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A Highly Stereoselective Synthesis of Plaunotol and Its Thiourea Derivatives as Potent Antibacterial Agents against *Helicobacter Pylori*

Hiroshi Kogen,* Keiko Tago, Masami Arai, Emiko Minami, Kayoko Masuda and Toshiyuki Akiyama

Exploratory Chemistry Research Laboratories, Sankyo Co., Ltd., 2-58, Hiromachi 1-chome, Shinagawa-ku, Tokyo 140-8710, Japan

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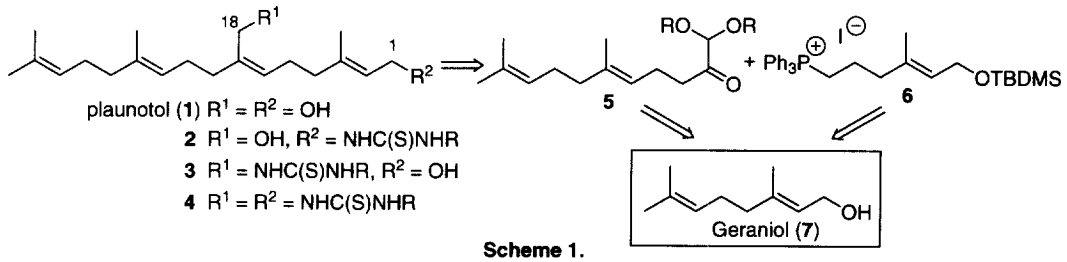
Abstract: Practical and highly stereoselective synthesis of diterpene alcohol, plaunotol (**1**) and its thiourea derivatives **2a**, **3a** and **4a**, *via* Z-selective Wittig reaction between α-acetal ketone **5** and phosphonium salt **6** and their antibacterial activity against *Helicobacter pylori* are described. © 1999 Elsevier Science Ltd. All rights reserved.

Since it was first discovered in human stomach tissue in 1983,[1] *Helicobacter pylori* has been demonstrated to be a major causative agent in gastritis,[2] gastric ulcer,[3] and duodenal ulcer.[4] The World Health Organization (WHO) recently labeled *H. pylori* as a class 1 carcinogen,[5] as chronic infection is known to be associated with the development of gastric adenocarcinoma, one of the most common types of cancer in humans.[6] Thus, an effective antibiotic therapy to eliminate *H. pylori* would reduce the risk of ulcer recurrence and gastric cancers. Recently, Koga *et al.*[7] reported that plaunotol (**1**), which is the most important component of Plaunoi, a Thai folk medicine, and which is a known antiulcer drug,[8] has antibacterial activities against *H. pylori*.

In order to develop an efficient antibacterial drug against *H. pylori*, we designed several plaunotol thiourea derivatives **2–4** (Scheme 1), which were expected to possess higher antibacterial activities against *H. pylori* than plaunotol (**1**). Since thiourea is known to have inhibitory activity against urease,[9] an enzyme that helps to cleave urea into ammonia, a substance that neutralizes stomach acid. This communication reports an effective synthetic route to plaunotol (**1**) and its thiourea derivatives **2–4** *via* highly stereoselective trisubstituted olefination and their antibacterial activities against *H. pylori*.



plaunotol (**1**) $R^1 = R^2 = OH$
2 $R^1 = OH$, $R^2 = NHC(S)NHR$
3 $R^1 = NHC(S)NHR$, $R^2 = OH$
4 $R^1 = R^2 = NHC(S)NHR$

Scheme 1.

Several groups[8,10] have succeeded in the total synthesis of **1**; however, the methods lack synthetic efficiency and/or stereoselectivity. Our retrosynthetic analysis is dictated by considerations of practicality and highly stereoselective trisubstituted olefination between α-acetal ketone **5** and Wittig reagent **6** (Scheme 1). Chemical highlights of this synthetic route include the use of a common and inexpensive reagent, commercially available geraniol (**7**), as the starting material for each of two intermediates, and the use of the highly stereoselective Wittig reaction, as a key step, which provides trisubstituted Z-allylic alcohol.

In 1980, Still *et al.* achieved the Z-selective Wittig reaction of unstabilized ylides and acyclic α-alkoxy ketones, which lead to protected trisubstituted allylic alcohols, and they reported that substitutions at α-carbon of

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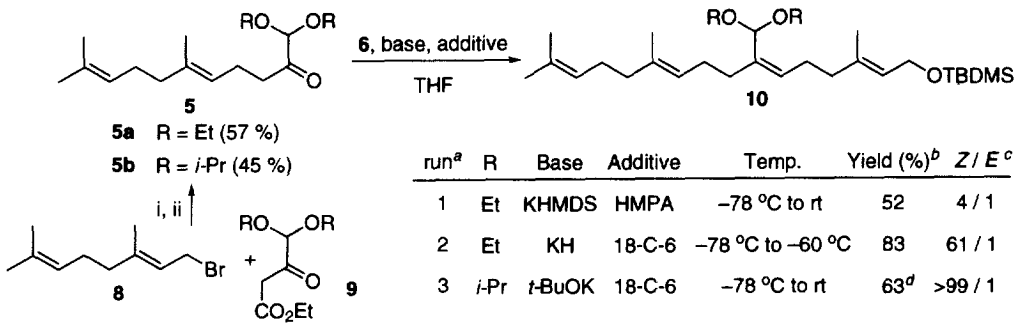
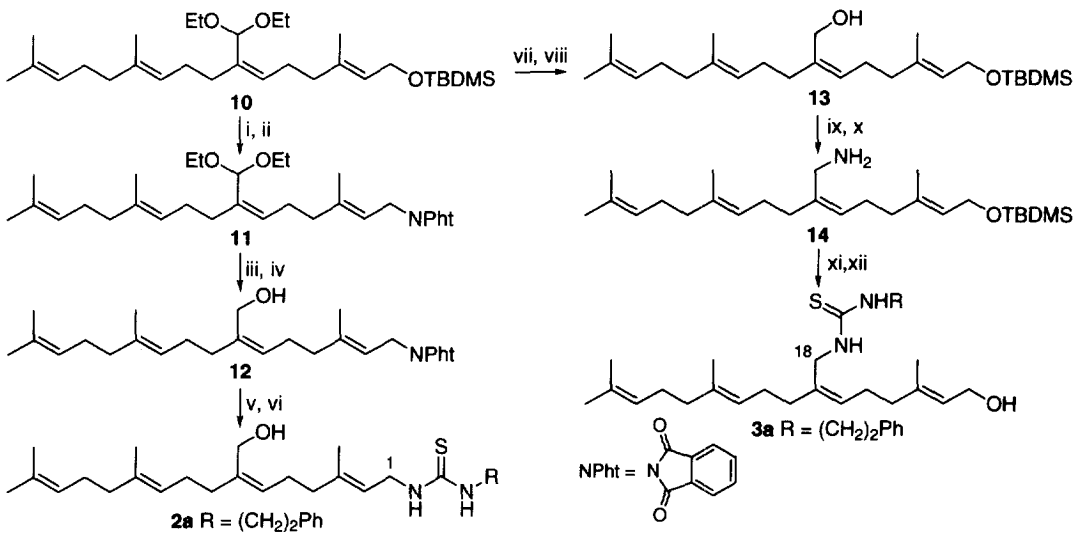
α -alkoxy ketone tended to improve stereoselectivity.[11] To obtain higher stereoselectivity, α-acetal ketone **2** was selected as a precursor of trisubstituted *Z*-allylic alcohol because **5** was expected to have bulkier α-substitutions than α-alkoxy ketone. In addition, it was also expected that **5** would be more readily prepared by alkylation of ethyl dialkoxyacetoacetate **9** than by the synthesis of corresponding α-alkoxy ketone.[10d]



run[a]	R	Base	Additive	Temp.	Yield (%)[b]	*Z* / *E* [c]
1	Et	KHMDS	HMPA	−78 °C to rt	52	4 / 1
2	Et	KH	18-C-6	−78 °C to −60 °C	83	61 / 1
3	*i*-Pr	*t*-BuOK	18-C-6	−78 °C to rt	63[d]	>99 / 1

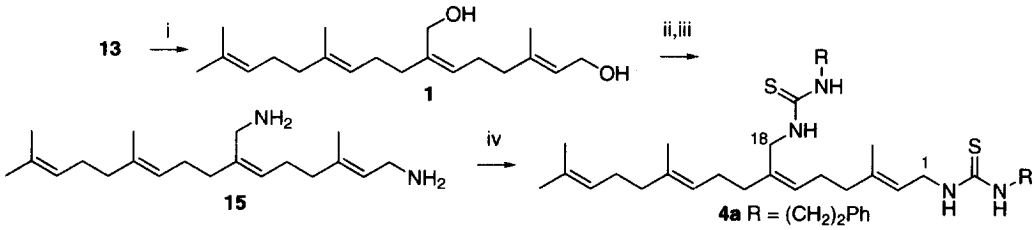
Scheme 2. *Reagents and conditions*: i, RONa, ROH, 0°C to room temp.; ii, KOH, H_2O, EtOH, reflux.
[a] One equiv. of **5**, 1.5 equiv. of **6**, 1.5 equiv. of base and 1.8 equiv. of additive were used in all runs except for run 1. For run 1, see ref. 11. [b] Isolated yield. [c] Determined by ^{1}H-NMR analysis of the aldehyde proton after deprotection of acetal. [d] Aldehyde yield after deprotection of acetal (2 steps).

O-TBDMS protected phosphonium iodide **6** was prepared from geraniol (**7**) according to the method reported for the synthesis of *O*-benzyl derivative.[10d] The second precursors, α-acetal ketones **5a**[12] and **5b**[13], were easily prepared from corresponding ethyl dialkylacetoacetate **9**[13] and geranyl bromide (**8**) (Scheme 2). The results of the *Z*-selective Wittig reaction between phosphonium salt **6** and α-acetal ketones **5** are summarized in Scheme 2. The combined use of KHMDS and HMPA, a method which has been reported by Still *et al.*,[11] gave poor results in terms of both yield and stereoselectivity (run 1). However, using 18-crown-6 ether (18-C-6) as an additive instead of HMPA, high *Z*-selectivity and excellent yield were observed (run 2). As we had anticipated, the bulkier α-acetal ketone exclusively yielded *Z*-olefin (run 3).[14]



Scheme 3. *Reagents and conditions*: i,TBAF, AcOH, THF, 99 %; ii phthalimide, PPh_3, DEAD, THF, 89 %; iii, 50 % AcOH aq., THF, r.t. 92 % ; iv, $Zn(BH_4)_2$, MeOH, 89 % ; v, *n*-$BuNH_2$, EtOH, 74 %; vi, $Ph(CH_2)_2NCS$, EtOH, 57 %; vii, AcOH–H_2O (1 : 1), THF, room temp.; viii, $NaBH_4$, EtOH, 0°C, 73% (2 steps); ix, phthalimide, PPh_3, DEAD, THF, 59 %; x, *n*-$BuNH_2$, EtOH, 68 %; xi, TBAF, AcOH, THF, 67 %; xii, $Ph(CH_2)_2NCS$, EtOH, quant.

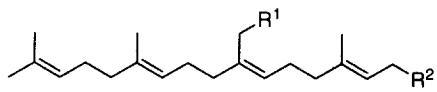
C-1 and C-18 thiourea derivatives were prepared from the common precursor **10** by the following procedure (Scheme 3). Deprotection of the *O*-TBDMS group of **10** and subsequent Mitsunobu reaction[15] with phthalimide yielded **11**. Treatment of the phthalimide derivative **11** with 50% aqueous acetic acid produced aldehyde, and then selective reduction of the aldehyde by treatment with zinc borohydride[16] in ether produced alcohol **12** in 89% yield. The alcohol **12** was treated with *n*-$BuNH_2$ to provide amine, and the amine was transformed to C-1 thiourea derivative **2a** by treatment with phenethyl isothiocyanate. Selective cleavage of acetal in **10** was achieved by treatment with 50 % aqueous acetic acid and THF for 5 min. and precursor **13** was converted to amine **14** by the same method as synthesis of C-1 derivatives. The amine **14** led to the corresponding C-18 thiourea derivative **3a**.



Scheme 4. *Reagents and conditions*: i, cat. *p*-TsOH, MeOH, room temp., 98 % ii, phthalimide, PPh_3, DEAD, THF, 0°C to room temp., 23 %; iii, $NH_2NH_2{\bullet}H_2O$, EtOH, reflux, 85 %; iv, $Ph(CH_2)_2NCS$, EtOH, 0°C to room temp, 68 %.

1 and C-1, 18-dithiourea derivatives were synthesized from **13** as shown in Scheme 4. Plaunotol (**1**) was synthesized readily from **13** by treating with a catalytic amount of *p*-TsOH in MeOH. The spectroscopic data of synthetic product **1** (^1H NMR and ^{13}C NMR) were identical with those of the authentic sample. **1** was subjected to Mitsunobu reaction with 4 equivalents of phthalimide and subsequent treatment with $NH_2NH_2{\bullet}H_2O$ to give diamine **15**. The diamine **15** was converted to corresponding C-1, 18-dithiourea derivative **4a**.

Table 1. Minimum inhibitory concentration (MIC) values (μg/ml) of plaunotol thiourea derivatives against three strains of *Helicobacter pylori*[a]



Compound	R^1	R^2	MIC (μg/ml) NCTC 11637	CPY 2052	No.7
1	OH	OH	12.5[b]	6.25[b]	6.25–12.5[b]
2a	OH	$NHC(S)NH(CH_2)_2Ph$	≤0.10	≤0.10	≤0.10
3a	$NHC(S)NH(CH_2)_2Ph$	OH	25	1.56	1.56
4a	$NHC(S)NH(CH_2)_2Ph$	$NHC(S)NH(CH_2)_2Ph$	6.25	0.78	6.25
Amoxycillin			0.025	0.05	0.10

[a] For detail on *in vitro* assay, see ref. 7. [b] Ref. 7

The antibacterial activities of these newly synthesized compounds against three strains of *H. pylori*—one standard strain (NCTC 11637) and two clinical isolates (CPY 2052 and No.7)—are summarized in Table 1. Among various types of plaunotol thiourea derivatives, C-1 derivatives showed higher activities than the other analogues, and compound **2a** showed the most potent antibacterial activity and antipeptic ulcer activity *in vivo*.[17] It is noteworthy that the activity of **2a** is comparable to that of amoxycillin, an antibiotic used in clinical therapy. Further work on these plaunotol thiourea derivatives and on more potent analogues is underway

to confirm the clinical utility of these antibacterial agents.

In summary, we have achieved high *Z*-selective trisubstituted olefination and developed a practical synthetic route to plaunotol (**1**) and its thiourea derivatives **2**–**4**. And among the derivatives we synthesized, C-1 *N*-phenethyl thiourea derivative **2a** showed the strongest antibacterial activity against *H. pylori*.

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