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A Highly Stereoselective Synthesis of (*E*)-α-Bromoacrylates

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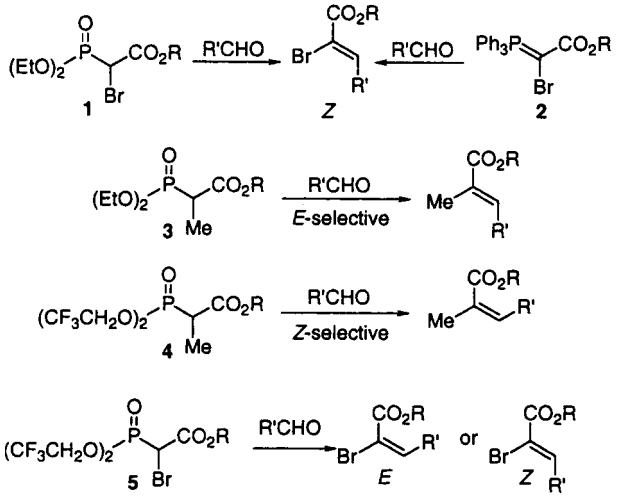
Abstract—Novel reagent, methyl bis(2,2,2-trifluoroethoxy)bromophosphonoacetate (**5a**), was designed and prepared in order to efficiently synthesize (*E*)-α-bromoacrylates **7**, from which widely useful precursors for various C–C bond formations were prepared. Horner–Wadsworth–Emmons (HWE) reaction of various aldehydes with **5a** in the presence of *t*-BuOK and 18-C-6 gave corresponding (*E*)-α-bromoacrylate derivatives with high stereoselectivity and excellent yield. Using the product (*E*)-α-bromoacrylate **7s** as a key intermediate, we succeeded in developing the most effective route of plaunotol synthesis via Suzuki cross-coupling.

Introduction

Many natural products possess various trisubstituted alkene moieties, and highly stereoselective construction of trisubstituted alkenes is one of the most challenging problems in synthetic organic chemistry.[1] Although many skillful and selective synthetic methods for the preparation of this important functional group have been devised for decades,[2] there is still the need for a general and stereoselective method for the efficient synthesis of trisubstituted alkenes.[1] We anticipated that trisubstituted bromoalkenes, for example, α-bromoacrylate derivatives, would provide a useful method to synthesize various trisubstituted olefins because vinyl bromides are widely used as precursors for C–C bond formation. Reactions such as Suzuki coupling[3] or Stille coupling,[4] are known to proceed with conservation of olefin geometry.

Wittig and Horner–Wadsworth–Emmons (HWE) reactions, which provide a direct introduction of C–C double bond from carbonyl compounds, are powerful and attractive methods for the construction of various alkenes.[5] However, there are some limitations to the stereoselective construction of tri-and tetrasubstituted alkenes. It is known that the HWE reaction with diethoxybromophosphonoacetate **1** and Wittig reaction with the stabilized ylide **2** give (*Z*)-α-bromoacrylates predominantly (Scheme 1),[6,7] and that there are other general synthetic methods for (*Z*)-α-bromoacrylates.[8] On the other hand, only a few procedures for the synthesis of (*E*)-α-bromoacrylates have been reported in the literature[9] and these procedures are generally not efficient because of their multiple steps or limitation of substrate. Thus, a general method for the synthesis of (*E*)-α-bromoacrylates would be a beneficial synthetic achievement. (*E*)-α-Fluoroacrylates are synthesized stereoselectively by the HWE reaction of diethoxyfluorophosphonoacetate with lithium base,[10] but it is apparent that fluoroalkenes cannot be used as precursors for C–C bond formation. Therefore, we investigated HWE reagents and reaction conditions to develop a stereoselective synthetic method for (*E*)-α-bromoacrylates from which precursors for C–C bond formation could be readily synthesized.

While the HWE reaction using diethoxyphosphonoacetate **3** shows a preference for the formation of the more stable, disubstituted *E*-olefins,[5a,11] Still's electrophilic bis(2,2,2-trifluoroethoxy)phosphonoacetate **4** reacts with aldehydes in the presence of KHMDS and 18-crown-6 ether (18-C-6) to afford *Z*-α,β-unsaturated esters selectively.[2a,12,13]



Scheme 1.

Keywords: olefination; synthetic methods; stereocontrol; phosphonic acid and derivatives.

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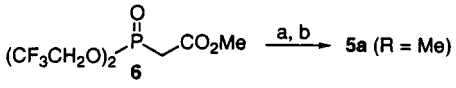


Scheme 2. (a) aq. NaOBr, 85%; (b) $SnCl_2{\cdot}2H_2O$ (0.96 equiv.), EtOH, H_2O, 70%.

Still's reagent **4** is complementary to **3** for the stereoselectivity of the HWE reaction. In view of the above fact, we designed a novel reagent, bis(2,2,2-trifluoroethyl)bromophosphonoacetate **5** anticipating that (*E*)-α-bromoacrylates would be synthesized by the HWE reaction (Scheme 1).[14] Here, we describe the preparation of a novel reagent **5** and the *E*-selective HWE reaction of **5**. Also we report the most effective route to synthesize plaunotol, an antibacterial agent against *Helicobacter pylori*, using (*E*)-α-bromoacrylate as a key intermediate.

Results and Discussion

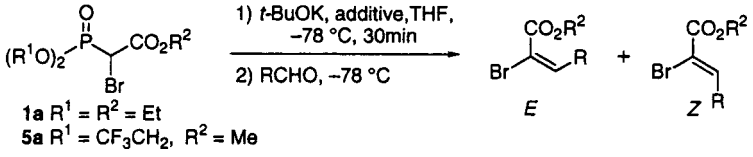
Synthesis of novel HWE reagent 5a

The novel reagent **5a** was readily prepared from methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (**6**)[2a] using a similar procedure to that reported by McKenna et al (Scheme 2).[15] Treatment of **6** with freshly prepared sodium hypobromide afforded the corresponding dibromide, which was subsequently reduced by one equivalent of $SnCl_2$. The reagent $SnCl_2{\cdot}2H_2O$ which was purchased from Aldrich Chemical Co. gave the best result for reduction. A small amount of unreacted dibromide and over-reduced product **6** were removed by flash chromatography (dichloromethane/acetone=50:1) using silica gel which was pretreated with dichloromethane and 4 N HCl in ethyl acetate because normal silica gel column chromatography caused decomposition of **5a**. Finally, the residue was distilled under reduced pressure (bp 85–87°C, 0.4 mmHg) to give pure **5a** (60% yield from **6**), and purified **5a** was stable enough to be stored in a freezer (−20°C) for over 3 years without decomposition.

The HWE reaction with 5a

The results of the HWE reaction between **1a** or **5a** and aldehydes using potassium *tert*-butoxide (*t*-BuOK) are summarized in Table 1. Excess amounts of *t*-BuOK reduced the yield and stereoselectivity.[16] Thus phosphonoacetates were used slightly in excess of *t*-BuOK. *E*/*Z* ratios of the product were determined by ^{1}H NMR analysis of the crude products and the geometry of α-bromoacrylate was determined by NOE analysis of the allylic alcohols which were derived from the corresponding esters by DIBAL-H reduction. As we anticipated, HWE reactions with **5a** and various aldehydes proceeded with high *E*-selectivity (entries 1, 9, 11, and 15). Stereoselectivity was extremely diminished when using DMF as solvent (entry 3). The HWE reaction with **1a** and benzaldehyde or cinnamylaldehyde gave (*Z*)-α-bromoacrylate predominantly (entries 7, 8, and 10). In contrast, the same reaction with aliphatic aldehydes gave (*E*)-α-bromoacrylate (entries 13 and 16). A similar tendency of stereoselectivity has been reported by Still.[2a]

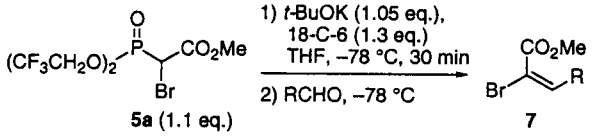
Table 1. Results of the HWE reaction with **1a** or **5a** and a range of aldehydes



1a $R^1 = R^2 = Et$
5a $R^1 = CF_3CH_2$, $R^2 = Me$

Entry [a]	R	Reagent	Additive	Time (h)	Yield (%)[b]	*E*:*Z*[c]
1	Ph	**5a**	18-C-6	0.3	94	30:1
2		**5a**	none	2	65	10:1
3[d]		**5a**	18-C-6	1.5	95	2:1
4[e]		**5a**	18-C-6	0.5	95	31:1
5[e]		**5a**	none	8	74	29:1
6[f]		**5a**	none	2.5	89	51:1
7		**1a**[g]	18-C-6	overnight	93	1:14
8		**1a**	none	overnight	94	1:6
9	cinnamyl	**5a**	18-C-6	17	quant.	*E* only[h]
10[i]		**1a**	18-C-6	5	87	1:2
11[j]	*n*-Bu	**5a**	18-C-6	2	86	60:1
12[j]		**5a**	none	1.5	36	2:1
13[i,j]		**1a**	18-C-6	5	80	3:1
14[i,j]		**1a**	none	5	72	1:3
15[j]	cyclohexyl	**5a**	18-C-6	6.5	64	76:1
16[i,j]		**1a**	18-C-6	5	47	3:1

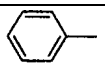
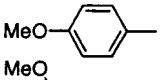
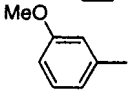
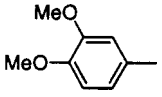
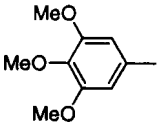
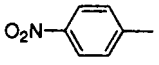
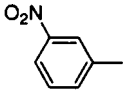
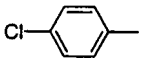
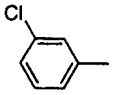
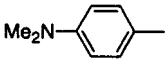
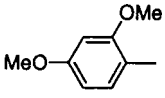
[a] One equiv. of aldehyde, 1.1 equiv. of **1a** or **5a**, 1.05 equiv. of *t*-BuOK, and 1.3 equiv. of additive were used.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis of the products.
[d] At 0°C in DMF.
[e] KHMDS was used as a base.
[f] NaHMDS was used as a base.
[g] For preparation of **1a**, see Ref. 14.
[h] *Z*-product cannot be detected by ^{1}H NMR analysis.
[i] At −40°C.
[j] Aldehyde was distilled before it was used in the reaction.



Scheme 3.

Furthermore, stereoselectivity and/or yield of the HWE reaction with **5a** were markedly improved using 1.3 equiv. of 18-C-6 as an additive (entries 1, 2 and 11, 12). Interestingly, the addition of 18-C-6 reversed the stereoselectivity as shown in entries 7 and 8, whereas a similar reaction with benzaldehyde proceeded with high stereoselectivity in the presence of 18-C-6. The HWE reaction of **5a** and benzaldehyde using KHMDS as a base gave (*E*)-2-bromo-3-phenylacrylate with high stereoselectivity, and the addition of 18-C-6 promoted the reaction (entries 4 and 5). When using NaHMDS as a base without additive, the yield and stereoselectivity of the HWE reaction were comparable to those obtained by the combined use of *t*-BuOK and 18-C-6 (entry 6). When using LHMDS as a base, however, higher temperature (even at rt) was needed to obtain the HWE reaction with **5a** and benzaldehyde, and both yield and stereoselectivity were extremely decreased (38%, *E*/*Z*= 2:1).

Table 2. Results of the HWE reaction with **5a** and a range of aromatic aldehydes

Entry[a]	R	Time (h)	Product	Yield (%)[b]	*E*:*Z*[c]
1		0.3	**7a**	94	30:1
2		4	**7b**	94	30:1
3		1.5	**7c**	98	28:1
4		7	**7d**	89	14:1
5		2	**7e**	83	10:1
6		1.5	**7f**	97	19:1
7		1	**7g**	94	9:1
8		0.3	**7h**	99	30:1
9		1	**7i**	97	30:1
10[d]		overnight	**7j**	87	7:1
11[d]		overnight	no reaction	–	
12		1.5	**7k**	98	25:1

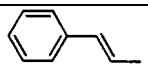
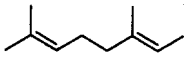
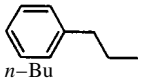
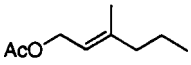
[a] See Scheme 3.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis of the products.
[d] From −78 to 0°C.

For further evaluation of the applicability of this *E*-selective reaction, we examined the HWE reaction using **5a** with various aldehydes (Scheme 3). As shown in Table 2, olefination of most aromatic aldehydes with **5a** in the presence of *t*-BuOK and 18-C-6 gave (*E*)-α-bromoacrylates **7** with high stereoselectivities and excellent yields. The HWE reaction of some aldehydes resulted in poor stereoselectivities; the reaction of aromatic aldehydes possessing electron donating groups were less reactive and stereoselective (entries 5 and 10). Aromatic aldehydes possessing electron withdrawing groups were highly reactive while their selectivities were moderate (entries 6 and 7). Since 2,4-dimethoxybenzaldehyde remained unreactive (entry 11), we consider that the HWE reaction is very sensitive to ortho-substitution of benzaldehyde.

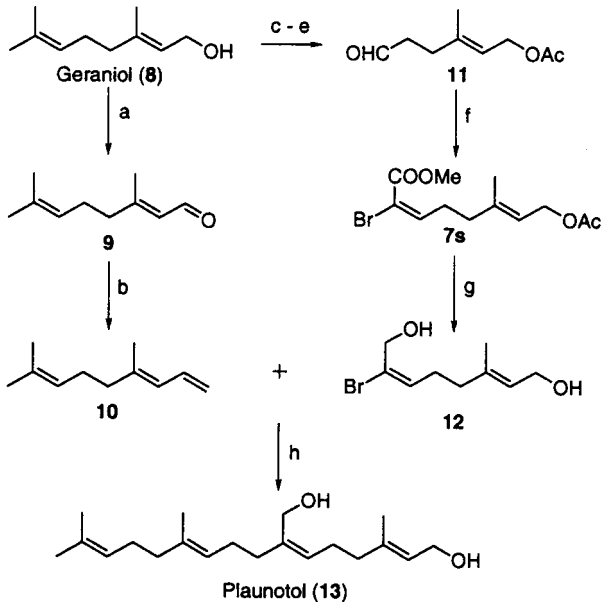
The results of the HWE reaction with **5a** and conjugated or aliphatic aldehydes are shown in Table 3. The corresponding (*E*)-α-bromoacrylates **7** were obtained from these aldehydes with high stereoselectivities, though the reaction of conjugated aldehydes proceeded slowly. However the *E*/*Z* ratios and yields were sufficiently high (entries 1 and 2). When using branched aliphatic aldehydes, chemical yields were comparatively low but high stereoselectivity still remained (entries 5 and 6).

This HWE reagent **5a** provides an efficient and highly stereoselective method to synthesize various (*E*)-α-bromoacrylates **7**, which are very useful reagent for C–C bond formation. We developed a general protocol for the stereoselective synthesis of trisubstituted alkenes from (*E*)-α-bromoacrylates **7** via Pd-catalyzed cross-coupling reactions.[14]

Table 3. Results of the HWE reaction with **5a** and a range of conjugated or aliphatic aldehydes.

Entry[a]	R	Time (h)	Product	Yield (%)[b]	*E*:*Z*[c]
1		17	**7l**	quant.	*E* only[d]
2[e]		5	**7m**	84	15:1
3		3	**7n**	75	32:1
4[f]	*n*–Bu	2	**7o**	86	60:1
5[f]	*i*–Pr	1.5	**7p**	43	41:1
6[f]		6.5	**7q**	64	76:1
7[f]		1.5	**7r**	96	26:1
8		1	**7s**	85	*E* only[d]

[a] See Scheme 3.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis of the products.
[d] *Z*-product cannot be detected by ^{1}H NMR analysis.
[e] At −20°C.
[f] Aldehyde was distilled before it was used in the reaction.



Scheme 4. (a) MnO_2, CH_2Cl_2, 79%; (b) $MePPh_3Br$, *n*-BuLi, THF, 90%; (c) Ac_2O, Py, ether, 85%; (d) *m*-CPBA, CH_2Cl_2, 81%; (e) $HIO_4{\cdot}H_2O$, THF–H_2O, 76%; (f) **5a**, *t*-BuOK, 18-C-6, THF, 94%; (g) DIBAL-H, CH_2Cl_2, 57%; (h) **10**, 9-BBN, THF, rt, then **12**, $PdCl_2$(dppf), Ph_3As, Cs_2CO_3, DMF, 50°C, 77%.

Total synthesis of plaunotol via the HWE reaction

Using this (*E*)-α-bromoacrylate **7s** as a key intermediate, we investigated the most effective route to synthesize plaunotol (**13**), the most important component of the Thai folk medicine-*Plau-noi*.[17] Plaunotol has antibacterial activity against *Helicobacter pylori*,[18] which is a causative agent of, for example, gastric ulcer and gastric adenocarcinoma. Several groups have achieved the total synthesis of plaunotol[19] and previously, we have also developed a practical total synthesis of plaunotol via *Z*-selective Wittig reaction of α-acetal ketone.[20] Construction of the C7–C8 trisubstituted allylic alcohol is the principal problem in the total synthesis of plaunotol. Therefore, we applied our protocol for constructing trisubstituted alkenes via (*E*)-α-bromoacrylates to the synthesis of plaunotol.

The new synthetic route of plaunotol (**13**) using **7s** is summarized in Scheme 4. Compound **10** and aldehyde **11** were readily prepared from commercially available geraniol (**8**).[20b,21] The HWE reaction with **5a** and **11** gave **7s** with high stereoselectivity, and **7s** was reduced by DIBAL-H to yield diol **12**, a precursor of Pd-catalyzed C–C bond formation. Finally the synthesis of plaunotol (**13**) was achieved via Suzuki coupling of **10** and vinyl bromide **12**. The spectroscopic data of synthetic product **13** (^{1}H NMR and ^{13}C NMR) were identical with those of the authentic sample. It is notable that the Suzuki coupling proceeded without protecting the hydroxyl groups, making this the shortest route for the total synthesis of plaunotol (**13**), completed in only 6 steps from geraniol (**8**).

Conclusions

In conclusion, a novel HWE reagent **5a** was designed and prepared. (*E*)-α-Bromoacrylates **7** were synthesized stereoselectively and efficiently from **5a** with various aldehydes in the presence of *t*-BuOK and 18-C-6. Using the product **7s** as a key intermediate, we succeeded in developing the shortest route for the synthesis of plaunotol (**13**) via Pd-catalyzed cross-coupling.

Experimental

General methods

Unless otherwise noted, all reactions were carried out in oven-dried glassware under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. All other dry solvents were purchased from Aldrich in SureSeal™ containers. All other commercially obtained reagents were used as supplied. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 spectrometer. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Infrared spectra were recorded on a JASCO FT-IR-8900 spectrometer. Mass spectra were obtained on a JEOL HX-100, an SX-102A or a JMS-AX-505H mass spectrometer. Analytical TLC was performed on 0.25 mm pre-coated Merck silica gel 60 F_{254} plates. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh).

Methyl bis(trifluoroethyl)bromophosphonoacetate *5a*

A solution of sodium hydroxide (40.0 g, 1.0 mol) in H_2O (120 ml) was cooled to 0°C in an ice salt bath, and bromine (25.5 ml, 0.50 mol) was slowly added while stirring for over 30 min such that the temperature of the mixture did not exceed 10°C. Methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (**6**) (50.0 g, 0.13 mol) was added to the solution for 5 min, and to the resulting mixture was added H_2O (200 ml). Then, the mixture was extracted with chloroform ($CHCl_3$) (200 ml×1, 100 ml×2). The combined organic extracts were washed with H_2O (100 ml×4), dried over $MgSO_4$, and concentrated in vacuo after filtration. The product was distilled under reduced pressure (bp 100–102°C, 1 mmHg) to obtain methyl bis(2,2,2-trifluoroethyl)-dibromophosphonoacetate (41.8 g, 85% yield) as a colorless oil. This dibromide (21.3 g, 44.2 mmol) was dissolved in EtOH (40 ml), and the solution was cooled to −30°C. A solution of $SnCl_2{\cdot}2H_2O$ (12.9 g, 56.0 mmol) in H_2O (100 ml) was added to the reaction mixture for 40 min such that the temperature did not exceed −25°C. After the addition was completed, the reaction mixture was extracted with $CHCl_3$ (200 ml×1, 100 ml×1, 50 ml×2). The combined extracts were washed with H_2O (100 ml×4), dried over $MgSO_4$, and concentrated in vacuo after filtration. In order to remove dibromide and **6**, the residue was purified by flash column chromatography. The column was packed with silica gel (290 g) using a mixture of CH_2Cl_2 (750 ml) and 4 N HCl in ethyl acetate (30 ml). After rinsing the column with the solvent (CH_2Cl_2:acetone=50:1, 500 ml), the crude product was applied and eluted (one fraction; 65 ml). Combined fractions (from No. 7 to 20), which contained only **5a**, were concentrated in vacuo. The residue was

dissolved in $CHCl_3$ (300 ml) and washed with H_2O (50 ml×4), dried over $MgSO_4$, and concentrated in vacuo after filtration. The residue was distilled under reduced pressure (bp 85–87°C, 0.4 mmHg) to obtain **5a** (12.2 g, 70% yield) as a colorless oil: IR (film) ν_{max} 3029, 2966, 1745, 1455, 1440, 1421, 1375, 1301, 1268, 1175, 1102, 1072, 1012, 964, 903, 886, 846, 808, 726, 659, 556, 535, 478, 448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 3.87 (s, 3H), 4.45–4.60 (m, 5H); HRMS (FAB) calcd for $C_7H_9O_5BrF_6P$ $(M+H)^+$ 396.9275, obsd 396.9271; Anal. Calcd for $C_7H_8O_5BrF_6P$: C, 21.18; H, 2.03. Found: C, 20.87; H, 2.14.

General procedure for HWE reaction

A solution of **1a** or **5a** (1.1 mmol) and 18-C-6/CH_3CN (397 mg, 1.3 mmol) in THF (8 ml) was cooled to −78°C. Then 1.0 M of potassium *tert*-butoxide solution in THF (1.05 ml, 1.05 mmol) was added to the solution. After stirring for 30 min at −78°C, aldehyde (1.0 mmol) was added to the reaction mixture and the stirring was continued. When the reaction was completed, saturated aqueous NH_4Cl was added to the solution and the organic material was extracted with AcOEt. The combined organic extracts were washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo after filtration. The residue was purified by silica gel flash chromatography to afford methyl α-bromoacrylate.

(*E*)-2-Bromo-3-phenylacrylic acid methyl ester (7a). IR ($CHCl_3$ soln.) ν_{max} 2954, 1728, 1611, 1576, 1496, 1447, 1435, 1346, 1316, 1289, 1244, 1210, 1183, 1077, 1031, 1018, 1007, 928, 902, 878, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (3H, s), 7.26–7.38 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.0, 111.1, 128.1, 128.5, 129.0, 134.8, 140.1, 164.8; HRMS (EI) calcd for $C_{10}H_9O_2Br$ $(M)^+$ 239.9786, obsd 239.9788.

(*E*)-2-Bromo-3-(4-methoxyphenyl)acrylic acid methyl ester (7b). IR ($CHCl_3$ soln.) ν_{max} 2954, 2937, 2911, 2841, 1724, 1605, 1575, 1511, 1464, 1437, 1422, 1349, 1300, 1257, 1223, 1206, 1176, 1115, 1033, 1004, 941, 908, 887, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.79 (3H, s), 3.82 (3H, s), 6.81 (2H, d, J=9.5 Hz), 7.28 (2H, d, J=9.5 Hz), 7.32 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.0, 55.3, 108.7, 113.9, 127.2, 130.2, 132.5, 140.4, 160.3; HRMS (EI) calcd for $C_{11}H_{11}O_3Br$ $(M)^+$ 269.9892, obsd 269.9892.

(*E*)-2-Bromo-3-(3-methoxyphenyl)acrylic acid methyl ester (7c). IR ($CHCl_3$ soln.) ν_{max} 2954, 2914, 2839, 1729, 1600, 1579, 1489, 1466, 1456, 1435, 1341, 1292, 1261, 1216, 1184, 1151, 1142, 1087, 1051, 1042, 1019, 1009, 956, 937, 928, 906, 878, 825, 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (3H, s), 3.79 (3H, s), 6.80–6.89 (3H, m), 7.23–7.27 (1H, m), 7.32 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.0, 55.2, 111.2, 113.3, 114.8, 120.6, 129.5, 135.9, 139.5, 159.5, 164.9; HRMS (EI) calcd for $C_{11}H_{11}O_3Br$ $(M)^+$ 269.9892, obsd 269.9989.

(*E*)-2-Bromo-3-(3,4-dimethoxyphenyl)acrylic acid methyl ester (7d). IR ($CHCl_3$ soln.) ν_{max} 4214, 2957, 2939, 2913, 2841, 1726, 1601, 1583, 1514, 1465, 1440, 1422, 1349, 1322, 1271, 1231, 1221, 1209, 1181, 1160, 1145, 1109, 1074, 1025, 964, 904, 853, 804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.79 (3H, s), 3.86 (3H, s), 3.90 (3H, s), 6.82 (1H, d, J=8.2 Hz), 6.91 (1H, dd, J=8.2, 2.0 Hz), 6.95 (1H, d, J=2.0 Hz), 7.30 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.0, 55.85, 55.89, 108.8, 110.8, 111.3, 122.2, 127.4, 140.2, 148.7, 150.0, 165.1; HRMS (EI) calcd for $C_{12}H_{13}O_4Br$ $(M)^+$ 299.9997, obsd 300.0004.

(*E*)-2-Bromo-3-(3,4,5-trimethoxyphenyl)acrylic acid methyl ester (7e). IR ($CHCl_3$ soln.) ν_{max} 2954, 2940, 2841, 1727, 1582, 1505, 1464, 1435, 1418, 1350, 1330, 1298, 1250, 1212, 1185, 1152, 1130, 1075, 1041, 1014, 1001, 978, 905, 837, 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.79 (3H, s), 3.84 (6H, s), 3.86 (3H, s), 6.57 (2H, s), 7.27 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.1, 56.1, 60.1, 105.8, 110.1, 130.0, 139.5, 152.9, 153.1, 165.1; HRMS (EI) calcd for $C_{13}H_{15}O_5Br$ $(M)^+$ 330.0103, obsd 330.0102.

(*E*)-2-Bromo-3-(4-nitrophenyl)acrylic acid methyl ester (7f). Mp 80–81°C; IR ($CHCl_3$ soln.) ν_{max} 2955, 1731, 1600, 1525, 1493, 1437, 1348, 1293, 1243, 1184, 1112, 1016, 1003, 882, 861, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (3H, s), 7.44 (1H, s), 7.45 (2H, d, J=8.7 Hz), 8.21 (2H, d, J=8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.3, 115.2, 123.7, 128.9, 138.2, 141.1, 147.6, 163.9; HRMS (FAB) calcd for $C_{10}H_8O_4NBrK$ $(M+K)^+$ 323.9274, obsd 323.9272; Anal. Calcd for $C_{10}H_8O_4NBr$: C, 41.99; H, 2.82; N, 4.90. Found: C, 41.90; H, 2.96; N, 4.71.

(*E*)-2-Bromo-3-(3-nitrophenyl)acrylic acid methyl ester (7g). Mp 79–80°C; IR ($CHCl_3$ soln.) ν_{max} 3089, 2955, 1731, 1611, 1578, 1534, 1480, 1437, 1355, 1311, 1295, 1282, 1243, 1224, 1185, 1101, 1082, 1008, 907, 889, 869, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (3H, s), 7.44 (1H, s), 7.54 (1H, t, J=7.8 Hz), 7.61 (1H, d, J=7.8 Hz), 8.19–8.22 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.3, 114.6, 123.1, 123.6, 129.4, 134.0, 136.3, 138.1, 163.8, 170.3; HRMS (EI) calcd for $C_{10}H_8O_4NBr$ $(M)^+$ 284.9637, obsd 284.9639; Anal. Calcd for $C_{10}H_8O_4NBr \cdot 1/3\ H_2O$: C, 41.12; H, 2.99; N, 4.80. Found: C, 40.84; H, 2.72; N, 4.60.

(*E*)-2-Bromo-3-(4-chlorophenyl)acrylic acid methyl ester (7h). Mp 43–45°C; IR ($CHCl_3$ soln.) ν_{max} 2954, 1728, 1611, 1592, 1496, 1448, 1436, 1404, 1343, 1304, 1275, 1244, 1216, 1183, 1099, 1015, 1005, 909, 883, 839, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (3H, s), 7.23 (2H, dt, J=8.8, 2.0 Hz), 7.32 (2H, dt, J=8.8, 2.0 Hz), 7.33 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.1, 111.8, 128.7, 129.5, 131.5, 133.1, 135.0, 164.5; HRMS (EI) calcd for $C_{10}H_8O_2BrCl$ $(M)^+$ 273.9396, obsd 273.9402; Anal. Calcd for $C_{10}H_8O_2BrCl$: C, 43.59; H, 2.93. Found: C, 43.68; H, 2.89.

(*E*)-2-Bromo-3-(3-chlorophenyl)acrylic acid methyl ester (7i). IR ($CHCl_3$ soln.) ν_{max} 2954, 1729, 1614, 1595, 1567, 1475, 1453, 1436, 1411, 1338, 1269, 1244, 1220, 1184, 1098, 1082, 1019, 1007, 925, 893, 872, 826, 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (3H, s), 7.15 (1H, d, J=7.3 Hz), 7.25–7.33 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.3, 114.6, 123.1, 123.6, 129.4, 134.0, 136.3, 138.1, 163.8, 170.3; HRMS (EI) calcd for $C_{10}H_8O_2BrCl$ $(M)^+$ 273.9396, obsd 273.9396.

(*E*)-2-Bromo-3-(4-dimethylaminophenyl)acrylic acid methyl ester (7j). Mp 58–60°C; IR ($CHCl_3$ soln.)ν_{max} 4214, 2953, 2902, 2865, 2812, 1717, 1609, 1591, 1524, 1483, 1445, 1437, 1414, 1367, 1324, 1305, 1273, 1250, 1223, 1212, 1183, 1167, 1145, 1131, 1065, 1045, 1021, 1003, 947, 908, 819, 808 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.99 (6H, s), 3.81 (3H, s), 6.62 (2H, d, J=8.8 Hz), 7.29 (1H, s), 7.30 (2H, d, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.1, 52.8, 105.4, 111.4, 122.2, 130.7, 142.1, 150.9, 165.3; HRMS (EI) calcd for $C_{12}H_{14}O_2NBr$ $(M)^+$ 283.0208, obsd 283.0216; Anal. Calcd for $C_{12}H_{14}O_2NBr \cdot 1/4\ H_2O$: C, 19.93; H, 5.02; N, 4.85. Found: C, 49.71; H, 4.68; N, 4.78.

(*E*)-2-Bromo-3-furan-2-ylacrylic acid methyl ester (7k). IR ($CHCl_3$ soln.) ν_{max} 2954, 2846, 1726, 1595, 1556, 1474, 1457, 1437, 1390, 1349, 1251, 1211, 1183, 1153, 1145, 1093, 1022, 962, 931, 921, 907, 886, 829, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.88 (3H, s), 6.47 (1H, dd, J=1.9, 3.5 Hz), 7.09 (1H, d, J=3.5 Hz), 7.23 (1H, s), 7.47 (1H, d, J=1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.0, 107.0, 112.4, 115.4, 129.4, 144.3, 149.3, 164.1; HRMS (EI) calcd for $C_8H_7O_3Br$ $(M)^+$ 229.9579, obsd 229.9578.

(*E*, *E*)-2-Bromo-5-phenylpenta-2,4-dienoic acid methyl ester (7l). IR ($CHCl_3$ soln.) ν_{max} 3083, 2954, 2846, 1713, 1613, 1579, 1568, 1490, 1448, 1436, 1357, 1329, 1316, 1302, 1268, 1246, 1222, 1206, 1189, 1181, 1160, 1146, 1110, 1172, 1045, 1030, 1016, 1000, 986, 975, 938, 910, 882, 852, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.88 (3H, s), 6.83 (1H, d, J=15.6 Hz), 7.31 (1H, d, J=11.5 Hz), 7.32–7.37 (3H, m), 7.50–7.52 (2H, m), 7.81 (1H, dd, J=11.5, 15.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.0, 110.3, 124.9, 127.6, 128.8, 128.9, 129.4, 136.0, 141.7, 146.5, 163.3; HRMS (EI) calcd for $C_{12}H_{11}O_2Br$ $(M)^+$ 265.9942, obsd 265.9933.

(*E*, *E*)-2-Bromo-5,9-dimethyldeca-2,4,8-trienoic acid methyl ester (7m). IR ($CHCl_3$ soln.) ν_{max} 2970, 2953, 2930, 2917, 2857, 1708, 1618, 1565, 1436, 1371, 1320, 1246, 1216, 1206, 1185, 1137, 1107, 1043, 1102, 941, 911, 822, 859, 825, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.61 (3H, s), 1.69 (3H, s), 1.84 (3H, s), 2.16 (4H, m), 3.83 (3H, s), 5.07–5.10 (1H, m), 6.86 (1H, d, J=11.7 Hz), 7.42 (1H, d, J=11.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 17.7, 25.7, 16.4, 40.7, 52.8, 108.3, 121.7, 132.3, 142.4, 151.1, 163.6; HRMS (EI) calcd for $C_{13}H_{19}O_2Br$ $(M)^+$ 286.0568, obsd 286.0571.

(*E*)-2-Bromo-5-phenylpent-2-enoic acid methyl ester (7n). IR ($CHCl_3$ soln.) ν_{max} 2954, 2929, 2862, 1718, 1611, 1497, 1454, 1437, 1354, 1306, 1247, 1224, 1173, 1087, 1030, 1003, 909, 880, 843, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.75–2.87 (4H, m), 3.80 (3H, s), 6.71 (1H, t, J=7.4 Hz), 7.18–7.23 (3H, m), 7.30 (2H, t, J=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.0, 34.7, 52.9, 111.3, 126.3, 128.4, 128.5, 140.5, 147.9, 163.2; HRMS (EI) calcd for $C_{12}H_{13}O_2Br$ $(M)^+$ 268.0099, obsd 268.0097.

(*E*)-2-Bromohept-2-enoic acid methyl ester (7o). IR ($CHCl_3$ soln.) ν_{max} 2958, 2931, 2873, 2863, 1717, 1611, 1466, 1458, 1437, 1380, 1352, 1319, 1297, 1250, 1209, 1189, 1134, 1035, 1007, 990, 943, 878, 814, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J=7.3 Hz), 1.31–1.48 (4H, m), 2.51 (2H, q, J=7.6 Hz), 3.82 (3H, s), 6.69 (1H, t, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.3, 30.9, 31.2, 52.8, 110.4, 149.5, 163.4; HRMS (EI) calcd for $C_8H_{13}O_2Br$ $(M)^+$ 220.0099, obsd 220.0101.

(*E*)-2-Bromo-4-methylpent-2-enoic acid methyl ester (7p). IR ($CHCl_3$ soln.) ν_{max} 2971, 2956, 2933, 2906, 2872, 1718, 1614, 1467, 1447, 1437, 1354, 1311, 1297, 1245, 1169, 1147, 1100, 1010, 944, 931, 895, 837, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (6H, d, J=6.6 Hz), 3.25 (1H, m), 3.82 (3H, s), 6.48 (1H, d, J=10.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 30.9, 52.8, 108.9, 155.1, 163.4; HRMS (EI) calcd for $C_7H_{11}O_2Br$ $(M)^+$ 205.9942, obsd 205.9945.

(*E*)-2-Bromo-3-cyclohexylacrylic acid methyl ester (7q). IR ($CHCl_3$ soln.) ν_{max} 2932, 2854, 1717, 1610, 1449, 1437, 1363, 1346, 1291, 1267, 1247, 1207, 1187, 1146, 1096, 1005, 964, 932, 903, 879, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07–1.37 (5H, m), 1.63–1.77 (5H, m), 2.91–3.01 (1H, m), 3.82 (3H, s), 6.50 (1H, d, J=10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 25.7, 32.1, 40.4, 52.8, 109.1, 154.0, 163.4; HRMS (EI) calcd for $C_{10}H_{15}O_2Br$ $(M)^+$ 246.0255, obsd 246.0249.

(*E*)-4-Benzyloxy-2-bromobut-2-enoic acid methyl ester (7r). IR ($CHCl_3$ soln.) ν_{max} 3086, 2954, 2888, 2862, 1715, 1621, 1498, 1454, 1438, 1351, 1317, 1246, 1221, 1211, 1194, 1091, 1029, 987, 909, 879, 830, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (3H, s), 4.47 (2H, d, J=5.1 Hz), 4.54 (2H, s), 6.91 (1H, t, J=5.1 Hz), 7.29–7.38 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.1, 69.2, 72.9, 110.5, 127.8, 127.9, 128.5, 137.5, 148.0, 163.0; HRMS (EI) calcd for $C_{12}H_{14}O_3Br$ $(M+H)^+$ 287.0106, obsd 287.0095.

(*E*, *E*)-8-Acetoxy-2-bromo-6-methylocta-2,6-dienoic acid methyl ester (7s). IR ($CHCl_3$ soln.) ν_{max} 2954, 2848, 1724, 1672, 1613, 1437, 1384, 1367, 1357, 1306, 1252, 1213, 1181, 1116, 1079, 1023, 995, 956, 923, 878, 806 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.71 (3H, s), 2.06 (3H, s), 2.19 (2H, t, J=7.6 Hz), 2.66 (2H, q, J=7.6 Hz), 3.82 (3H, s), 4.59 (2H, d, J=7.1 Hz), 5.33–5.39 (1H, m), 6.65 (1H, t, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 21.0, 29.5, 38.1, 52.9, 61.1, 111.1, 119.8, 140.3, 148.2, 163.2, 171.0; HRMS (FAB) calcd for $C_{12}H_{17}O_4BrK$ $(M+K)^+$ 342.9947, obsd 342.9970.

(*E*)-2-Bromo-6-methylocta-2,6-diene-1,8-diol (12). A solution of **7s** (1.0 g, 3.3 mmol) in CH_2Cl_2 (20 ml) was cooled to −78°C and to the solution was added DIBAL-H (20 ml, 20 mmol). The reaction mixture was stirred at −78°C for 1 h. Then $Na_2SO_4 \cdot 10H_2O$ (6 g) was added and warmed up to rt. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (hexane/ethyl acetate=1:1) to give allylic alcohol as a colorless solid (442 mg, 57% yield): mp 61–62°C; IR ($CHCl_3$ soln.) ν_{max} 3676, 3610, 3445, 2932, 1732, 1668, 1664, 1646, 1603, 1457, 1448, 1385, 1351, 1246, 1220, 1189, 1109, 1078, 1037, 999, 922, 865, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.69 (3H, s), 1.75 (1H, br), 2.10 (2H, t, J=7.2 Hz), 2.26 (2H, q, J=

7.2 Hz), 2.49 (1H, br), 4.14 (2H, d, J=7.5 Hz), 4.26 (2H, s), 5.42 (1H, tt, J=7.2, 1.3 Hz), 6.00 (1H, t, J=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 27.9, 38.1, 59.0, 62.4, 124.9, 125.2, 133.9, 138.0; HRMS (FAB) calcd for $C_9H_{15}O_2BrNa$ $(M+Na)^+$ 257.0153, obsd 257.0163.

Plaunotol (13). A solution of **10** (128 mg, 0.85 mmol) in THF (1 ml) was cooled to 0°C and to the solution was added 0.5 M of 9-BBN in THF (3.4 ml, 1.7 mmol). Then the reaction mixture was stirred at rt for 4 h. After addition of water (0.1 ml), the resulting mixture was concentrated in vacuo to give a boron reagent. Compound **12** (100 mg, 0.43 mmol), Cs_2CO_3 (250 mg, 0.76 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (7 mg, 2 mol%), and Ph_3As (5 mg, 4 mol%) were dissolved in DMF (3 ml) and stirred at rt for 10 min. Then, to the mixture was added the boron reagent and stirred at 50°C for 2.5 h. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, concentrated in vacuo after filtration. The residue was purified by Lobar column chromatography (RP-18, MeOH/H_2O= 80:20) to give **13** as a colorless oil (100 mg, 77% yield): IR (film) ν_{max} 3322, 2966, 2923, 2857, 1669, 1445, 1381, 1006 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.60 (6H, s, CH_3C═C×2), 1.69 (6H, s, CH_3C═C×2), 1.93–2.28 (12H, m, CH_2C═C×6), 4.10 (2H, s, CH_2OH), 4.14 (2H, d, J=7.0 Hz, CH_2OH), 5.05–5.19 (2H, m, C═CH×2), 5.28 (1H, t, J=7.4 Hz, C═CH), 5.40 (1H, t, J=7.4 Hz, C═CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 16.4, 17.7, 25.7, 25.9, 26.8, 26.9, 35.0, 39.4, 39.7, 59.2, 60.1, 124.0, 124.1, 124.3, 127.7, 131.4, 135.4, 138.9, 139.1; HRMS (EI), calcd for $C_{20}H_{34}O_2$ $(M)^+$ 306.2559, obsd 306.2554.

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