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CHIBA-G-CATALYZED INTRAMOLECULAR OXO-MICHAEL ADDITION: SYNTHETIC APPROACHES TO VITAMINE E SKELETON

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Abstract – A chroman skeleton with quaternary carbon chiral center, leadable to vitamin E after manipulation, was constructed through 6-*exo*-*trig* type intramolecular oxo-Michael addition in up to 44% yield with 81% *ee* when a phenol with (*Z*)-α,β-unsaturated ester at *ortho* position was reacted in the presence of a guanidine-type organocatalyst, Chiba-G [(-)-(4*R*,5*R*)-2-[(*S*)-1-hydroxymethyl-2-phenylethyl]imino-1,3-dimethyl-4,5-diphenylimidazolidine (or the enantiomer)].

INTRODUCTION

Development of enantioselective construction of 2,2-disubstituted chroman skeletons is an important issue in the synthesis of biologically active natural products, such as vitamin E (**1**)[1] with lipophilic antioxidant activity and *trans*-*δ*-tocotrienoloic acid (**2**)[2] with antibacterial activity, for the purpose of further therapeutic modification (Figure 1).

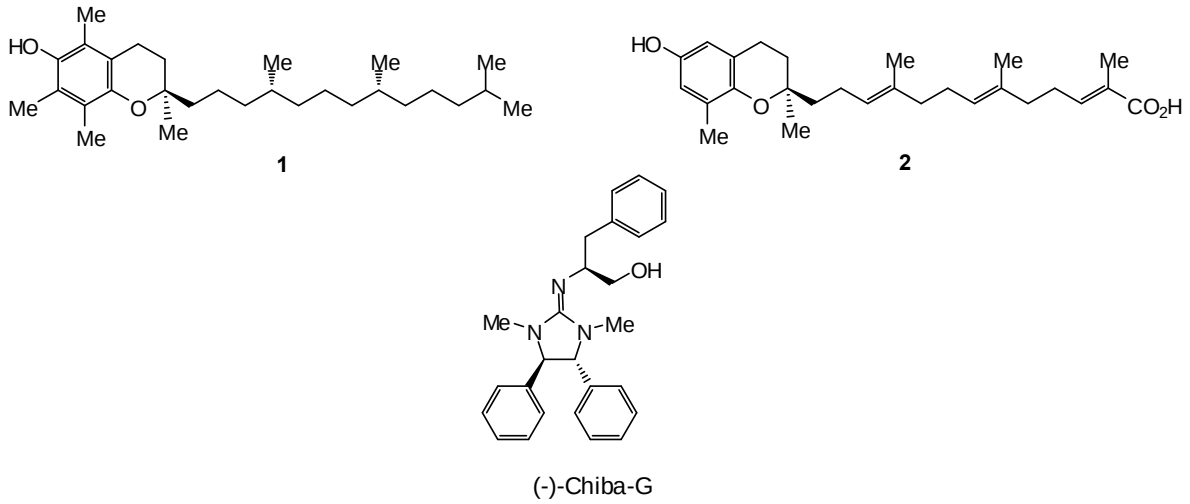
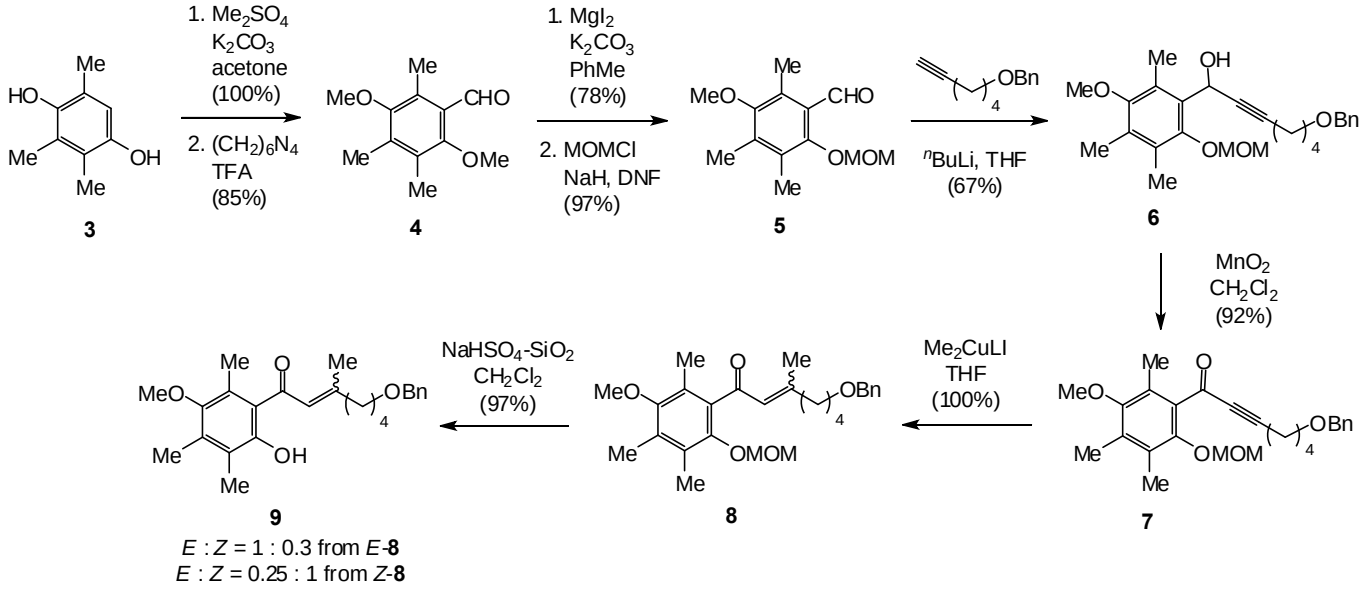


Figure 1. Structures of vitamine E (**1**), *trans*-δ–tocotrienolic acid (**2**) and (-)-Chiba-G

Hayashi,[3] Achiwa,[4] Trost,[5] and Tietze[6] and their co-workers have reported the palladium-catalyzed asymmetric synthesis of 2,2-disubstituted chiral chromans. However, although much attention has been paid for the use of organocatalyst instead of metal catalyst in asymmetric synthesis,[7] there had been no reports on the construction of 2,2-disubstituted chiral chroman skeletons by using organocatalyst. We have uncovered potential functionality of guanidine compounds as chiral auxiliaries[8] and recently reported the model asymmetric construction of 2,2-disubstituted chroman skeleton from phenols with tri-substituted α,β-unsaturated esters by 6-*exo-trig* type intramolecular oxo-Michael addition (IOMA) catalyzed by chiral guanidines.[9] In this paper we present the synthetic application of this methodology using a backbone guanidine catalyst in the model reaction, Chiba-G [(-)-(4*R*,5R)-2-[(*S*)-1-hydroxymethyl-2-phenylethyl]imino-1,3-dimethyl-4,5-diphenylimidazolidine (or its enantiomer)] (Figure 1), to the construction of vitamin E core.

RESULTS AND DISCUSSION

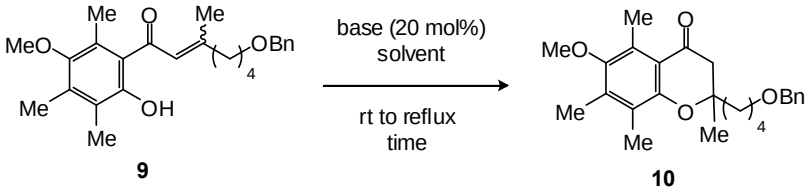
Trials for IOMA of 2-hydroxy-5-methoxy-3,4,6-trimethylphenyl vinyl ketone 9: 6-*endo-trig* type reaction. We have developed 6-*endo-trig* type IOMA catalyzed by quinine for the preparation of 2,3-disubstituted chroman-4-one system and applied the method to the enantioselective synthesis of anti-HIV-1 active coumarins such as (+)-calanolide A.[10] Thus, at first, we examined Chiba-G-catalyzed 6-*endo-trig* type IOMA of 2-hydroxy-5-methoxy-3,4,6-trimethylphenyl vinyl ketone **9**, which was prepared as shown in Scheme 1. Reaction of a MOM-protected benzaldehyde **5**, which was derived from a commercially available 2,3,6-trimethylhydroquinone (**3**) by conventional methods in 4 steps, with 6-benzyloxyhex-1-yne afforded an alkynyl alcohol **6** in 67% yield. Oxidation of **6** with MnO_2 followed by treatment with



Scheme 1. Preparation of substrate **9** for 6-*endo-trig* type IOMA

Me_2CuLi yielded an alkenyl ketone **8**. After the repeated chromatographic separation of the *E*/*Z*-isomers of **8**, removal of the MOM-deprotection was examined under various conditions. The use of $NaHSO_4$-SiO_2 complex[11] successfully provided a targeted vinyl ketone **9** in high yield; however, a partial isomerization was observed during the deprotection [*E* : *Z* = 1 : 0.3 from *E*-**7**; *E* : *Z* = 0.25 : 1 from *Z*-**7**]. The results of separate IOMA on (*E*)- and (*Z*)-enriched 2-hydroxy-5-methoxy-3,4,6-trimethylphenyl vinyl ketone **9** were summarized in Table 1. No reactions occurred in the presence of a tertiary amine such as quinine or quinidine (runs 1 and 2), while Chiba-G worked as a catalyst; but both chemical yield and enantioselectivity of cyclized product **10** were low in the use of $CHCl_3$ as solvent (runs 3 and 4) or without solvent (run 6). Reaction rate was greatly accelerated when reaction was carried out in MeOH; however, no asymmetric induction was observed (run 5). The recovered starting vinyl ketone **9** was found to be an (*E*)-enriched mixture, even from a (*Z*)-enriched **9**, suggesting a possible retro-IOMA. Thus, the 6-*endo*-*trig* type IOMA of a vinyl ketone **9** resulted in unfruitful cyclization.

Table 1. 6-*endo*-*trig* type IOMA of a vinyl ketone **9**



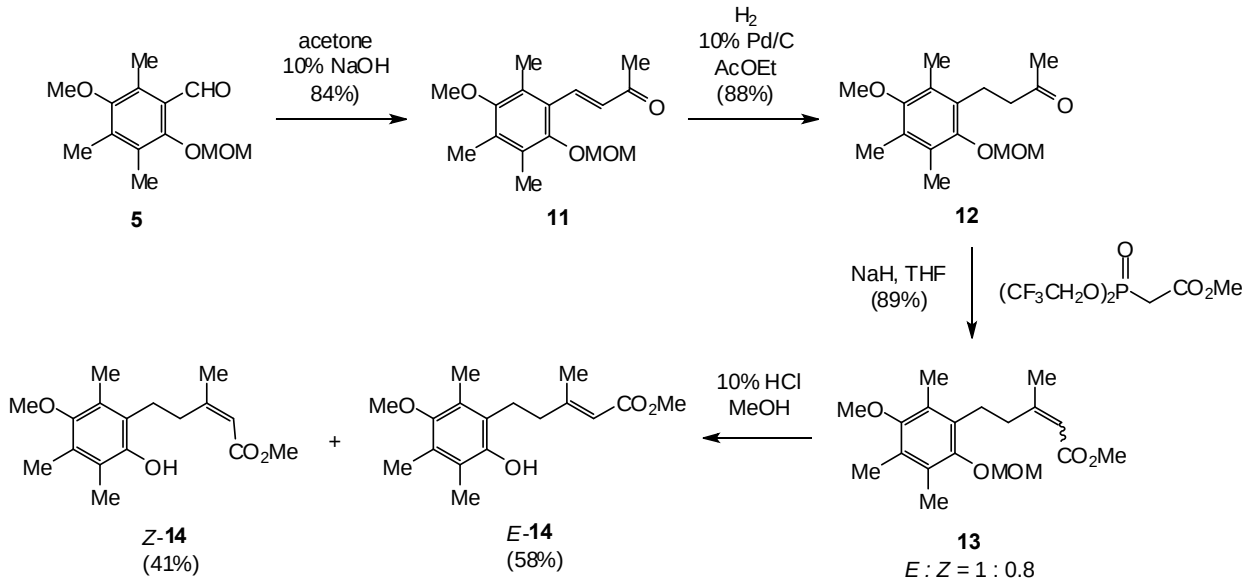
9 **10**

run	**9** (*E* : *Z*)	base / solvent	time (d)	**10**		**9**	
				yield (%)	ee(%)	yield (%)	(*E* : *Z*)
1	0.2 : 1	quinine / $CHCl_3$	4	0	-	76	1 : 0.8
2	0.2 : 1	quinidine / $CHCl_3$	4	0	-	73	1 : 0.7
3	1 : 0.3	(-)-Chiba-G / $CHCl_3$	1	29	4	51	1 : 0.5
4	0.25 : 1	(-)-Chiba-G / $CHCl_3$	1	37	4	33	1 : 0.5
5	0.4 : 1	(-)-Chiba-G / MeOH	1	95	0	0	-
6	0.4 : 1	(-)-Chiba-G / none	6	20	0	91	1 : 0.4

Trials for IOMA of methyl 5-(2-hydroxy-5-methoxy-3,4,6-trimethylphenyl)-3-methylpent-2-enoate (14): 6-*exo*-*trig* type reaction. Next, we turned our attention to 6-*exo*-*trig* type reaction and methyl 5-(2-hydroxy-5-methoxy-3,4,6-trimethylphenyl)-3-methylpent-2-enoate (**14**) was chosen as a substrate for the IOMA. The ester **14** was prepared from the MOM-protected benzaldehyde **5,** according to the procedure adopted in our model examination[9] (Scheme 2). Four-successive reactions of aldol condensation with acetone, catalytic hydrogenation, Hornor-Emmons-Wadsworth reaction with methyl *p*,*p*-bis(2,2,2-trifluoroethyl)phosphonoacetate, and the MOM-deprotection afforded (*E*)- methyl ester *E*-**14** and (*Z*)-methyl ester *Z*-**14**.

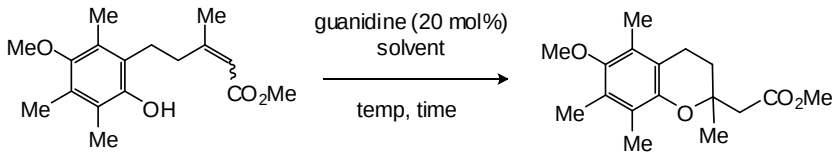
Smooth cyclization of both (*E*)- and (*Z*)-isomers was, as expected, observed in the tetramethylguanidine (TMG)-catalyzed reactions (Table 2, runs 1 and 2). Similarly, Chiba-G worked well as a catalyst in the

reaction of (*E*)-substrate *E*-**14** to give a chroman product **15** in 81% yield, but selectivity was not satisfactory (30% ee) (run 3). On the other hand, acceptable enantioselectivity (81% ee) was obtained, even moderate chemical yield (44%), when (*Z*)-substrate *Z*-**14** was subjected to the IOMA (run 4). This



Scheme 2. Preparation of substrate **14** for 6-*exo-trig* type IOMA

Table 2. Guanidine-catalyzed 6-*exo-trig* type IOMA of an unsaturated ester **14**



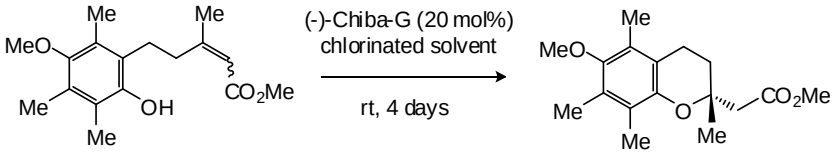
run	**14**	guanidine / solvent	temp. (°C)	time	**15** yield (%)	**15** ee (%)
1	*E*	TMG / $CHCl_3$	rt	7 h	77	-
2	*Z*	TMG / $CHCl_3$	rt	3 d	93	-
3	*E*	(-)-Chiba-G / $CHCl_3$	rt	4 d	81	30 (*S*)
4	*Z*	(-)-Chiba-G / $CHCl_3$	rt	4 d	44[a]	81 (*R*)
5	*Z*	(-)-Chiba-G / $CHCl_3$	50	2 d	62[a]	74 (*R*)
6	*Z*	(-)-Chiba-G / PhMe	rt	4 d	23[a]	58 (*R*)
7	*Z*	(-)-Chiba-G / THF	rt	4 d	27[a]	63 (*R*)
8	*Z*	(-)-Chiba-G / acetone	50	2 d	14[a]	62 (*R*)
9	*Z*	(-)-Chiba-G / DMF	rt	4 d	38[a]	3 (*R*)

[a] Estimated by ^{1}H NMR

reaction was tolerant to temperature and, interestingly, the increment of chemical yield (62%) with slight loss of enantioselectivity (81% → 74% ee) was observed (run 5). Unfortunately, both chemical yield and enantioselectivity in the IOMA of *Z*-**14** were not improved in the screening of solvents (runs 6-9); however, no occurrence of a retro-path in these reactions was suggested by the recovery of the staring *Z*-**14**.

Thus, it was found that chloroform was the best solvent among solvents examined for the 6-*exo*-*trig* type IOMA of *Z*-**14** (run 4 in Table 2). We had observed the rate acceleration of 6-*endo*-*trig* type IOMA in calanolide A synthesis when chlorobenzene was used as a solvent,[10] Next, (-)-Chiba-G-catalyzed IOMA of *Z*-**14** in a chlorinated solvent was examined (Table 3). In general, high enantioselectivity, especially 87% ee in the use of dichloromethane (run 4), was obtained, but chemical yields were not improved in spite of their permittivity.

Table 3. (-)-Chiba-G-catalyzed IOMA of *Z*-**14** in a chlorinated solvent

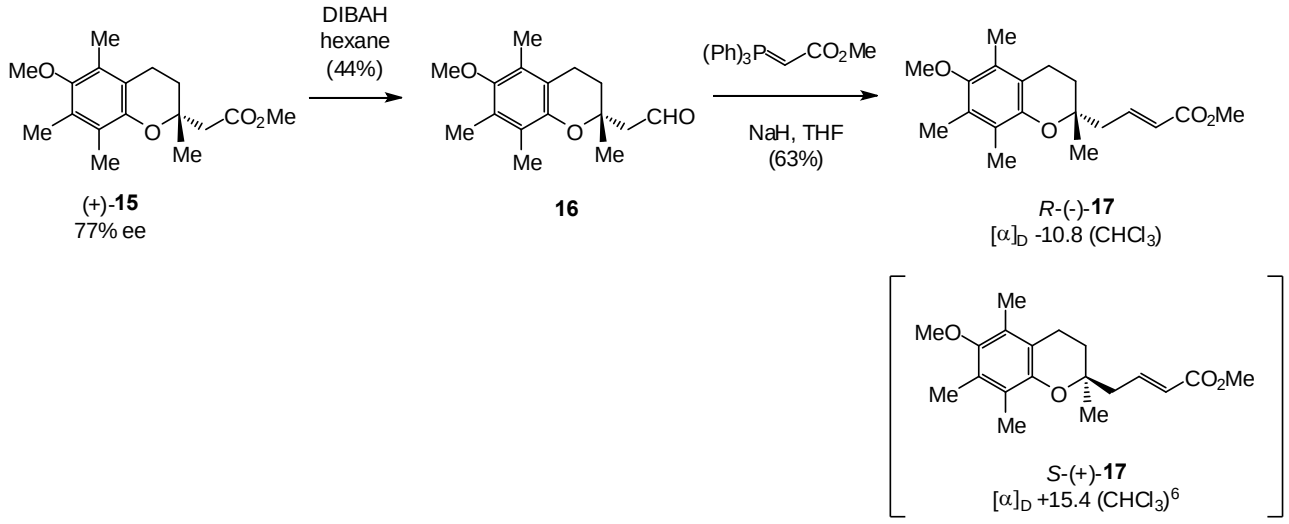


14 **15**

run	solvent	relative permittivity (ε)	**15** yield (%)	**15** ee(%)
1	CCl_4	2.30	7	79
2	PhCl	5.74	11	82
3[a]	$CHCl_3$	4.89	44	81
4	CH_2Cl_2	9.02	39	87
5	$(CH_2Cl_2)_2$	10.74	25	84

[a] The data of run 4 in Table 2.

Absolute configuration of the cyclization product **15** was determined by comparison with a known (*S*)-(+)-vinylogous chroman *S*-(+)-**17** {$[\alpha]_D$ +15.4 ($CHCl_3$)}.[6] DIBAH-reduction of (+)-**15** {$[\alpha]_D$ +2.8 ($CHCl_3$)}with 77% *ee*, derived from the (-)-Chiba-G-catalyzed IOMA of *Z*-**14**, followed by Wittig reaction afforded (-)-vinylogous chroman *R*-(-)-**17** {$[\alpha]_D$ -10.8 ($CHCl_3$)}, the ee of which was estimated to be 68% (Scheme 3). These facts indicated that asymmetric induction leading *R*-configuration was controlled in the (-)-Chiba-G-catalyzed IOMA of *Z*-**14**, with accordance to the results of our model IOMA.[9]



Scheme 3. Determination of the absolute configuration of (+)-chroman (+)-**15**

CONCLUSION

We examined 6-*endo-trig* and 6-*exo-trig* type IOMAs for the asymmetric construction of vitamin E core carrying a 2,2-disubstituted chroman skeleton and found that the latter 6-*exo-trig* type cyclization could be effectively catalyzed by Chiba-G when (*Z*)-unsaturated ester was used as a substrate.

EXPERIMENTAL

General. Melting points were determined on a micro melting point hot-stage instrument Yanagimoto MP-SI and are uncorrected. IR spectra were recorded with ATR on a JASCO FT/IR-300E spectrometer. Specific rotation, $[\alpha]_D$, was recorded on a JASCO DIP-140 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded with JEOL JNM ECP 400 spectrometer in $CDCl_3$. HREIMS was performed on JASCO MS-GCMATE spectrometer. For column chromatography silica gel 60 or 60N (spherical, 70-230 mesh, Kanto) and for flash chromatography silica gel (230-400 mesh, Merck) were used.

Compound 6. To a solution of 6-benzyloxy-1-hexyne (3.76 g, 20.0 mmol) in THF (40 mL) was added a 1.57 M solution of ^{n}BuLi in hexane (13.5 mL, 21.2 mmol) at 0 °C over 5 min under Ar, and the mixture was stirred at the same temperature for 1 h and then cooled to -42 °C. To the cooled mixture was added a solution of **5** (4.07 g, 17.1 mmol) in THF (30 mL) over 10 min, and the whole was stirred at -42 °C for 1 h, quenched with sat. $NaHCO_3$ (50 mL), and extracted with AcOEt (50 mL x 3). The combined organic solutions were washed with brine (50 mL), dried ($MgSO_4$), and evaporated. Column chromatography of the residue (hexane : AcOEt = 6 : 1) afforded **6** (4.86 g, 67%) as a colorless oil; IR ν_{max}: 3422, 2361 cm^{-1}; ^{1}H NMR δ: 1.58-1.64, 1.67-1.72 (each 2H, m, CH_2), 2.16, 2.19, 2.44 (each 3H, s, Me), 2.25 (2H, dt, J = 7.0, 2.1 Hz, CH_2), 3.47 (2H, t, J = 6.3 Hz, CH_2), 3.57 (1H, d, J = 7.4 Hz, OH, exchangeable), 3.635, 3.943 (each 3H, s OMe), 4.48 (2H, s, OCH_2O), 4.94, 5.01 (each 1H, d, J = 5.7 Hz, OCH_2Ph), 5.85 (1H, dt, J =

7.4, 2.1 Hz, CH), 7.28-7.36 (5H, m, ArH); ^{13}C NMR δ: 12.1, 12.6, 13.1, 18.4, 25.0, 28.5, 57.3, 58.5, 59.6, 69.4, 72.4, 80.5, 85.1, 99.8, 127.1, 127.2, 127.6, 128.0, 130.5, 131.2, 138.2, 149.2, 153.5; HREIMS: *m*/*z* 426.2409 (calcd for $C_{26}H_{34}O_5$: 426.2406).

Compound 7. A mixture of **6** (0.392 g, 0.92 mmol) and MnO_2 (0.804 g, 9.25 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 10 h and filtered through celtie pad. Evaporation of the filtrate gave **7** (0.358 g, 92%) as a yellow oil; IR ν_{max}: 2205, 1651 cm^{-1}; ^{1}H NMR δ: 1.69-1.72 (4H, m, CH_2 x 2), 2.18, 2.21, 2.25 (each 3H, s, Me), 2.43 (2H, dif. t, *J* = 6.6 Hz, CH_2), 3.48 (2H, dif. t, *J* = 5.8 Hz, CH_2), 3.54, 3.65 (each 3H, s OMe), 4.48 (2H, s, OCH_2O), 4.89 (2H, s, OCH_2Ph), 7.28-7.36 (5H, m, ArH); ^{13}C NMR δ: 12.1, 12.6, 18.5, 24.1, 28.4, 57.1, 59.5, 69.0, 72.3, 82.5, 95.7, 100.1, 125.4, 127.0, 127.8, 129.0, 132.8, 133.5, 138.0, 148.2, 152.9, 181.0; HREIMS: *m*/*z* 424.2262 (calcd for $C_{26}H_{32}O_5$: 424.2250).

Compound 8. A 0.83 M solution of MeLi in Et_2O (24 mL, 19.9 mmol) was added to a mixture of CuI (1.87 g, 9.82 mmol) in THF (40 nL) at -40 °C over 10 min, and the whole was stirred at the same temperature for 15 min. After addition of a solution of **7** (1.81 g, 4.26 mmol) in THF (20 mL) over 20 min at -40 °C the mixture was stirred at the same temperature for 20 min, poured into ice-water (150 mL), and extracted with AcOEt (100 mL x 3). The combined organic solutions were washed with brine (50 mL), dried ($MgSO_4$), and evaporated. Column chromatography of the residue (hexane : AcOEt = 15 : 1) afforded a 1 : 0.6 mixture of *E*- and *Z*-**8** (1.87 g, 100%) as a pale yellow oil, which could be separated to be each isomer by repeated chromatographies; IR ν_{max}: 1669 cm^{-1}; ^{1}H NMR δ: For (*E*)-isomer: 1.60-1.61 (4H, m, CH_2 x 2), 2.13, 2.15, 2.19, 2.21 (each 3H, s, Me), 2.18-2.19 (2H, m, CH_2), 3.46-3.48 (2H, m, CH_2), 3.46, 3.65 (each 3H, s OMe), 4.49 (2H, s, OCH_2O), 4.83 (2H, s, OCH_2Ph), 6.26 (1H, s, CH), 7.31-7.35 (5H, m, ArH); For (*Z*)-isomer: 1.58-1.70 (4H, m, CH_2 x 2), 1.91, 2.13, 2.18, 2.20 (each 3H, s, Me), 2.64 (2H, dif. t, *J* = 8.1 Hz, CH_2), 3.46, 3.64 (each 3H, s OMe), 3.51 (2H, dif. t, *J* = 8.1 Hz, CH_2), 4.52 (2H, s, OCH_2O), 4.83 (2H, s, OCH_2Ph), 6.26 (1H, s, CH), 7.28-7.35 (5H, m, ArH); ^{13}C NMR δ: For (*E*)-isomer: 12.44, 12.89, 12.98, 19.3, 24.2, 29.2, 41.0, 57.4, 59.98, 69.8, 72.78, 100.3, 125.14, 126.0, 127.42, 127.496, 128.24, 129.05, 136.10, 138.4, 147.51, 153.323, 159.0, 196.4; For (*Z*)-isomer: 12.43, 12.88, 12.97, 24.8, 25.5, 29.7, 33.5, 57.5, 59.96, 70.0, 72.75, 100.4, 125.12, 126.37, 127.35, 127.504, 128.22, 129.03, 136.13, 138.6, 147.49, 153.316, 159.9, 195.8; HREIMS: *m*/*z* 440.2572 (calcd for $C_{27}H_{36}O_5$: 440.2563).

Compound 9 from *E*-8. A mixture of *E*-**8** (25.3 mg, 57.4 mmol) and $NaHSO_4$·SiO_2 (12. 0 mg) in CH_2Cl_2 (0.5 mL) was stirred at rt for 1 h and filtered through celite pad. After evaporation of the filtrate column chromatography of the residue (hexane : AcOEt = 15 : 1) gave a 1 : 0.3 mixture of *E*- and *Z*-**9** (21.8 mg, 96%) as a yellow oil; IR ν_{max}: 3734, 1633 cm^{-1}; ^{1}H NMR δ: For (*E*)-isomer: 1.61-1.71 (4H, m,

CH_2 x 2), 2.16-2.18 (6H, br, Me x 2), 2.19-2.27 (2H, m, CH_2), 2.24, 2.39 (each 3H, s, Me), 3.48-3.53 (2H, m, CH_2), 3.65 (3H, s OMe), 4.51 (2H, s, OCH_2Ph), 6.34-6.35 (1H, m, CH), 7.25-7.34 (5H, m, ArH), 11.26 (1H, s, OH, exchangeable); For (*Z*)-isomer: 1.61-1.71 (4H, m, CH_2 x 2), 1.96 (3H, d, *J* = 1.3 Hz, Me), 2.16, 2.24, 2.39 (each 3H, s, Me), 2.61 (2H, dif. t, *J* = 7.6 Hz, CH_2), 3.48-3.53 (2H, m, CH_2), 3.65 (3H, s OMe), 4.51 (2H, s, OCH_2Ph), 6.32-6.33 (1H, m, CH), 7.25-7.34 (5H, m, ArH), 11.30 (1H, s, OH, exchangeable); ^{13}C NMR δ: For (*E*)-isomer: 11.7, 13.3, 15.8, 19.7, 24.1, 29.4, 40.9, 60.1, 69.8, 72.9, 121.5, 123.7, 126.7, 127.49, 127.53, 127.58, 128.30, 136.8, 138.4, 149.6, 154.9, 157.9, 198.0; For (*Z*)-isomer: 11.7, 13.3, 15.7, 24.8, 25.3, 29.7, 33.7, 60.1, 70.0, 72.8, 121.4, 123.7, 126.7, 127.4, 127.55, 127.58, 128.27, 136.8, 138.6, 149.6, 155.0, 158.0, 197.7; HREIMS: *m*/*z* 396.2297 (calcd for $C_{25}H_{32}O_4$: 396.2300).

IOMA of 9 (Table 1, run 3): 2-(4-Benzyloxybutyl)-6-methoxy-2,5,7,8-tetramethylbenzo[*b*]pyran-4(3*H*)-one (10). A solution of an (*E*)-majored **9** (22.8 mg, 57.5 μmol) and (-)-Chiba-G (4.6 mg, 11.5 μmol) in $CHCl_3$ (0.5 mL) was stirred at rt and then under reflux (total 1 day). After evaporation of the solvent, flash chromatography of the residue (hexane : AcOEt = 15 : 1) afforded **10** (6.7 mg, 29%) as a yellow oil together with the recovery of the staring **9** (*E* : *Z* = 1 : 0.5) (11.6 mg, 51%); IR ν_{max}: 1678 cm^{-1}; ^{1}H NMR δ: 1.35 (3H, s, Me), 1.46-1.68 (5H, m, CH_2 x 2, CH_2 x 1/2), 1.78 (1H, ddd, *J* = 13.6, 11.6, 5.3 Hz, CH_2 x 1/2), 2.12, 2.24, 2.54 (each 3H, s, Me), 2.58, 2.72 (each 1H, d, *J* = 15.7 Hz, CH_2), 3.47 (2H, t, *J* = 6.2 Hz, CH_2), 3.62 (3H, s, OMe), 4.49 (2H, s, OCH_2Ph), 7.27-7.36 (5H, m, ArH); ^{13}C NMR δ: 12.0, 13.6, 13.9, 20.3, 23.7, 29.9, 39.2, 49.2, 60.3, 70.0, 72.9, 79.6, 117.1, 124.1, 127.5, 127.6, 128.3, 129.5, 138.2, 138.5, 150.4, 154.8, 194.7; HREIMS *m*/*z*: 396.2308 (calcd for $C_{25}H_{32}O_4$: 396.2300); HPLC (CHIRALCEL OD-H, λ = 254 nm, eluent: hexane : ^{i}PrOH = 100 : 1, flow rate: 1.1 mL/min): t_R for a major **10**: 24.7 min (52%), t_R for a minor **10**: 29.6 min (48%).

Compound 11. A mixture of **5** (0.657 g, 2.76 mmol) and acetone (0.67 mL, 9.12 mmol) in 10% NaOH (2.6 mL, 6.5 mmol) and H_2O (4 mL) was stirred at 45 °C for 1 day under Ar, quenched with H_2O (10 mL), and extracted with $CHCl_3$ (20 mL and then 10 mL x 2). The combined organic solutions were washed with brine (10 mL), dried ($MgSO_4$), and evaporated. Column chromatography of the residue (hexane : AcOEt = 10 : 1) afforded **11** (0.645 g, 84%) as colorless solid; IR ν_{max}: 1682 cm^{-1}; ^{1}H NMR δ: 2.21, 2.23, 2.31, 2.38 (each 3H, s, Me), 3.56, 3.65 (each 3H, s OMe), 4.84 (2H, s, OCH_2O), 6.67 (1H, d, *J* = 16.7 Hz, CH), 7.75 (1H, d, *J* = 16.7 Hz, C4-H); ^{13}C NMR δ: 13.25, 13.32, 13.6, 27.6, 57.9, 60.2, 99.9, 126.4, 128.4, 129.1, 132.1, 132.7, 139.5, 150.9, 153.6, 198.8; Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.00; H, 8.07.

Compound 12. A mixture of **11** (0.642 g, 2.31 mmol) and 5% Pd/C (0.057 g) in AcOEt (20 mL) was stirred at rt for 2 h under H_2 atmosphere and filtered through celite pad. After evaporation of the filtrate column chromatography of the residue (hexane : AcOEt = 7 : 1) afforded **12** (0.567 g, 88%) as a colorless oil; IR ν_{max}: 1711 cm^{-1}; ^{1}H NMR δ: 2.16 (6H, s Me x 2), 2.18, 2.21 (each 3H, s, Me), 2.64, 2.91 (each 2H, dif. t, *J* = 8.1 Hz, CH_2), 3.58, 3.63 (each 3H, s OMe), 4.89 (2H, s, OCH_2O); ^{13}C NMR δ: 12.2, 12.8, 13.6, 21.8, 29.8, 43.6, 57.4, 60.1, 99.9, 127.1, 128.2, 128.6, 131.1, 150.7, 153.4, 208.6; HREIMS *m*/*z*: 280.1671 (calcd for $C_{16}H_{24}O_4$: 280.1674).

Compound 13. A 60% mineral oil of NaH (0.308 g, 7.71 mmol) was washed with dry hexane (5 mL) and suspended in THF (6 mL). To the suspension was added methyl *p*,*p*-bis(2,2,2-trifluoroethyl)-phosphonoacetate (1.3 mL, 6.13 mmol) under ice-cooling over 10 min, and the mixture was stirred at rt for 1 h. To the mixture was added a solution of **12** (0.839 g, 2.99 mmol) in THF (7 mL) over 5 min, and the whole was stirred at rt for 4.5 h, quenched with H_2O (50 mL), and extracted with AcOEt (10 mL x 3). The combined organic solutions were washed with brine (20 mL), dried ($MgSO_4$), and evaporated. Column chromatography of the residue (hexane : AcOEt = 12 : 1) afforded a 1 : 0.8 mixture of *E*– and *Z*-**13** (0.890 g, 89%) as colorless solid; IR ν_{max}: 1716 cm^{-1}; ^{1}H NMR δ: For (*E*)-isomer: 2.16, 2.18, 2.23 (each 3H, s, Me), 2.26 (3H, d, *J* = 1.3 Hz, Me), 2.27-2.32, 2.79-2.83 (each 2H, m, CH_2), 3.60, 3.64, 3.71 (each 3H, s OMe), 4.90 (2H, s, OCH_2O), 5.77 (1H, m, CH); For (*Z*)-isomer: 1.97 (3H, d, *J* = 1.3 Hz, Me), 2.18 (6H, s, Me x 2), 2.32 (3H, s, Me), 2.79-2.83 (4H, m, CH_2 x 2), 3.62, 3.65, 3.68 (each 3H, s OMe), 4.92 (2H, s, OCH_2O), 5.69 (1H, m, CH); ^{13}C NMR δ: For (*E*)-isomer: 12.1, 12.8, 13.6, 18.9, 25.3, 40.8, 50.8, 57.4, 60.0, 99.8, 114.8, 126.9, 128.1, 128.6, 131.2, 150.6, 153.3, 160.3, 167.2; For (*Z*)-isomer: 12.0, 12.8, 13.6, 26.0, 26.2, 33.4, 50.7, 57.5, 60.0, 99.8, 115.9, 127.6, 128.0, 128.3, 131.7, 150.4, 153.2, 159.9, 166.5; HREIMS: *m*/*z* 336.1921 (calcd for $C_{19}H_{28}O_5$: 336.1937).

Compound 14. A mixture of **13** (0.825 g, 2.45 mmol) in MeOH (35 mL) containing 10% HCl (7.8 mL, 21.4 mmol) was heated at 70 °C for 1 h, quenched with H_2O (60 mL), and extracted with AcOEt (30 mL x 3). The combined organic solutions were washed with brine (20 mL), dried ($MgSO_4$), and evaporated. Column chromatography of the residue (hexane : AcOEt = 15 : 1 to 7 : 1) afforded *E*-**14** (0.412 g, 58%) and *Z*-**14** (0.291 g, 41%). (i) *E*-**14**: colorless solids, mp 88 °C; IR ν_{max}: 3375, 1712 cm^{-1}; ^{1}H NMR δ: 2.14, 2.20, 2.22 (each 3H, s, Me), 2.25 (3H, d, *J* = 1.3 Hz, Me), 2.27-2.31, 2.76-2.80 (each 2H, m, CH_2), 3.62, 3.70 (each 3H, s OMe), 4.55 (1H, s, OH, exchangeable), 5.75 (1H, q, *J* = 1.3 Hz, CH); ^{13}C NMR δ: 11.8, 12.1, 12.7, 18.9, 25.5, 40.2, 50.8, 60.2, 115.0, 120.1, 124.5, 126.9, 127.7, 147.9, 150.4, 160.4, 167.3; *Anal*. Calcd for $C_{15}H_{22}O_3$: C, 69.84; H, 8.27. Found: C, 70.00; H, 8.51. (ii) *Z*-**14**: pale yellow solids, mp 97 °C; IR ν_{max}: 3462, 1687 cm^{-1}; ^{1}H NMR δ: 2.04 (3H, d, *J* = 1.3 Hz, Me), 2.21, 2.22, 2.26 (each 3H, s, Me), 2.56-2.60 (2H, m, CH_2), 2.71-2.76 (2H, m, CH_2), 3.63, 3.77 (each 3H, s OMe), 5.78 (1H, q, *J* = 1.3

Hz, CH), 7.38 (1H, s, OH, exchangeable); ^{13}C NMR δ: 11.8, 12.3, 12.6, 26.0, 26.5, 34.0, 51.6, 60.3, 115.3, 122.2, 125.4, 128.4, 149.3, 149.8, 161.7, 167.8; *Anal*. Calcd for $C_{15}H_{22}O_3$: C, 69.84; H, 8.27. Found: C, 69.77; H, 8.45.

IOMA of *E*-14 (Table 2, run 1): 6-Methoxy-2-(methoxycarbonylmethyl)-2,5,7,8-tetramethylbenzo[*b*]pyran (15). To a solution of *E*-**14** (50.4 mg, 0.172 mmol) in $CHCl_3$ (0.1 mL) was added a solution of TMG in $CHCl_3$ (25 μL/mL, 0.17 mL, 33.9 mmol), and the whole was stirred at rt for 7 h. After evaporation of the solvent, column chromatography of the residue (hexane : AcOEt = 7 : 1) afforded **15** (38.8 mg, 77%) as a colorless oil; IR ν_{max}: 1736 cm^{-1}; ^{1}H NMR δ: 1.42 (3H, s, Me), 1.86-1.93, 1.99-2.04 (each 1H, m, CH_2), 2.06, 2.14, 2.18 (each 3H, s, Me), 2.58-2.65 (4H, m, CH_2 x 2), 3.36, 3.69 (each 3H, s, OMe); ^{13}C NMR δ: 11.6, 12.5, 20.4, 24.7, 31.1, 43.7, 51.5, 60.3, 73.4, 117.1, 123.1, 125.8, 128.0, 146.9, 149.7, 171.1; HREIMS *m*/*z*: 292.1673 (calcd for $C_{17}H_{24}O_4$: 292.1674).

IOMA of *Z*-14 (Table 2, run 4). A solution of *Z*-**14** (50.8 mg, 0.174 mmol) and (-)-Chiba-G (14.6 mg, 0.037 mmol) in $CHCl_3$ (0.2 mL) was stirred at rt for 4 days. After evaporation of the solvent, column chromatography of the residue (hexane : AcOEt = 7 : 1) afforded an inseparable 1 : 0.8 mixture of *Z*-**14** and **15** (49.8 mg, 98%) as an yellow oil; HPLC (CHIRALCEL OD-H, λ = 285 nm, eluent: hexane : ^{i}PrOH = 100 : 1, flow rate: 1.1 mL/min): t_R for a major **15**: 6.79 min (91%), t_R for a minor **15**: 8.48 min (9%); $[\alpha]_D^{21}$ +2.8 (c 1.0, $CHCl_3$).

2-(Formylmethyl)-6-methoxy-2,5,7,8-tetramethylbenzo[*b*]pyran (16). A 1.04 M solution of DIBAH in hexane (1.0 mL, 1.04 mmol) was added to a solution of the inseparable mixture of *Z*-**14** and **15** [0.282 g; calculated to be 0.108 g as **15** (77% ee)] in hexane (16 mL) at -7 °C over 5 min under Ar, and the whole was stirred at the same temperature for 1 h. After successive addition of MeOH (1 mL) and H_2O (20 mL) the mixture was extracted with Et_2O (20 mL x 3). The combined organic solutions were washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue (hexane : AcOEt = 20 : 1) afforded **16** (0.044 g, 44% from a calculated **15**) as a colorless oil together with *Z*-**14** (0.049 g, 28%); IR ν_{max}: 1721 cm^{-1}; ^{1}H NMR δ: 1.40 (3H, s, Me), 1.84, 1.94 (each 1H, ddd, *J* = 13.6, 6.8, 6.8 Hz, CH_2), 2.08, 2.15, 2.19 (each 3H, s, Me), 2.55 (1H, dd, *J* = 15.0, 3.5 Hz, CH_2 x 1/2), 2.61-2.66 (2H, m, CH_2), 2.72 (1H, dd, *J* = 15.0, 2.4 Hz, CH_2 x 1/2), 3.64 (3H, s, OMe), 9.93 (1H, dd, *J* = 3.5, 2.4 Hz, CHO); ^{13}C NMR δ: 11.7, 11.8, 12.5, 20.3, 24.8, 31.9, 52.3, 60.4, 73.5, 117.0, 123.1, 126.0, 128.3, 146.7, 150.0, 202.0; HREIMS *m*/*z*: 262.1568 (calcd for $C_{16}H_{22}O_3$: 262.1569).

(*E*)-Methyl (6-Methoxy-2,5,7,8-tetramethylchroman-2-yl)but-2-enoate (17). A mixture of **16** (0.041 g, 0.158 mmol) and methyl triphenylphosphonoacetate (0.071 g, 0.214 mmol) in THF (1.75 mL) was

stirred at 45 °C for 2 h. After evaporation of the solvent flash chromatography of the residue (hexane : AcOEt = 20 : 1) afforded **17** (0.032 g, 63%) as a colorless oil; IR ν_{max}: 1723 cm^{-1}; ^1H NMR δ: 1.27 (3H, s, Me), 1.78, 1.85 (each 1H, ddd, *J* = 19.1, 6.8, 6.8 Hz, CH_2), 2.09, 2.14, 2.19 (each 3H, s, Me), 2.46 (1H, ddd, *J* = 14.1, 8.1, 1.2 Hz, CH_2 x 1/2), 2.53 (1H, ddd, *J* = 14.1, 7.4, 1.2 Hz, CH_2 x 1/2), 3.63, 3.74 (each 3H, s, OMe), 5.88 (1H, dt, *J* = 15.7, 1.2 Hz, CH), 7.05 (1H, dif. t, *J* = 15.7, 7.7 Hz, CH); HREIMS *m*/*z*: 318.1817 (calcd for $C_{19}H_{26}O_4$: 318.1831); HPLC (CHIRALCEL OD-H, λ = 254 nm, eluent: hexane : ^{i}PrOH = 150 : 1, flow rate: 1.1 mL/min): t_R for a major **17**: 12.5 min (84%), t_R for a minor **17**: 13.6 min (16%); $[\alpha]_D^{18}$ -10.8 (*c* 1.0, $CHCl_3$).

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