A practical total synthesis of plaunotol *via* highly *Z*-selective Wittig olefination of α-acetal ketones† [1]

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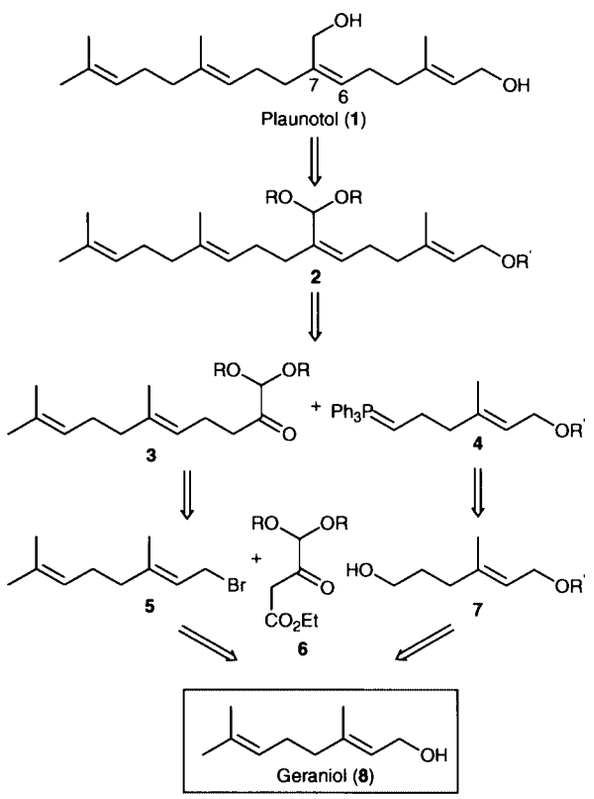
Plaunotol (**1**), a known antiulcer drug, is the most important component of the Thai folk medicinal plant, *Plau-noi*, which has remarkable antipeptic ulcer activity. Recently, it was found that plaunotol (**1**) has antibacterial activity against *Helicobacter pylori*, a causative agent in gastric ulcers and gastric adenocarcinoma, for example. In our investigation of the practical synthesis of **1**, we have developed an efficient method for stereoselective synthesis of trisubstituted olefins *via* a *Z*-selective Wittig reaction. The olefination of readily available aliphatic α-acetal ketones with triphenylphosphonium salts in the presence of a potassium base and 18-crown-6 ether proceeded with excellent *Z*-selectivity. The *Z*-selective olefination provides a useful method for the construction of a range of trisubstituted olefin moieties; the practical and stereoselective total synthesis of plaunotol (**1**) was achieved *via* this Wittig reaction.

Introduction

Since it was first discovered in human stomach tissue in 1982,[2] *Helicobacter pylori* (*H. pylori*) has been demonstrated to be a major causative agent in gastritis,[3] gastric ulcers,[4] and duodenal ulcers.[5] The World Health Organization (WHO) recently labeled *H. pylori* as a class 1 carcinogen[6] since chronic infection is known to be associated with the development of gastric adenocarcinoma, one of the most common types of cancer in humans. Thus, an effective antibiotic therapy to eliminate *H. pylori* would reduce the risk of ulcer recurrence and gastric cancers. Recently, Koga and co-workers[8] reported that plaunotol (**1**), a known antiulcer drug,[7] has antibacterial activity against *H. pylori*. Plaunotol (**1**), an acyclic diterpene alcohol, is the most important component of *Plau-noi*, a Thai folk medicine with remarkable activity against peptic ulcers.[7] In our recent studies to develop an antibacterial drug against *H. pylori*, we have been investigating an efficient method for the synthesis of **1** and its derivatives. Several groups[7,9] have succeeded in the total synthesis of **1**, however, these methods lack synthetic efficiency and/or stereoselectivity.

Retrosynthetic analysis is dictated by considerations of practicality with highly stereoselective trisubstituted olefination as a key step (Scheme 1). Chemical advantages of this synthetic route include the use of a common and inexpensive reagent, commercially available geraniol (**8**), as the starting material for both intermediates (**3** and **4**), and the highly stereoselective Wittig reaction which provides trisubstituted *Z*-allylic alcohols. In addition, regioselective modification of each hydroxy group of **1** for synthesis of various derivatives would be readily accessible using this route.[1]

In order to achieve highly stereoselective olefination, we investigated *Z*-selective Wittig olefination of α-acetal ketones **3** as a key step of the synthesis of **1** (Scheme 1). In 1980, Still *et al.* achieved the *Z*-selective Wittig reaction of unstabilized ylides and acyclic α-alkoxyketones to provide protected trisubstituted allylic alcohols, and they reported that substitutions at the α-carbon of the α-alkoxyketone tended to improve stereoselectivity.[10] To obtain even higher stereoselectivity, α-acetal ketone **3** was selected as a precursor to the trisubstituted *Z*-allylic alcohol because **3** was expected to have bulkier α-substitutents than an α-alkoxyketone. It was also anticipated that **3** would be more readily prepared than the corresponding α-alkoxyketone, since various α-diethoxyketones can be prepared from commercially available ethyl diethoxyacetate in two steps.[11–14]



Scheme 1

This article reports an effective synthetic route to plaunotol (**1**) from geraniol (**8**) *via* a highly stereoselective trisubstituted olefination.

† Spectroscopic and analytical data for compound **21** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b001977l/

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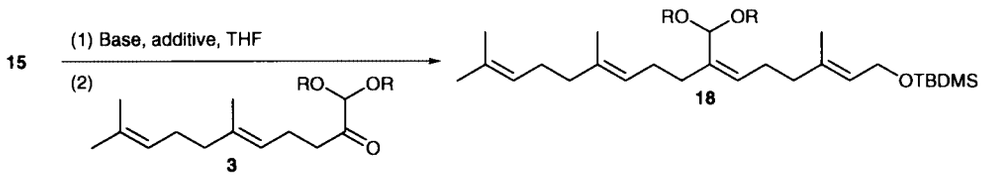
Table 1 Wittig reaction between α-acetal ketone **3** and phosphonium salt **12** under various conditions

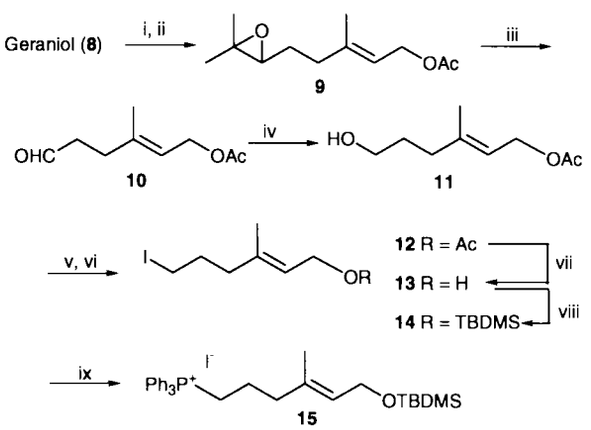


Run[a]	3 (R)	Base	Additive	Temp.	Time/h	Yield (%)[b]	$Z:E$[c]
1	**3a** (Et)	KHMDS	HMPA	−78 °C to rt	16	52	4:1
2	**3a** (Et)	KHMDS	18-C-6	−78 °C to 0 °C	1.5	82	13:1
3	**3a** (Et)	KHMDS	18-C-6	−78 °C to −20 °C	2	84	16:1
4	**3a** (Et)	KHMDS	18-C-6	−78 °C to −60 °C	16	95	38:1
5	**3a** (Et)	KH	18-C-6	−78 °C to −60 °C	16	83	61:1
6	**3a** (Et)	Bu^{t}OK	18-C-6	−78 °C to −45 °C	16	89	41:1
7	**3b** (Cy)	Bu^{t}OK	18-C-6	−78 °C to rt	16	62[d]	>99:1
8	**3c** (Pr^i)	Bu^{t}OK	18-C-6	−78 °C to rt	16	63[d]	>99:1

[a] One equiv. of **3**, 1.5 equiv. of **15**, 1.5 equiv. of base and 1.8 equiv. of additive were used in all runs except for run 1. For run 1, see ref. 10. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the aldehyde proton after deprotection of acetal. [d] Aldehyde yield after deprotection of acetal (2 steps).

Results and discussion

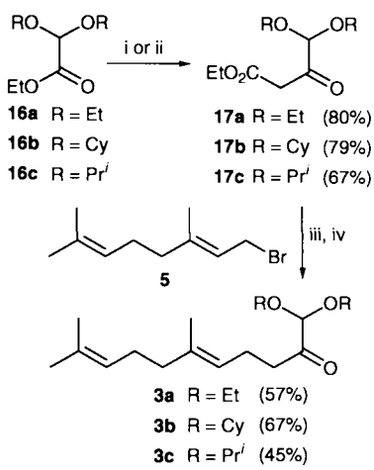
The synthesis of two precursors for the Wittig reaction is shown in Schemes 2 and 3. *O*-TBDMS protected phosphonium iodide



Scheme 2 *Reagents and conditions*: i, Ac_2O, Py, THF, 0 °C to rt, quant.; ii, MCPBA, CH_2Cl_2, 81%; iii, HIO_4, H_2O, THF, 0 °C, 89%; iv, $NaBH_4$, EtOH, 0 °C to rt, 67%; v, *p*-TsCl, Py, 0 °C to rt; vi, NaI, acetone, rt, 89% (2 steps); vii, K_2CO_3, MeOH, rt, 92%; viii, TBDMSCl, imidazole, 0 °C, 93%; ix, PPh_3, benzene, reflux, 96%.

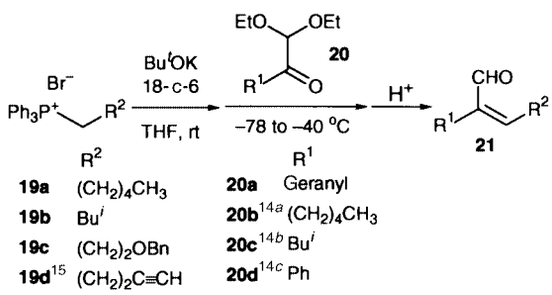
15 was prepared from geraniol (**8**) according to the literature procedure employed for the synthesis of the *O*-benzyl derivative (Scheme 2).[9d] The second precursor, α-acetal ketone **3a**, was easily prepared from geranyl bromide (**5**) and ethyl diethoxyacetoacetate (**17a**), which was prepared from commercially available ethyl diethoxyacetate (**16a**) (Scheme 3).[11,12] The bulkier α-acetal ketones **3b** and **3c** were also synthesized similarly from **16b** and **16c** respectively.

The results of the *Z*-selective Wittig reaction between phosphonium salt **15** and α-acetal ketones **3** are summarized in Table 1. The combined use of KHMDS and HMPA, a method which was reported by Still *et al.*,[10] gave poor results in terms of both yield and stereoselectivity (run 1). However, high *Z*-selectivity and excellent yield were observed (run 2) using 18-crown-6 ether (18-c-6) as an additive instead of HMPA. The additive for trapping the potassium cation was necessary because ylide formation scarcely occurred without 18-c-6. A lower reaction temperature increased the *Z*-selectivity (runs 2–4), and the use of other potassium bases gave similar results (runs 5 and 6). As we anticipated, the bulkier α-acetal ketones (**3b** and **3c**) exclusively yielded *Z*-olefins, even when the reaction was performed at room temperature (runs 7 and 8).



Scheme 3[11,12] *Reagents and conditions*: i, Na, EtOAc, reflux; ii, NaHMDS, EtOAc, THF, −78 °C to rt; iii, **5**, RONa, ROH, 0 °C to rt; iii, KOH, H_2O, EtOH, reflux.

In order to further evaluate the *Z*-selectivity of this Wittig reaction, we explored a range of α-acetal ketones and phosphonium salts as summarized in Scheme 4. All of the α-acetal



Scheme 4

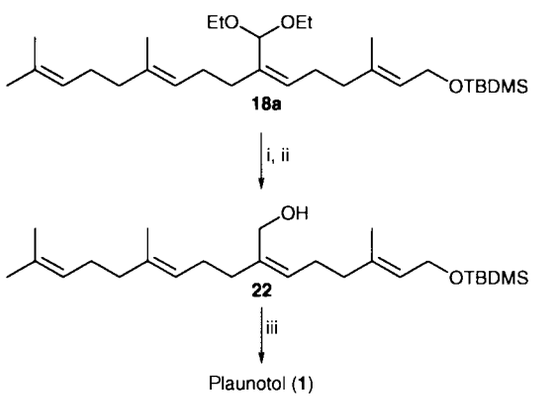
ketones except for **20a** were readily prepared by addition of the corresponding Grignard reagent to *N*-(diethylacetyl)piperidine.[13,14] As shown in Table 2, olefination of α-acetal ketones with triphenylphosphine ylides proceeded with excellent *Z*-selectivity, except for runs 13 and 14. The Wittig reaction between aromatic α-acetal ketone (**20d**) and triphenylphosphonium salts produced (*E*)-olefins predominately (runs 13 and 14).[16] To summarize, this *Z*-selective olefination of readily available aliphatic α-acetal ketones provides a useful method for the synthesis of natural products consisting of a range of trisubstituted olefin moieties.

Table 2 The results of the Wittig reaction shown in Scheme 4

Run[a]	**20** (R^1)	**19** (R^2)	Product	Method of deprotection[b]	Yield (%)[c]	$Z:E$[d]
1	**20a** (geranyl)	**19a** ($(CH_2)_4CH_3$)	**21aa**	A	56	95:5
2		**19b** (Bu^i)	**21ab**	A	44	93:7
3[e]		**19c** ($(CH_2)_2OBn$)	**21ac**	A	62	83:17
4		**19d** ($(CH_2)_2C{\equiv}CH$)	**21ad**	A	45	95:5
5	**20b** ($(CH_2)_4CH_3$)	**19a** ($(CH_2)_4CH_3$)	**21ba**	A	51	91:9
6		**19b** (Bu^i)	**21bb**	A	50	93:7
7		**19c** ($(CH_2)_2OBn$)	**21bc**	A	60	95:5
8		**19d** ($(CH_2)_2C{\equiv}CH$)	**21bd**	A	70	92:8
9	**20c** (Bu^i)	**19a** ($(CH_2)_4CH_3$)	**21ca**	B	48	94:6
10		**19b** (Bu^i)	**21cb**	B	46	93:7
11		**19c** ($(CH_2)_2OBn$)	**21cc**	B	51	97:3
12		**19d** ($(CH_2)_2C{\equiv}CH$)	**21cd**	B	49	98:2
13[f]	**20d** (Ph)	**19a** ($(CH_2)_4CH_3$)	**21da**	A	Quant.	18:82
14[f]		**19b** (Bu^i)	**21db**	A	93	28:72

[a] See the corresponding footnotes in Table 1. [b] Method A; Amberlyst 15, aqueous acetone, Method B; 50% aqueous AcOH, THF. [c] Isolated yields of **21** (2 steps). [d] Determined by ^{1}H NMR analysis of **21**. [e] For 3 days. [f] At −78 °C.

Finally, the total synthesis of plaunotol (**1**) was achieved by using the (*Z*)-olefin **18a** as shown in Scheme 5. Cleavage



Scheme 5 *Reagents and conditions*: i, AcOH–H_2O (1:1), THF, rt; ii, $NaBH_4$, EtOH, 0 °C, 90% (2 steps); iii, cat. *p*-TsOH, MeOH, rt, 93%.

of the acetal group in **18a** under acidic conditions gave an α,β-unsaturated aldehyde. We were concerned that the resulting (*Z*)-α,β-unsaturated aldehyde would isomerize to the (*E*)-α,β-unsaturated aldehyde; thus the (*Z*)-aldehyde was reduced immediately with sodium borohydride to give the allylic alcohol **22** as the sole product in 90% yield (2 steps). Finally, removal of the *O*-TBDMS group in **22** with a catalytic amount of *p*-TsOH in methanol provided plaunotol (**1**) in 98% yield. The spectroscopic data of synthetic product **1** (^{1}H NMR and ^{13}C NMR) were identical with those of an authentic sample.

In conclusion, we have developed a highly *Z*-selective trisubstituted olefination of aliphatic α-acetal ketones in the presence of a potassium base and 18-c-6, and using this Wittig reaction as the key step, a stereoselective and practical total synthesis of plaunotol (**1**) was achieved. Furthermore, over 10 grams of pure **1** were readily obtained and the two hydroxy groups of **1** were modified independently *via* this route.

Experimental

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 Sure-Seal™ containers. All other commercially obtained reagents were used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-EX-270 or Varian 400 spectrometer. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. In NMR spectral lists, chemical shifts that are assigned to the enol form are marked with an asterisk. 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).

(*E*,*E*)-3,7-Dimethyl-6,7-epoxyoct-2-enyl acetate 9

A solution of *m*-chloroperbenzoic acid (11.2 g, 51.9 mmol) in CH_2Cl_2 (100 mL) was added to a solution of geranyl acetate (9.3 g, 47.4 mmol) in CH_2Cl_2 (200 mL) at 0 °C and the reaction mixture was stirred for 4 h at room temperature. Calcium hydroxide (15.0 g, 202 mmol) was added to the solution, then the mixture was stirred at room temperature for 40 min. After filtration, the residue was washed with ether and the filtrate was concentrated *in vacuo*. The crude product was distilled under reduced pressure (3 mmHg, bp 89 °C) to give 8.1 g of epoxide **9** as a colorless liquid (81% yield): IR (film) ν_{max} 2963, 2928, 1740, 1450, 1379, 1368, 1234, 1122, 1024 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.26 (3 H, s), 1.31 (3 H, s), 1.63–1.71 (2 H, m), 1.73 (3 H, s), 2.05 (3 H, s), 2.10–2.30 (2 H, m), 2.70 (1 H, t, *J* 6.2 Hz), 4.60 (2 H, d, *J* 7.2 Hz), 5.39 (1 H, t, *J* 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 18.8, 21.0, 24.8, 27.1, 36.2, 58.4, 61.2, 63.9, 118.9, 141.2, 171.0; HRMS (EI) calc. for $C_{10}H_{17}O$ (M − OAc)$^+$: 153.1279; found 153.1276.

(*E*)-6-Acetoxy-4-methylhex-4-en-1-al 10

A solution of periodic acid dihydrate (44.9 g, 0.20 mol) in water (180 mL) was added to a solution of epoxide **9** (38.0 g, 0.18 mol) in THF (300 mL) at 0 °C. After stirring for 30 min, brine was added, and the organic material was extracted with ether. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. The residue was distilled under reduced pressure (3 mmHg, bp 84–86 °C) to give 27.8 g of aldehyde **10** as a colorless liquid (71% yield): IR (film) ν_{max} 2943, 2922, 2833, 2727, 1733, 1673, 1445, 1386, 1368, 1236, 1025, 956 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.73 (3 H, d, *J* 1.2 Hz), 2.05 (3 H, s), 2.38 (2 H, t, *J* 7.3 Hz), 2.58 (2 H, td, *J* 7.3, 1.3 Hz), 4.51 (2 H, d, *J* 7.0 Hz), 5.36 (1 H, td, *J* 7.0, 1.2

Hz), 9.78 (1 H, t, *J* 1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 21.0, 31.5, 41.7, 61.1, 119.3, 140.0, 171.0, 201.6; HRMS (EI) calc. for $C_7H_{11}O$ $(M - OAc)^+$: 152.0837; found 152.0824.

(*E*)-6-Acetoxy-4-methylhex-4-en-1-ol 11

Sodium borohydride (6.0 g, 0.16 mol) was added portionwise to a solution of aldehyde **10** (27.0 g, 0.16 mol) in ethanol (300 mL) at 0 °C, the reaction mixture was stirred for 2 h. Acetone and water were added, the organic material was extracted with ether, and the combined organic extracts were washed with 1 M HCl solution and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Purification by silica gel flash chromatography (*n*-hexane–ethyl acetate 3:1) furnished 18.3 g (67%) of alcohol **11** as a colorless oil: IR (film) ν_{max} 3411, 2943, 2876, 1739, 1671, 1445, 1382, 1368, 1237, 1060, 1024, 954 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.40 (1 H, br, D_2O exchangeable), 1.72 (3 H, d, *J* 1.3 Hz), 1.66–1.76 (2H, m), 2.06 (3 H, s), 2.13 (2 H, t, *J* 7.6 Hz), 3.65 (2 H, t, *J* 6.3, 1.3 Hz), 4.59 (2 H, d, *J* 7.2 Hz), 5.38 (1 H, td, *J* 7.2, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 21.0, 30.5, 35.8, 61.3, 62.5, 118.7, 141.9, 171.2; HRMS (EI) calc. for $C_9H_{17}O_3$ $(M + H)^+$: 173.1178; found 173.1183.

(*E*)-1-Acetoxy-6-iodo-3-methylhex-2-ene 12

A solution of toluene-*p*-sulfonyl chloride (30.5 g, 0.16 mol) in CH_2Cl_2 (200 mL) was added dropwise to a solution of alcohol **11** (18.3 g, 0.11 mol) in pyridine (100 mL) at 0 °C, then the reaction mixture was stirred for 7 h at room temperature. The reaction mixture was cooled to 0 °C, then water was added, and the organic material was extracted with AcOEt. The combined organic layers were washed with a 1 M aqueous HCl solution, a saturated aqueous solution of $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration to provide the crude tosylate. Sodium iodide (79.8 g, 0.53 mol) was added to a solution of the tosylate in acetone (300 mL), then the reaction mixture was stirred for 24 h at room temperature. The acetone was removed under reduced pressure, a 5% solution of $Na_2S_2O_3$ was added to the residue. The organic material was extracted with *n*-hexane, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Purification by silica gel flash chromatography (*n*-hexane–ethyl acetate 5:1) furnished 26.6 g (89%) of iodide **12** as a colorless oil: IR (film) ν_{max} 2938, 2852, 1739, 1671, 1444, 1381, 1367, 1233, 1169, 1023, 955 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.71 (3 H, d, *J* 1.2 Hz), 1.90–2.00 (2 H, m), 2.06 (3 H, s), 2.15 (2 H, t, *J* 7.3 Hz), 3.16 (2 H, t, *J* 6.9 Hz), 4.59 (2 H, d, *J* 7.1 Hz), 5.40 (1 H, td, *J* 7.1, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.1, 16.5, 21.0, 31.2, 39.9, 61.2, 119.7, 140.1, 171.0; HRMS (EI) calc. for $C_9H_{15}O_2I$ $(M)^+$: 282.0117; found 282.0101.

(*E*)-6-Iodo-3-methylhex-2-en-1-ol 13

Potassium bicarbonate (2.6 g, 7.2 mmol) was added to a solution of iodide **12** (24.6 g, 94.4 mmol) in methanol (200 mL), then stirred for 2 h. Water was added and the organic material was extracted with ether. The combined organic layers were washed with a 1 M aqueous HCl solution, a saturated aqueous solution of $NaHCO_3$ solution, and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* after filtration. Silica gel flash chromatography (*n*-hexane–ethyl acetate 4:1) provided 20.8 g (92%) of alcohol **13** as a colorless oil: IR (film) ν_{max} 3333, 2934, 1667, 1441, 1428, 1382, 1218, 1167, 1001 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.68 (3 H, d, *J* 1.1 Hz), 1.90–2.05 (2 H, m), 2.14 (2 H, t, *J* 7.3 Hz), 3.17 (2 H, t, *J* 6.8 Hz), 4.16 (2 H, d, *J* 6.7 Hz), 5.47 (1 H, td, *J* 6.7, 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.1, 16.2, 31.3, 39.9, 59.3, 124.7, 137.6; HRMS (EI) calc. for $C_7H_{13}OI$ $(M)^+$: 240.0011; found 240.0008.

(*E*)-1-*tert*-Butyldimethylsilyloxy-6-iodo-3-methylhex-2-ene 14

TBDMSCl (4.4 g, 27.5 mmol) was added to a solution of alcohol **13** (6.6 g, 27.5 mmol) and imidazole (2.1 g, 30.2 mmol) in DMF (30 mL) at 0 °C. After stirring for 1 h, a saturated aqueous $NaHCO_3$ solution was added, the organic material was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Silica gel flash chromatography (*n*-hexane–ethyl acetate 9:1) provided 9.09 g (93%) of silyl ether **14** as a colorless oil: IR (film) ν_{max} 2955, 2929, 2896, 2886, 2857, 1671, 1472, 1463, 1445, 1383, 1361, 1255, 1218, 1167, 1101, 1066, 1006, 836 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.07 (6 H, s), 0.91 (9 H, s), 1.62 (3 H, d, *J* 1.1 Hz), 1.91–2.00 (2 H, m), 2.10 (2 H, t, *J* 7.1 Hz), 3.16 (2 H, t, *J* 6.9 Hz), 4.19 (2 H, d, *J* 6.1 Hz), 5.36 (1 H, td, *J* 6.1, 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, 6.3, 16.3, 18.4, 26.0, 31.4, 40.0, 60.2, 125.8, 134.8; HRMS (EI) calc. for $C_9H_{18}SiI$ $(M - C_4H_9)^+$: 297.0172; found 297.0160.

(*E*)-(6-*tert*-Butyldimethylsilyloxy-4-methylhex-4-enyl)triphenylphosphonium iodide 15

A solution of silyl ether **14** (9.1 g, 25.6 mmol) and triphenylphosphine (20.1 g, 76.8 mmol) in benzene (50 mL) was refluxed for 8 h. The solvent was removed *in vacuo* and the resulting residue was recrystallized with ether to afford 15.1 g (96%) of phosphonium salt **15** as colorless prisms: mp 135–136 °C; IR (KBr) ν_{max} 2953, 2927, 2855, 1668, 1587, 1484, 1472, 1462, 1438, 1253, 1112, 1060, 1033 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.03 (6 H, s, $SiCH_3 \times 2$), 0.85 (9 H, s, $C(CH_3)_3$), 1.52 (3 H, d, *J* 1.2 Hz, CH=CCH_3), 1.72–1.88 (2 H, m, $CH_2CH_2CH_2$), 2.36 (2 H, t, *J* 7.3 Hz, CH_2CH_2C=C), 3.64–3.75 (2 H, m, CH_2PPh_3), 4.13 (2 H, d, *J* 6.4 Hz, CH_2OTBDMS), 5.26 (1 H, td, *J* 6.3, 1.2 Hz, CH=C), 7.68–7.75 (6 H, m, Ph), 7.79–7.93 (9 H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, 16.4, 18.4, 20.4, 22.4 (d, *J* 49 Hz), 26.0, 39.2 (d, *J* 15 Hz), 60.0, 118.2 (d, *J* 85 Hz), 126.4, 130.6 (d, *J* 12 Hz), 133.7 (d, *J* 9 Hz), 134.9, 135.2; anal. calc. for $C_{31}H_{42}OSiPI$: C, 60.38; H, 6.87. Found: C, 60.19; H, 6.72%.

Bis(cyclohexyloxy)acetic acid ethyl ester 16b

Using a known procedure,[11] **16b** was obtained in 49% yield as a colorless oil (bp 138–142 °C; 3 mmHg): IR (film) ν_{max} 2979, 2935, 2858, 1758, 1742, 1466, 1451, 1381, 1371, 1358, 1342, 1284, 1262, 1247, 1205, 1193, 1159, 1114, 1095, 1065, 1049, 1024, 973, 926, 890, 862, 846 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.17–1.57 (15 H, m), 1.73–1.82 (4 H, m), 1.82–1.90 (4 H, m), 3.56–3.66 (2 H, m), 4.24 (2 H, q, *J* 7.2 Hz), 5.00 (1 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 24.1, 24.2, 25.6, 32.4, 32.9, 61.2, 75.5, 95.5, 168.8; HRMS (FAB) calc. for $C_{16}H_{29}O_4$ $(M + H)^+$: 285.2066; found 285.2047.

Bis(isopropyloxy)acetic acid ethyl ester 16c

Using a known procedure,[11] **16c** was obtained in 46% yield as a colorless oil (bp 103–105 °C; 22 mmHg): IR (film) ν_{max} 2977, 2936, 2907, 2877, 1758, 1743, 1467, 1383, 1371, 1323, 1285, 1208, 1183, 1108, 1046, 964, 912, 851, 790, 460 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.20 (6 H, d, *J* 6.1 Hz), 1.24 (6 H, d, *J* 6.1 Hz), 1.31 (3 H, t, *J* 7.1 Hz), 3.88–4.02 (2 H, m), 4.25 (2 H, q, *J* 7.1 Hz), 4.92 (1 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.3, 22.9, 61.3, 69.7, 95.9, 168.7; HRMS (EI) calc. for $C_{10}H_{21}O_4$ $(M + H)^+$: 205.1440; found 205.1455.

4,4-Bis(cyclohexyloxy)-3-oxobutyric acid ethyl ester 17b

1.0 M NaHMDS solution in THF (37 mL, 37 mmol) was added dropwise to a solution of ethyl acetate (3.6 mL, 37 mmol) in THF (70 mL) at −78 °C. After stirring for 30 min at the same temperature, a solution of **16b** in THF (30 mL) was added to

the reaction mixture, then the stirring was continued at rt for 3 h. A saturated aqueous NH_4Cl solution was mixed in, the organic material was extracted with ether, and the combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. The crude product was purified by flash column chromatography (hexane–ethyl acetate 20:1) to afford 5.53 g (67%) of **17b** as a colorless oil: IR (film) ν_{max} 2980, 2935, 2859, 1754, 1730, 1659, 1641, 1466, 1451, 1405, 1390, 1367, 1319, 1303, 1260, 1223, 1195, 1157, 1112, 1097, 1039, 970, 927, 889, 846, 812 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.15–1.55 (15 H, m), 1.65–1.95 (8 H, m), 3.40–3.60 (2 H, m), 3.65 (1.8 H, s), 4.19 (2 H, q, *J* 7.2 Hz), 4.77 (1 H, s), 5.04* (0.1 H, s), 5.48* (0.1 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.15, 14.24*, 23.8, 24.0, 25.5, 32.2, 32.5*, 32.9, 33.1*, 43.2, 60.3*, 61.2, 74.8*, 76.0, 89.7*, 95.6*, 99.5, 167.5, 173.4*, 199.2; HRMS (FAB) calc. for $C_{18}H_{30}KO_5$ $(M + K)^+$: 365.1730; found 365.1759.

4,4-Bis(isopropyloxy)-3-oxobutyric acid ethyl ester 17c

Using a similar procedure to that described above, compound **17c** was obtained in 79% yield from **16c** as a colorless oil (bp 98–100 °C; 4 mmHg): IR (film) ν_{max} 2977, 2936, 2907, 2879, 1754, 1731, 1660, 1468, 1406, 1383, 1371, 1322, 1306, 1262, 1226, 1183, 1141, 1121, 1101, 1037, 964, 944, 850, 821, 639, 574 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.17 (6 H, d, *J* 6.2 Hz), 1.23 (6 H, d, *J* 6.2 Hz), 1.27 (3 H, t, *J* 7.2 Hz), 3.63 (1.8 H, s), 3.81–3.95 (2 H, m), 4.19 (2 H, q, *J* 7.2 Hz), 4.69 (1 H, s), 4.96 (0.1 H, s), 5.46* (0.1 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2*, 22.2, 22.4*, 22.9, 23.0*, 43.2, 43.4*, 60.4*, 61.2, 69.1*, 70.3, 89.8, 96.0*, 99.8*, 167.5, 172.7*, 173.0*, 199.1; HRMS (EI) calc. for $C_{10}H_{17}O_4$ $(M - OEt)^+$: 201.1127; found 201.1135.

1,1-Bis(cyclohexyloxy)-6,10-dimethylundeca-5,9-dien-2-one 3b

Using a known procedure,[12] compound **3b** was obtained in 67% yield from **17b** as a colorless oil: IR (film) ν_{max} 2934, 2858, 1728, 1450, 1407, 1376, 1357, 1341, 1310, 1270, 1262, 1247, 1193, 1159, 1112, 1094, 1093, 1061, 1049, 1037, 1025, 965, 926, 889, 846 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.10–2.10 (33 H, m, $CH_3 \times 3$, $CH_2 \times 10$, and $CH_2C{=}C \times 2$), 2.26 (2 H, q, *J* 7.4 Hz, CH_2CH_2CO), 2.65 (2 H, t, *J* 7.4 Hz, CH_2CH_2CO), 3.47–3.56 (2 H, m, $(CH_2)_2CHO \times 2$), 4.66 (1 H, s, $CH(OCy)_2$), 5.08–5.13 (2 H, m, $CH{=}C \times 2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 17.7, 21.8, 23.9, 24.1, 25.6, 25.7, 26.7, 32.4, 33.0, 36.1, 39.7, 75.8, 100.5, 123.0, 123.1, 124.3, 131.4, 136.0, 207.0; HRMS (FAB) calc. for $C_{25}H_{42}O_3$ $(M)^+$: 390.3134; found 390.3161.

1,1-Bis(isopropyloxy)-6,10-dimethylundeca-5,9-dien-2-one 3c

Using a known procedure,[12] compound **3c** was obtained in 45% yield from **17c** as a colorless oil (bp 136–140 °C; 4 mmHg): IR (film) ν_{max} 2975, 2929, 2732, 1728, 1681, 1466, 1455, 1408, 1381, 1321, 1311, 1235, 1183, 1142, 672, 449 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.15 (6 H, d, *J* 5.9 Hz, $(CH_3)_2CH$), 1.23 (6 H, d, *J* 6.6 Hz, $(CH_3)_2CH$), 1.59 (3 H, s, $CH_3C{=}C$), 1.61 (3 H, s, $CH_3C{=}C$), 1.68 (3 H, s, $CH_3C{=}C$), 1.91–2.00 (2 H, m, $CH_2C{=}C$), 2.00–2.11 (2 H, m, $CH_2C{=}C$), 2.25 (2 H, q, *J* 7.3 Hz, CH_2CH_2CO), 2.63 (2 H, t, *J* 7.3 Hz, CH_2CH_2CO), 3.78–3.92 (2 H, m, $OCH(CH_3)_2 \times 2$), 4.58 (1 H, s, $CH(OPr^i)_2$), 5.04–5.15 (2 H, m, $CH{=}C \times 2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 17.7, 21.8, 22.3, 22.9, 25.7, 26.7, 36.0, 39.7, 100.8, 123.0, 124.3, 131.3, 136.0, 206.8; HRMS (FAB) calc. for $C_{19}H_{35}O_3$ $(M + H)^+$: 311.2586; found 311.2565.

(*E*,*Z*,*E*)-1-*tert*-Butyldimethylsilyloxy-7-diethoxymethyl-3,11,15-trimethylhexadecatetra-2,6,10,14-ene 18a

1.0 M Potassium *tert*-butoxide in THF solution (1.5 mL, 1.5 mmol) was added to a solution of phosphonium salt **15** (925 mg, 1.5 mmol) and 18-crown-6–CH_3CN (550 mg, 1.8 mmol) in 10 mL of THF at room temperature. After mixing for 1 h at this temperature, and then cooling to −78 °C, a solution of diethoxyketone **3a** (285 mg, 1.0 mmol) in THF was added, and stirring was continued for another 15 min. The reaction mixture warmed up to −45 °C, the stirring was continued for 24 h. Next, a saturated aqueous NH_4Cl solution was mixed in, the organic material was extracted with *n*-hexane, and the combined organic extracts were washed with a 1 M solution of $Na_2S_2O_3$ and water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Silica gel flash chromatography (*n*-hexane–ethyl acetate 40:1) provided 443 mg (89%) of **18a** as a colorless oil: IR (film) ν_{max} 2958, 2929, 2858, 1671, 1445, 1382, 1255, 1109, 1064, 1005 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.07 (6 H, s, $SiCH_3 \times 2$), 0.91 (9 H, s, $C(CH_3)_3$), 1.22 (6 H, t, *J* 7.0 Hz, CH_3CH_2O), 1.60 (6 H, s, $CH_3C{=}C \times 2$), 1.63 (3 H, s, $CH_3C{=}C$), 1.68 (3 H, s, $CH_3C{=}C$), 1.91–2.00 (10 H, m, $CH_2C{=}C \times 5$), 2.20–2.34 (2 H, m, $CH_2{=}C$), 3.38–3.50 (2 H, m, OCH_2CH_3), 3.55–3.68 (2 H, m, OCH_2CH_3), 4.19 (2 H, d, *J* 6.3 Hz, $CH_2OTBDMS$), 5.04–5.19 (3 H, m, $CH{=}C \times 2$ and $CH(OEt)_2$), 5.28–5.42 (2 H, m, $CH{=}C \times 2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.0, 15.2, 15.3, 16.1, 16.4, 17.7, 18.5, 25.7, 25.8, 26.0, 26.8, 27.5, 31.0, 39.8, 60.3, 62.1, 100.4, 124.5, 124.6, 124.8, 129.1, 131.2, 134.8, 136.4, 137.0; anal. calc. for $C_{30}H_{56}O_3Si$: C, 73.11; H, 11.45. Found: C, 72.87; H, 11.42%.

(*E*,*Z*,*E*)-1-*tert*-Butyldimethylsilyloxy-7-hydroxymethyl-3,11,15-trimethylhexadecatetra-2,6,10,14-ene 22

Aqueous acetic acid (50%, 2 mL) was added to a solution of acetal **18a** (93 mg, 0.19 mmol) in THF (3 mL) at room temperature and the reaction mixture was stirred for 5 min at this temperature. Water was added, the organic material was extracted with *n*-hexane, and the combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* after filtration. The resulting residue was dissolved in ethanol (2 mL) and then cooled to 0 °C. Sodium borohydride (14 mg, 0.37 mmol) was added to this solution and the reaction mixture was stirred for 30 min at this temperature. Acetone and water were added, the organic material was extracted with *n*-hexane, and the combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Purification by silica gel flash chromatography (*n*-hexane–ethyl acetate 7:1) furnished 55 mg (90%) of alcohol **22** as a colorless oil: IR (film) ν_{max} 3359, 2957, 2928, 2857, 1670, 1472, 1463, 1446, 1382, 1255, 1109, 1064, 1006 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.07 (6 H, s, $SiCH_3 \times 2$), 0.91 (9 H, s, $C(CH_3)_3$), 1.60 (6 H, s, $CH_3C{=}C \times 2$), 1.64 (3 H, s, $CH_3C{=}C$), 1.68 (3 H, s, $CH_3C{=}C$), 1.92–2.25 (12 H, m, $CH_2C{=}C \times 6$), 4.10 (2 H, d, *J* 4.9 Hz, CH_2OH), 4.18 (2 H, d, *J* 6.5 Hz, $CH_2OTBDMS$), 5.04–5.17 (2 H, m, $CH{=}C \times 2$), 5.23–5.33 (2 H, m, $CH{=}C \times 2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, 16.1, 16.5, 17.7, 18.5, 25.7, 25.9, 26.1, 26.8, 27.0, 35.1, 39.5, 39.7, 60.2, 60.3, 124.1, 124.4, 125.0, 127.9, 131.3, 135.4, 136.6, 138.9; HRMS (FAB) calc. for $C_{26}H_{48}O_2SiK$ $(M + K)^+$ 459.3061, found 459.3053. Anal. calc. for $C_{26}H_{48}O_2Si$: C, 74.22; H, 11.50. Found: C, 74.47; H, 11.64%.

Plaunotol 1

Toluene-*p*-sulfonic acid monohydrate (2 mg, 0.01 mmol) was added to a solution of alcohol **22** (53 mg, 0.13 mmol) in methanol (5 mL) and the reaction mixture was stirred for 15 min at room temperature. Water was added, the organic material was extracted with *n*-hexane, and the combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Flash chromatography (*n*-hexane–ethyl acetate 3:2) provided 38 mg (93%) of plaunotol **1** as a colorless oil: IR (film) ν_{max} 3322, 2966, 2923, 2857, 1669, 1445, 1381, 1006 cm^{-1}; ^1H NMR (270 MHz,

$CDCl_3$) δ 1.60 (6 H, s, CH_3C=C × 2), 1.69 (6H, s, CH_3C=C × 2), 1.93–2.28 (12 H, m, CH_2C=C × 6), 4.10 (2 H, s, CH_2OH), 4.14 (2 H, d, *J* 7.0 Hz, CH_2OH), 5.05–5.19 (2 H, m, CHC=C × 2), 5.28 (1 H, t, *J* 7.4 Hz, CHC=C), 5.40 (1 H, t, *J* 7.4 Hz, CHC=C); ^{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) calc. for $C_{20}H_{34}O_2$ $(M)^+$ 306.2559, found 306.2554.

General procedure: Wittig reaction

A solution of phosphonium salt **19** (1.5 mmol) and 18-crown-6–CH_3CN (1.8 mmol) in toluene (2 mL) was dried *in vacuo*, then it was dissolved in THF (9 mL). 1.0 M Potassium *tert*-butoxide solution in THF (1.5 mL, 1.5 mmol) was added to the solution at room temperature and the reaction mixture was stirred for 1 h at room temperature, and was then cooled to −78 °C. After a solution of diethoxyketone **20** (1.0 mmol) in THF was added, the mixture was warmed up to −40 °C and stirring was continued overnight. Next, a saturated aqueous NH_4Cl solution was added, and the organic material was extracted with ether. Combined organic extracts were washed with a 10% solution of $Na_2S_2O_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* after filtration. Triphenylphosphine oxide was removed by short silica gel flash chromatography, then the resulting crude product was deprotected.

Deprotection: Method A[17]

Amberlyst 15 (20 mg) was added to a solution of acetal (crude product of Wittig reaction) in aqueous acetone (5 mL), and the reaction mixture was stirred at room temperature. After the reaction was completed, the reaction mixture was filtered and evaporated. The residue was purified by flash column chromatography.

Deprotection: Method B[17]

Aqueous acetic acid (50%, 2 mL) was added to a solution of acetal in THF (3 mL) at room temperature and the reaction mixture was stirred for 5 min at this temperature. Water was added, the organic material was extracted with ether, and combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* after filtration. The residue was purified by flash column chromatography.

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