, J = 9.4 Hz), 5.18 (1H, s), 7.29–7.37 ppm (4H, m); ^{13}C NMR ($CDCl_3$): δ = 42.3, 51.4, 55.8, 72.3, 92.7, 127.0 (2C), 128.4 (2C), 132.9, 142.9, 169.7, 172.9 ppm; IR (neat): $\tilde{\nu}$ = 3415, 2947, 1705, 1617, 1134 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{13}H_{15}O_4Cl$: 270.0659; found: 270.0657.

*6-(4-Chlorophenyl)-5,6-dihydro-4-methoxy-2H-pyran-2-one (**3h**)*

Spectral data were identical with those reported in the literature.[1k]

*(2E)-5-Hydroxy-3-methoxy-5-(naphthalen-2-yl)-2-pentenoic Acid Methyl Ester (**2i**)*

Colorless oil; ^{1}H NMR ($CDCl_3$): δ = 3.00 (1H, dd, J = 3.4, 13.7 Hz), 3.40 (1H, dd, J = 9.6, 13.7 Hz), 3.66 (3H, s), 3.73 (3H, s), 3.92 (1H, d, J = 5.6 Hz), 5.14–5.16 (1H, m), 5.21 (1H, s), 7.44–7.47 (2H, m), 7.55 (1H, dd, J = 1.6, 8.4 Hz), 7.81–7.85 (3H, m), 7.89 ppm (1H, s); ^{13}C NMR ($CDCl_3$): δ = 42.4, 51.4, 55.8, 73.1, 92.7, 123.9, 124.1, 125.7, 126.0, 127.7, 128.0, 128.1, 132.9, 133.3, 141.9, 169.8, 173.2 ppm; IR (neat): $\tilde{\nu}$ = 3415, 2946, 1704, 1616, 1133 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{17}H_{18}O_4$: 286.1205; found: 286.1210.

*5,6-Dihydro-4-methoxy-6-(naphthalen-2-yl)-2H-pyran-2-one (**3i**)*

Spectral data were identical with those reported in the literature.[1l]

*(2E)-5-(Furan-2-yl)-5-hydroxy-3-methoxy-2-pentenoic Acid Methyl Ester (**2j**)*

Yellow oil; ^{1}H NMR ($CDCl_3$): δ = 2.97 (1H, dd, J = 3.9, 13.7 Hz), 3.53 (1H, dd, J = 9.8, 13.7 Hz), 3.66 (3H, s), 3.70 (3H, s), 4.97 (1H, dd, J = 3.9, 9.8 Hz), 5.20 (1H, s), 6.28 (1H, dt, J = 0.8, 3.2 Hz), 6.32 (1H, dd, J = 2.0, 3.2 Hz), 7.37 ppm (1H, dd, J = 0.8, 2.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 38.8, 51.3, 55.8, 66.5, 92.9, 105.6, 110.1, 141.9, 156.4, 169.5, 172.5 ppm; IR (neat): $\tilde{\nu}$ = 3429, 2949, 1706, 1619, 1133 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{11}H_{14}O_5$: 226.0841; found: 226.0837.

*5,6-Dihydro-6-(furan-2-yl)-4-methoxy-2H-pyran-2-one (**3j**)*

Spectral data were identical with those reported in the literature.[1k]

*(2E)-5-(Furan-3-yl)-5-hydroxy-3-methoxy-2-pentenoic Acid Methyl Ester (**2k**)*

Yellow oil; ^{1}H NMR ($CDCl_3$): δ = 2.95 (1H, dd, J = 3.7, 13.7 Hz), 3.35 (1H, dd, J = 9.2, 13.7 Hz), 3.44 (1H, br-s), 3.66 (3H, s), 3.69 (3H, s), 4.95 (1H, dd, J = 3.7, 9.2 Hz), 5.18 (1H, s), 6.44 (1H, s), 7.37 (1H, t, J = 1.2 Hz), 7.42 ppm (1H, d, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$): δ = 40.8, 51.3, 55.7, 65.9, 92.7, 108.6, 129.1, 138.9, 143.2, 169.4, 173.0 ppm; IR (neat): $\tilde{\nu}$ = 3434, 2949, 1705, 1618, 1134 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{11}H_{14}O_5$: 226.0841; found: 226.0850.

*5,6-Dihydro-6-(furan-3-yl)-4-methoxy-2H-pyran-2-one (**3k**)*

Colorless needles; m.p.: 124–125 °C; ^{1}H NMR ($CDCl_3$): δ = 2.62 (1H, ddd, J = 0.6, 4.1, 17.0 Hz), 2.81 (1H, dd, J = 11.2, 17.0 Hz), 3.78 (3H, s), 5.21 (1H, s), 5.42 (1H, dd, J = 4.1, 11.2 Hz), 6.46–6.46 (1H, m), 7.42–7.43 (1H, m), 7.50 ppm (1H, dd, J = 1.0, 1.4 Hz); ^{13}C NMR ($CDCl_3$): δ = 33.6, 56.2, 70.5, 90.6, 108.6, 123.7, 139.9, 143.7, 166.7, 172.4 ppm; IR (KBr): $\tilde{\nu}$ = 3119, 2952, 1680, 1620, 1076 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{10}H_{10}O_4$: 194.0579; found: 194.0573.

*(2E)-3,5-Dimethoxy-7-phenyl-2-heptenoic Acid Methyl Ester (**2l**)*

Colorless oil; ^{1}H NMR ($CDCl_3$): δ = 1.78–1.83 (2H, m), 2.59–2.66 (1H, m), 2.77–2.82 (1H, m), 2.87 (1H, dd, J = 6.4, 13.2 Hz), 3.16 (1H, dd, J = 6.4, 13.2 Hz), 3.39 (3H, s), 3.55 (1H, quintet, J = 6.4 Hz), 3.62 (3H, s), 3.67 (3H, s), 5.06 (1H, s), 7.17–7.29 ppm (5H, m); ^{13}C NMR ($CDCl_3$): δ = 31.5, 36.0, 36.4, 50.8, 55.5, 56.8, 78.8, 91.6, 125.7, 128.3 (2C), 128.4 (2C), 142.5, 167.8, 173.8 ppm; IR (neat): $\tilde{\nu}$ = 2943, 1710, 1619, 1133, 1051 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{16}H_{22}O_4$: 278.1518; found: 278.1516.

*(2E)-5-Acetoxy-3-methoxy-7-phenyl-2-heptenoic Acid Methyl Ester (**2m**)*

Colorless oil; ^{1}H NMR ($CDCl_3$): δ = 1.88–1.94 (2H, m), 1.99 (3H, s), 2.59–2.74 (2H, m), 3.06 (1H, dd, J = 8.0, 13.9 Hz), 3.13 (1H, dd, J = 5.0, 13.9 Hz), 3.59 (3H, s), 3.68 (3H, s), 5.06 (1H, s), 5.21–5.27 (1H, m), 7.15–7.29 ppm (5H, m); ^{13}C NMR ($CDCl_3$): δ = 21.1, 31.7, 35.9, 36.4, 50.9, 55.5, 71.9, 92.2, 125.9, 128.4 (2C), 128.4 (2C), 141.6, 167.8, 170.6, 172.2 ppm; IR (neat): $\tilde{\nu}$ = 2947, 1737, 1712, 1624, 1134 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{17}H_{22}O_5$: 306.1467; found: 306.1461.

*(2E)-3-Methoxy-5-(methoxymethoxy)-7-phenyl-2-heptenoic Acid Methyl Ester (**2n**)*

Colorless oil; ^{1}H NMR ($CDCl_3$): δ = 1.82–1.88 (2H, m), 2.61–2.69 (1H, m), 2.79–2.86 (1H, m), 2.98 (1H, dd, J = 6.5, 13.2 Hz), 3.14 (1H, dd, J = 6.5, 13.2 Hz), 3.39 (3H, s), 3.61 (3H, s), 3.67 (3H, s), 3.96 (1H, quintet, J = 6.5 Hz), 4.65 (1H, d, J = 7.0 Hz), 4.73 (1H, d, J = 7.0 Hz), 5.07 (1H, s), 7.15–7.29 ppm (5H, m); ^{13}C NMR ($CDCl_3$): δ = 31.6, 36.7, 37.3, 50.9, 55.5, 55.7, 75.7, 91.8, 95.6, 125.7, 128.3 (2C), 128.4 (2C), 142.4, 167.8, 173.4 ppm; IR (neat): $\tilde{\nu}$ = 2946, 1711, 1620, 1134, 1028 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{17}H_{24}O_5$: 308.1624; found: 308.1618.

*(2E)-5-(tert-Butyldimethylsilyloxy)-3-methoxy-7-phenyl-2-heptenoic Acid Methyl Ester (**2o**)*

Colorless oil; ^{1}H NMR ($CDCl_3$): δ = 0.02 (3H, s), 0.05 (3H, s), 0.89 (9H, s), 1.75–1.81 (2H, m), 2.61–2.79 (2H, m), 2.97 (1H, dd, J = 6.0, 13.1 Hz), 3.03 (1H, dd, J = 7.4, 13.1 Hz), 3.60 (3H, s), 3.67 (3H, s), 4.08–4.14 (1H, m), 5.04 (1H, s), 7.14–7.28 ppm (5H, m); ^{13}C NMR ($CDCl_3$): δ = −4.67, −4.58, 18.0, 25.8, 31.2, 39.4, 39.5, 50.8, 55.3, 70.3, 91.7, 125.6, 128.3 (2C), 128.4 (2C), 142.8, 167.8, 173.8 ppm; IR (neat): $\tilde{\nu}$ = 2950, 2856, 1713, 1621, 1134 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{21}H_{34}O_4Si$: 378.2226; found: 378.2230.

*4-Methoxy-5-(phenylethyl)furan-2(5H)-one (**3p**)*

Colorless needles; m.p.: 35 °C; ^{1}H NMR ($CDCl_3$): δ = 1.87–1.96 (1H, m), 2.15–2.24 (1H, m), 2.72–2.84 (2H, m), 3.83 (3H, s), 4.74 (1H, dd, J = 3.6, 8.4 Hz), 5.05 (1H, d, J = 0.8 Hz) 7.18–7.31 ppm (5H, m); ^{13}C NMR

($CDCl_3$): δ = 30.5, 33.5, 59.4, 77.8, 88.7, 126.3, 128.5 (2C), 128.6 (2C), 140.4, 172.6, 182.4 ppm; IR (KBr): $\tilde{\nu}$ = 3106, 2949, 1735, 1624, 1249 cm^{-1}; HRMS-EI: *m/z*: [M^+] calcd for $C_{13}H_{14}O_3$: 218.0943; found:218.0942 .

*4-Methoxy-5-nonylfuran-2(5H)-one (**3q**)*

Colorless needles; m.p.: 42 °C; ^{1}H NMR ($CDCl_3$): δ = 0.88 (3H, t, *J* = 6.9 Hz), 1.26–1.44 (14H, m), 1.55–1.66 (1H, m), 1.85–1.93 (1H, m), 3.89 (3H, s), 4.76 (1H, dd, *J* = 3.7, 7.6 Hz), 5.06 ppm (1H, s); ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 24.2, 29.2, 29.3, 29.4, 29.5, 31.8, 31.9, 59.4, 78.9, 88.6, 172.8, 182.6 ppm; IR (KBr): $\tilde{\nu}$ = 3122, 2919, 1744, 1626, 1247 cm^{-1}; HRMS-EI: *m/z*: [M^+] calcd for $C_{14}H_{24}O_3$: 240.1726; found: 240.1728.

*One-pot Synthesis of Kawa Lactones **3a**, **3r**, and **3s**.*

The carbonylation reaction was performed in a similar manner to that described above. After stirring for 24 h, (+)-10-camphorsulfonic acid (CSA) (1 equiv) or K_2CO_3 (5 equiv) was added to the reaction mixture and stirring was continued at room temperature for 24 h. The mixture was diluted with EtOAc (50 mL), and washed with saturated $NaHCO_3$ aq. (30 mL) or brine (30 mL). The aqueous layer was extracted with EtOAc (20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/ethyl acetate (5/1–3/1) afforded (±)-kawa lactones **3a**, **3r**, and **3s** in 67–73% yields.

*(±)-Tetrahydroyangonine (**3r**)[1m]*

Colorless needles; m.p.: 98–99 °C; ^{1}H NMR ($CDCl_3$): δ = 1.84–1.93 (1H, m), 2.05–2.14 (1H, m), 2.29 (1H, dd, *J* = 4.0, 17.1 Hz), 2.50 (1H, ddd, *J* = 1.6, 12.0, 17.1 Hz), 2.68–2.85 (2H, m), 3.72 (3H, s), 3.78 (3H, s), 4.34 (1H, octet, *J* = 4.0 Hz), 5.13 (1H, d, *J* = 1.6 Hz), 6.81–6.85 (2H, m), 7.10–7.14 ppm (2H, m); ^{13}C NMR ($CDCl_3$): δ = 30.0, 33.0, 36.5, 55.3, 56.0, 74.8, 90.3, 114.0 (2C), 129.4 (2C), 132.8, 158.0, 167.4, 172.8 ppm; IR (KBr): $\tilde{\nu}$ = 3374, 2935, 1711, 1622, 1249 cm^{-1}; HRMS-EI: *m/z*: [M^+] calcd for $C_{15}H_{18}O_4$: 262.1205; found: 262.1202.

*(±)-Dihydromethysticin (**3s**)[1i]*

Colorless needles; m.p.: 115–116 °C; ^{1}H NMR ($CDCl_3$): δ = 1.83–1.91 (1H, m), 2.03–2.13 (1H, m), 2.29 (1H, dd, *J* = 4.0, 16.9 Hz), 2.50 (1H, ddd, *J* = 1.6, 12.0, 16.9 Hz), 2.66–2.83 (2H, m), 3.73 (3H, s), 4.29–4.40 (1H, m), 5.14 (1H, d, *J* = 1.6 Hz), 5.92 (2H, s), 6.64–6.74 ppm (3H, m); ^{13}C NMR ($CDCl_3$): δ = 30.7, 33.0, 36.6, 56.0, 74.7, 90.4, 100.8, 108.3, 108.9, 121.3, 134.6, 145.9, 147.7, 167.3, 172.7 ppm; IR (KBr): $\tilde{\nu}$ = 3376, 3107, 2952, 1687, 1618, 1260 cm^{-1}; HRMS-EI: *m/z*: [M^+] calcd for $C_{15}H_{16}O_5$: 276.0998; found: 276.0997.

*(2R, 3S)-3-Methyl-4-pentyne-1,2-diol 1-Benzoate (**1t**)*

To a solution of known hydroxyester **(−)-8** (462 mg, 2.16 mmol, 95% *ee*) and ethyl vinyl ether (187 mg, 2.59 mmol) in CH_2Cl_2 (15 mL) was added PPTS (54 mg, 0.22 mmol) at room temperature and the mixture was stirred for 1 h. The mixture was diluted with saturated $NaHCO_3$ aq. (25 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. To a solution of the crude product in THF (10 mL) was added $LiBH_4$ (188 mg, 8.62 mmol) at room temperature and the solution was stirred for 3 h at 40 °C. After cooling, the mixture was diluted with MeOH/H_2O/EtOAc (10:30:10 mL) and stirred for 12 h. The mixture was diluted with H_2O/EtOAc (30:30 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. To a solution of the crude product in MeOH (10 mL) was added K_2CO_3 (357 mg, 2.59 mmol) at room temperature and the mixture was stirred for 2 h. The mixture was diluted with brine (30 mL) and EtOAc (30 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. To a solution of the crude product in pyridine (5 mL) was added BzCl (364 mg, 2.59 mmol) at room temperature and the solution was stirred for 1 h. The mixture was diluted with brine (30 mL) and EtOAc (30 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (20 mL), and the combined organic layers were washed with 10% HCl aq. (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. To a solution of the crude product in MeOH (5 mL) was added PPTS (54 mg, 0.216 mmol) at room temperature and the solution was stirred for 2 h. The mixture was diluted with EtOAc (30 mL) and saturated $NaHCO_3$ aq. (30 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/EtOAc (15/1) afforded benzoate **1s** in 57% yield. Colorless oil; $[\alpha]_D^{24} = -45.0$ (*c* = 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 1.33 (3H, d, *J* = 7.2 Hz), 2.17 (1H, d, *J* = 2.5 Hz), 2.64 (1H, br-s), 2.70–2.78 (1H, m), 3.91 (1H, dt, *J* = 3.1, 7.0 Hz), 4.46 (1H, dd, *J* = 7.0, 11.9 Hz), 4.62 (1H, dd, *J* = 3.1, 11.9 Hz), 7.42–7.46 (2H, m), 7.55–7.60 (1H, m), 8.04–8.07 ppm (2H, m); ^{13}C NMR ($CDCl_3$): δ = 16.7, 29.9, 67.2, 71.0, 72.8, 77.3, 84.8, 128.5 (2C), 129.7 (2C), 133.3, 166.9 ppm; IR (KBr): $\tilde{\nu}$ = 3505, 3262, 2977, 1704, 1285 cm^{-1}; HRMS-FAB: *m/z*: [M^++H] calcd for $C_{13}H_{15}O_3$: 219.1021; found: 219.1022.

*Intermolecular Methoxycarbonylation of **1t***

See the general procedure. (*R*)-Phbox ligand was employed.

*(2E)-(4R,5R)-6-(Benzoyloxy)-5-hydroxy-3-methoxy-4-methyl-2-hexenoic Acid Methyl Ester (**(+)-2t**)*

Colorless oil; $[\alpha]_D^{22} = +16.6$ (*c* = 0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 1.26 (3H, d, *J* = 6.8 Hz), 2.91 (1H, br-s), 3.60 (3H, s), 3.65 (3H, s), 4.11 (1H, dt, *J* = 3.2, 6.8 Hz), 4.20–4.26 (2H, m), 4.41 (1H, dd, *J* = 3.2, 11.6 Hz), 5.07 (1H, s), 7.41–7.46 (2H, m), 7.53–7.58 (1H, m), 8.05–8.07 ppm (2H, m); ^{13}C NMR ($CDCl_3$): δ = 14.0, 38.0, 51.0, 55.7, 67.2, 72.4, 91.6, 128.3 (2C), 129.8 (2C), 130.0, 133.0, 166.8, 168.2, 176.0 ppm; IR (neat): $\tilde{\nu}$ = 3488, 2949, 1711, 1619, 1270 cm^{-1}; HRMS-FAB: *m/z*: [M^++H] calcd for $C_{16}H_{21}O_6$: 309.1338; found: 309.1307.

*6-(Benzoyloxymethyl)-5,6-dihydro-4-methoxy-5-methyl-2H-pyran-2-one (**(+)-3t**)*

Colorless oil; $[\alpha]_D^{24} = +67.7$ (*c* = 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 1.24 (3H, d, *J* = 7.2 Hz), 2.53–2.59 (1H, m), 3.77 (3H, s), 4.48–4.59 (2H, m), 4.76–4.80 (1H, m), 5.13 (1H, s), 7.43–7.47 (2H, m), 7.56–7.61 (1H, m), 8.04–8.06 ppm (2H, m); ^{13}C NMR ($CDCl_3$): δ = 11.1, 34.5, 56.3, 63.1, 75.5, 89.4, 128.5 (2C), 129.4, 129.8 (2C), 133.4, 166.1, 166.1, 177.7 ppm. IR (KBr): $\tilde{\nu}$ = 2956, 1725, 1698, 1621, 1221 cm^{-1}; HRMS-EI: *m/z*: [M^+] calcd for $C_{15}H_{16}O_5$: 276.0998; found: 276.1001.

*(2E)-(4R,5R)-5,6-Dihydroxy-3-methoxy-4-methyl-2-hexenoic Acid Methyl Ester (**(+)-9**)*

To a solution of **(+)-2t** (49.5 mg, 0.16 mmol) in H_2O-saturated *i*Pr_2O (7 mL) was added lipase OF (100 mg) and the mixture was stirred for 30 h at 33 °C. The mixture was filtered, and the filtrate was washed with EtOAc (20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/EtOAc (1/1) afforded diol **(+)-9** in 70% yield. Colorless oil; $[\alpha]_D^{24} = +84.8$ (*c* = 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 1.22 (3H, d, *J* = 6.8 Hz), 3.08 (2H, br-s), 3.57 (2H, d, *J* = 3.2 Hz), 3.63–3.66 (4H, m), 3.70 (3H, s), 3.84–3.91 (1H, m), 5.07 ppm (1H, s); ^{13}C NMR ($CDCl_3$): δ = 14.4, 38.0, 51.4, 55.8, 64.0, 73.9, 91.4, 169.7, 177.0 ppm; IR (neat): $\tilde{\nu}$ = 3398, 2941, 1707, 1614, 1145 cm^{-1}; HRMS-FAB: *m/z*: [M^++H] calcd for $C_9H_{17}O_5$: 205.1076; found: 205.1091.

*(2E)-(4R,5R)-5,6-Bis-(tert-butyldimethylsilyloxy)-3-methoxy-4-methyl-2-hexenoic Acid Methyl Ester (**(+)-10**)*

To a solution of **(+)-9** (20.8 mg, 0.10 mmol) and 2,6-lutidine (98.3 mg, 0.41 mmol) in CH_2Cl_2 (1 mL) was added TBDMSOTf (107.7 mg, 0.41 mmol) at 0 °C and the mixture was stirred for 1.5 h at room temperature. The mixture was diluted with EtOAc (30 mL) and H_2O (25 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by

column chromatography on silica gel. The fraction eluted with hexane/EtOAc (100/1) afforded benzoate **(+)-10** in 97% yield. The spectral data were identical with those reported in the literature.[3g]

(S)-3-(Phenylmethoxy)-1-pentanoic Acid Ethyl Ester ((+)-12)

To a solution of **(+)-11** (2.0 g, 13.7 mmol) and benzyl 2,2,2-trichloroacetimidate (3.45 g, 13.7 mmol) in cyclohexane/CH_2Cl_2 (2:1, 150 mL) was added TfOH (0.2 mL) and the mixture was stirred for 40 h at room temperature. The mixture was diluted with saturated $NaHCO_3$ aq. (100 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (240 mL×3), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/EtOAc (60:1) afforded **(+)-12** in 80% yield. Colorless oil; $[\alpha]_D^{13}=+11.6$ ($c=1.06$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=0.95$ (3H, t, $J=7.4$ Hz), 1.24 (3H, t, $J=7.2$ Hz), 1.59–1.66 (2H, m), 2.46 (1H, dd, $J=5.2$, 14.8 Hz), 2.60 (1H, dd, $J=7.6$, 14.8 Hz), 3.82–3.88 (1H, m), 4.13 (2H, dq, $J=1.2$, 7.2 Hz), 4.54 (2H, s), 7.23–7.33 ppm (5 H m); ^{13}C NMR ($CDCl_3$): $\delta=9.4$, 14.2, 27.0, 39.6, 60.4, 71.5, 77.2, 127.5, 127.7 (2C), 128.3 (2C), 138.6, 171.9 ppm; IR (neat): $\tilde{\nu}=2974$, 2935, 2877, 1732, 1455, 1372, 1062, 1029 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{14}H_{20}O_3$: 236.1413; found: 236.1413.

(S)-3-(Phenylmethoxy)-1-pentanal ((+)-13)

To a solution of **(+)-12** (1.83 g, 7.74 mmol) in THF (35 mL) was added $LiAlH_4$ (347 mg, 9.13 mmol) at 0 °C and the mixture was stirred for 1.5 h. The reaction was quenched with acetone (3 mL) and H_2O (30 mL), and stirred for an additional 1 h. The mixture was filtered through Celite and the filter cake was washed with EtOAc (40 mL×3). The layers were separated, the aqueous layer was extracted with ethyl acetate (20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. To a solution of the crude product in CH_2Cl_2 (15 mL) was added DMP reagent (6.02 g, 14.2 mmol) at room temperature and the mixture was stirred for 2 h. The mixture was diluted with saturated $NaHCO_3$ aq. (15 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (30 mL×3), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/EtOAc (40/1) afforded **(+)-13** in 78% yield. Spectral data were identical with those reported in the literature.[13]

Synthesis of (+)-14a and (+)-14b

To a solution of trimethylsilylacetylene (715 mg, 7.28 mmol) in THF (15 mL) was added *n*BuLi (1.6 M in hexane) (4.55 mL, 7.28 mmol) at −40 °C and the mixture was stirred for 0.5 h at 0 °C. A solution of **(+)-13** (1.0 g, 5.2 mmol) in THF (7 mL) was added to the above mixture at −40 °C, followed by stirring for 1.5 h. The reaction was quenched with saturated NH_4Cl aq. (5 mL), and the mixture was diluted with H_2O (40 mL) and EtOAc (40 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. To a solution of the crude product in MeOH (8 mL) was added K_2CO_3 (1.79 g, 13 mmol) and the solution was stirred for 2 h. The mixture was diluted with H_2O (40 mL) and EtOAc (40 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/EtOAc (30:1) afforded **(+)-14a** and **(+)-14b** in 31 and 46% yields, respectively.

(3R,5S)-5-(Phenylmethoxy)-1-heptyn-3-ol ((+)-14a)

Colorless oil; $[\alpha]_D^{18}=+100.8$ ($c=1.13$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=0.94$ (3H, t, $J=7.6$ Hz), 1.59–1.73 (2H, m), 1.83–2.01 (2H, m), 2.45 (1H, d, $J=2$ Hz), 3.49 (1H, d, $J=7.2$ Hz), 3.91–3.97 (1H, m), 4.49–4.64 (3H, m), 7.23–7.37 ppm (5H, m); ^{13}C NMR ($CDCl_3$): $\delta=9.0$, 25.8, 39.8, 60.4, 71.2, 72.7, 78.0, 84.9, 127.8, 128.0 (2C), 128.5 (2C), 138.1 ppm; IR (neat): $\tilde{\nu}=$ 3410, 2964, 2926, 2875, 1454, 1354 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{14}H_{18}O_2$: 218.1307; found: 218.1313.

(3R,5S)-5-(Phenylmethoxy)-1-heptyn-3-ol ((+)-14b)

Colorless oil; $[\alpha]_D^{18}=+78.8$ ($c=1.05$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=0.93$ (3H, t, $J=6.4$ Hz), 1.62–1.69 (2H, m), 1.82–1.87 (1H, m), 2.00–2.08 (1H, m), 2.43 (1H, d, $J=2.0$ Hz), 3.14 (1H, d, $J=3.2$ Hz), 3.63–3.69 (1H, m), 4.39–4.62 (3H, m), 7.25–7.34 ppm (5H, m); ^{13}C NMR ($CDCl_3$): $\delta=8.8$, 26.0, 41.5, 61.3, 70.9, 72.7, 78.9, 84.7, 127.8, 127.9 (2C), 128.4 (2C), 138.1 ppm; IR (neat): $\tilde{\nu}=3389$, 2963, 2928, 2876, 1455 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{14}H_{18}O_2$: 218.1307; found: 218.1316.

Intermolecular Methoxycarbonylation of 1s

See the general procedure. (±)-Phbox ligand was employed.

(5R)-4-Methoxy-5-[(2S)-2-(phenylmethoxy]butyl]-2(5H)-furanone ((+)-16a)

Colorless oil; $[\alpha]_D^{18}=+124.8$ ($c=0.37$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=0.93$ (3H, t, $J=7.6$ Hz), 1.51–1.70 (3H, m), 2.02–2.09 (1H, m), 3.71–3.77 (1H, m), 3.85 (3H, s), 4.50 (1H, d, $J=11.2$ Hz), 4.63 (1H, d, $J=11.2$ Hz), 5.01–5.04 (2H, m), 7.22–7.41 ppm (5H, m); ^{13}C NMR ($CDCl_3$): $\delta=8.9$, 26.7, 37.5, 59.4, 71.9, 76.2, 76.4, 88.2, 127.6, 127.8 (2C), 128.4 (2C), 138.6, 172.7, 183.3 ppm; IR (neat): $\tilde{\nu}=2965$, 2938, 2875, 1750, 1629 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{16}H_{20}O_4$: 276.1362; found: 276.1358.

(5S)-4-Methoxy-5-[(2S)-2-(phenylmethoxy]butyl]-2(5H)-furanone ((+)-16b)

Colorless oil; $[\alpha]_D^{19}=+61.0$ ($c=1.11$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=0.95$ (3H, t, $J=7.4$ Hz), 1.60–1.74 (2H, m), 1.94–2.11 (2H, m), 3.56–3.62 (1H, m), 3.65 (3H, s), 4.32 (1H, d, $J=11.4$ Hz), 4.53 (1H, d, $J=11.4$ Hz), 4.89 (1H, t, $J=5.4$ Hz), 4.96 (1H, d, $J=0.8$ Hz), 7.24–7.35 ppm (5H, m); ^{13}C NMR ($CDCl_3$): $\delta=9.1$, 26.1, 35.4, 59.2, 70.9, 75.6, 76.1, 88.0, 127.6, 127.8 (2C), 128.3 (2C), 138.5, 172.8, 183.2 ppm; IR (neat): $\tilde{\nu}=2968$, 2939, 2876, 1748, 1627 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_{16}H_{20}O_4$: 276.1362; found: 276.1364.

General Procedure for the Synthesis of (+)-Annularine G ((+)-17a) and (+)-17b

To a solution of **(+)-16a** (36.8 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) was added $FeCl_3$ (64.8 mg, 0.4 mmol) and the mixture was stirred for 0.5 h at room temperature. The mixture was diluted with CH_2Cl_2 (8 mL) and H_2O (15 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (10 mL×3), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/EtOAc (1/1) afforded **(+)-17a** in 70% yield.

(5R)-4-Methoxy-5-[(2S)-2-hydroxybutyl]-2(5H)-furanone ((+)-annularine G ((+)-17a))

Colorless needles; m.p.: 107–109 °C; $[\alpha]_D^{21}=+56.4$ ($c=0.59$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta=0.96$ (3H, t, $J=7.2$ Hz), 1.49–1.56 (2H, m), 1.58 (1H, ddd, $J=2.4$, 10.8, 13.2 Hz), 1.94 (1H, ddd, $J=2.4$, 10.4, 12.8 Hz), 2.17 (1H, br), 3.81–3.87 (1H, m), 3.90 (3H, s), 5.07 (1H, d, $J=0.9$ Hz), 5.08 ppm (1H, ddd, $J=1.0$, 2.8, 10.0 Hz); ^{13}C NMR ($CDCl_3$): $\delta=9.7$, 30.8, 39.4, 59.5, 69.1, 76.3, 88.3, 172.7, 183.3 ppm; IR (KBr): $\tilde{\nu}=3490$, 2968, 2950, 2919, 1742, 1628 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_9H_{14}O_4$: 186.0892; found: 186.0897.

(5S)-4-Methoxy-5-[(2S)-2-hydroxybutyl]-2(5H)-furanone ((+)-17b)

(+)-17b was obtained in 85% yield as colorless needles; m.p.: 61–62 °C; $[\alpha]_D^{21}=+15.6$ ($c=0.57$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta=0.96$ (3H, t, $J=$ 7.4 Hz), 1.49–1.60 (2H, m), 1.78 (1H, tt, 5.07, $J=8.4$, 14.8 Hz), 2.06 (1H, tt, $J=4.0$, 8.0 Hz), 2.10 (1H, br), 3.80–3.86 (1H, m), 3.90 (3H, s), 4.93 (1H, dd, $J=4.4$, 7.6 Hz), 5.08 ppm (1H, s); ^{13}C NMR ($CDCl_3$): $\delta=9.7$, 30.2, 38.8, 59.5, 70.0, 77.3, 88.3, 172.4, 183.0 ppm; IR (KBr): $\tilde{\nu}=3472$, 2963, 2939, 2916, 1748, 1637 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_9H_{14}O_4$: 186.0892; found: 186.0891.

*General Procedure for the Synthesis of ent-*Annularine H (**(+)-18a**) and Annularine H (**(−)-18b**)

To a solution of **(+)-17a** (11.9 mg, 0.064 mmol) in CH_2Cl_2 (4 mL) was added DMP (54.3 mg, 0.128 mmol) and the mixture was stirred for 1 h at room temperature. The mixture was diluted with CH_2Cl_2 (15 mL) and H_2O (15 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (15 mL × 2), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/EtOAc (1:1) afforded **(+)-18a** in 89% yield.

*(5R)-4-Methoxy-5-(2-oxobutyl)- 2(5H)-furanone (ent-*Annularine H (**(+)-18a**))

Colorless needles; m.p.: 58–61 °C; $[\alpha]_D^{19} = +42.5$ ($c = 0.44$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta = 1.08$ (3H, t, $J = 7.4$ Hz), 2.51 (2H, q, $J = 7.2$ Hz), 2.72 (1H, dd, $J = 8.6$, 16.8 Hz), 2.88 (1H, dd, $J = 3.6$, 16.8 Hz), 3.90 (3H, s), 5.10 (1H, d, $J = 1.2$ Hz), 5.26 ppm (1H, ddd, $J = 1.2$, 4.0, 8.4 Hz); ^{13}C NMR ($CDCl_3$): $\delta = 7.4$, 37.0, 43.8, 59.6, 74.6, 88.9, 171.9, 181.8, 206.1 ppm; IR (KBr): $\tilde{\nu} = 3484$, 3416, 2973, 2958, 2925, 1783, 1750, 1646 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_9H_{12}O_4$: 184.0736; found: 184.0734.

*(5S)-4-Methoxy-5-(2-oxobutyl)- 2(5H)-furanone ((−)-Annularine H (**(−)-18b**))*

95% yield. Colorless needles; m.p.: 58–62 °C; $[\alpha]_D^{20} = -43.5$ ($c = 0.45$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta = 1.08$ (3H, t, $J = 7.4$ Hz), 2.51 (2H, q, $J = 7.6$ Hz), 2.72 (1H, dd, $J = 8.4$,16.8 Hz), 2.88 (1H, dd, $J = 3.6$, 16.8 Hz), 3.90 (3H, s), 5.10 (1H, d, $J = 0.8$ Hz), 5.26 ppm (1H, ddd, $J = 1.2$, 3.6, 8.4 Hz); ^{13}C NMR ($CDCl_3$): $\delta = 7.4$, 37.0, 43.8, 59.6, 74.6, 88.9, 171.9, 181.8, 206.1 ppm; IR (KBr): $\tilde{\nu} = 3483$, 3416, 2974, 2958, 2925, 1783, 1759, 1643 cm^{-1}; HRMS-EI: m/z: [M^+] calcd for $C_9H_{12}O_4$: 184.0736; found: 184.0733.

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