

MODIFICATION OF α -SANTONIN VII.

SYNTHESIS OF Z-4-GERMACRANOLIDE

Takeshi Shimizu, Masahiro Saitō, Yukinori Ohgoshi, Yasuo Fujimoto* and
Takashi Tatsuno

The Institute of Physical and Chemical Research
Wako-Shi, Saitama 351, Japan

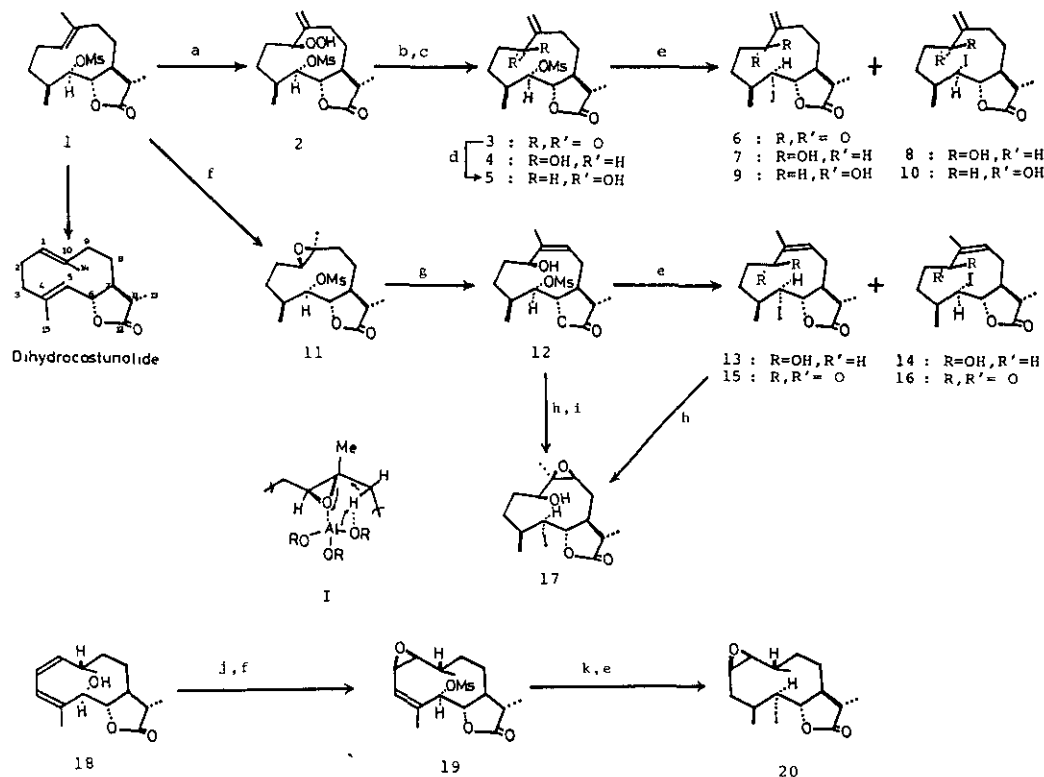
Abstract Z-4-germacranolides(heliangolides) were synthesized from α -santonin. The regio- and stereoselective introduction of Z-4-double bond into the cyclodecane ring required for the synthesis of naturally occurring heliangolide is performed in excellent yield via 5S-iodo derivatives of Z-9-germacranolides.

Recently, a number of cytotoxic and antitumor active germacranolides have been isolated from various species of compositae¹. Although there are some reports on the synthesis of E-4-germacranolide², the synthesis of Z-4-germacranolide(heliangolide) has not been reported yet to our knowledge. This may be attributed to the difficulties of the construction of Z-4-cyclodecene ring bearing γ -lactone at C-6, C-7 position.

In this communication, we wish to report the regio- and stereoselective introduction of Z-double bond into the C-4 position of germacranolide obtained from α -santonin. In our previous reports, we have reported the synthesis of (+)-deoxyvernolepin³, a bis-lactone antitumor sesquiterpenoid, and dihydrocostunolide⁴, a typical E-1(10), E-4-diene germacranolide. The latter was prepared from the mesylate(1) by the action of tetrabutylammonium oxalate. In spite of extensive efforts, treatment of 1 with DBU or any other organic bases did not give dihydrocostunolide. Thus, we prepared several 5-mesylates functionalized at various positions on the cyclodecane ring of germacranolides and converted them to the corresponding 5-iodo derivatives which were then submitted to elimination reaction in order to investigate the regio- and stereoselectivities on double bond formation.

Photooxygenation of 1⁵ with visible light in the presence of methylene blue as a sensitizer in ethanol produced a hydroperoxy derivative(2) in excellent yield[2 : ν (KBr) : 3400 cm^{-1} , $^1\text{H-nmr}$ (CDCl_3 , δ) : 5.29(2H, bs, H-14), 8.30(1H, bs, OOH), $^{13}\text{C-nmr}$ (CDCl_3 , δ) : 86.2(C-1), 116.1(C-14), 145.7(C-10)]. While treatment of 2 with acetic anhydride-pyridine gave a ketone(3)[ν (KBr) : 1670 cm^{-1}], reduction of 2 with triphenylphosphine afforded a 1S-hydroxy derivative(4)[ν (CHCl₃) : 3580 cm^{-1} , $^1\text{H-nmr}$ (CDCl_3 , δ) : 4.33(1H, J=6.5, 6.5 Hz, H-1)] in quantitative yield. Sodium borohydride-

cerous chloride reduction of 3 exclusively produced a 1R-hydroxy compound(5)[89% yield, $\text{ir}(\text{CHCl}_3)$: 3600 cm^{-1} , $^1\text{H-nmr}(\text{CDCl}_3)$: $4.10(1\text{H}, \text{m}, \text{H-1})$]. The compound 3, 4, 5 were transformed into the corresponding 5S- and 5R-iodides(6, 7, 9 and 8, 10) with sodium iodide in refluxing glyme(Entry 1, 2 and 3 in Table 1). Treatment of epoxy-mesylate(11)⁵ with aluminum isopropoxide in refluxing

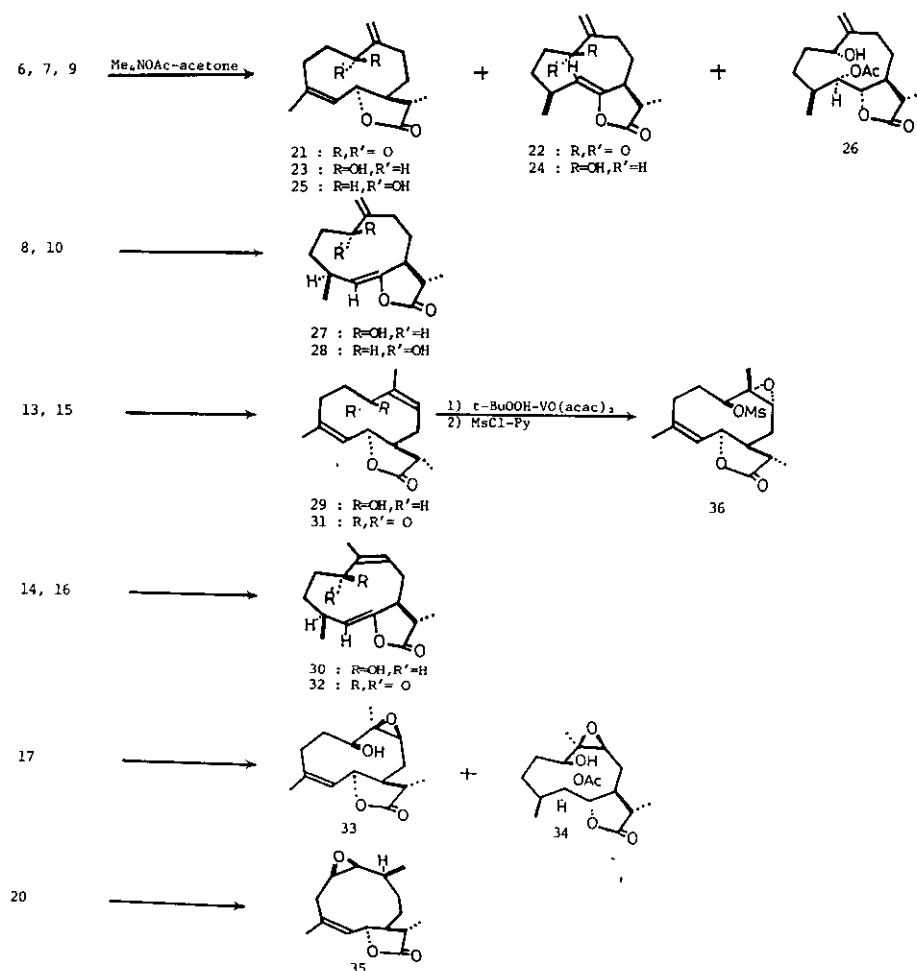


a) O_2 , hv, methylene blue, b) $\text{Ac}_2\text{O-Py}$, c) Ph_3P , d) $\text{NaBH}_4\text{-CeCl}_3$, e) NaI-glyme , f) m-CPBA
g) $\text{Al}(\text{O}^i\text{Pr})_3$, h) $\text{t-BuOOH-VO(acac)}_2$, i) NaI-acetone , j) MsCl-Py , k) $\text{H}_2\text{-PtO}_2$

Table 1. Reaction of 5-mesyloxy derivatives with NaI

Entry	Substrate	NaI/Substrate (mol)	Solvent	Time (h)	Product(Yield,%) 5S 5R
1	3	4.0	glyme	8	6(95)
2	4	4.0	glyme	4	7(51) 8(32)
3	5	4.0	glyme	5	9(70) 10(25)
4	11	2.0	acetone	48	13(77) 14(12)
5	12	2.0	acetone	48	13(77) 14(12)
6	dihydro der. of 19	3.0	glyme	96	20(85)

toluene quantitatively gave an allylic alcohol(12) which was then reacted with sodium iodide in refluxing acetone to yield 5S- and 5R-iodo derivatives(13 and 14)[13; 77% yield, mp 197-199°, ir (KBr): 3540 cm^{-1} , $^1\text{H-nmr}(\text{CDCl}_3)$: 3.96(1H, bd, $J=10.0$ Hz, H-5), 4.49(1H, dd, $J=10.0, 10.0$ Hz, H-6), 14; 12% yield, mp 178-180°, ir(KBr): 3550 cm^{-1} , $^1\text{H-nmr}(\text{CDCl}_3)$: 3.82(1H, dd, $J=8.5, 2.5$ Hz, H-5), 4.33(1H, dd, $J=12.5, 2.5$ Hz, H-6)]. When the iodide 13 or 14 was treated under the iodination conditions, each iodide gave the same equilibrium mixture of 13 and 14(5-6:1) which was also obtained directly from 11 by the same reaction conditions(Entry 4 and 5 in Table 1).



The alcohols 12, 13 and 14 were converted to the corresponding ketones(15)[$\text{PCC-CH}_2\text{Cl}_2$, rt, 15 min, quantitative yield, mp 169-172°], (16)[$\text{PCC-CH}_2\text{Cl}_2$, rt, 3.5 h, quantitative yield, mp 193-195°], and an epoxy-alcohol(17)[75% yield from 12, 80% yield from 13, $^1\text{H-nmr}(\text{CDCl}_3)$: 1.32(3H, s, H-14), 4.23(1H, bd, $J=4.0$ Hz, H-1)] respectively by the usual manner. Z-configuration of 9, 10-double bond of 13 was determined from the reaction mechanism of epoxide ring opening(I) with aluminum iso-

propoxide and vicinal ^{13}C - ^1H coupling constant ($^3J_{\text{C-14},\text{H-9}}=4.3\text{ Hz}$), and the configurations of C-5 of 13 and 14 were confirmed in comparison with the coupling pattern of H-5 and H-6 of the compound 11). The dienol(18)⁴ obtained from α -santonin was also transformed to a 5-iodo derivative(20) by successive treatment with the following reagents(i, MsCl-Py , ii, $m\text{-CPBA}$, iii, $\text{H}_2\text{-PtO}_2$, iv, NaI-glyme)[19; 86% yield, mp 157-159°, $^1\text{H-nmr}(\text{CDCl}_3)$: 4.1-4.5(2H, m, H-2 and H-6), 5.22(1H, d, $J=2.5\text{ Hz}$, H-5), 5.60(1H, dq, $J=5.5, 1.5\text{ Hz}$, H-3), 20; 65% yield, mp 105-107°, $^1\text{H-nmr}(\text{CDCl}_3)$: 3.52(1H, bd, $J=9.0\text{ Hz}$, H-5), 4.65(1H, bs, H-6)](Entry 6 in Table 1). After various attempts, we found that

Table 2. Reaction of 5-iodo derivatives with tetramethylammonium acetate(3.0 eq.) in acetone

Entry	Substrate	Time (h)	Product(yield,%)	$^1\text{H-nmr}(\text{CDCl}_3, \delta, \text{Hz})$						$J_{3,4}$	$J_{8,9}$
				H-14	H-15	H-1	H-5	H-6			
1	6	4.0	21(40)	5.78, 5.78	1.78		5.11	4.87	9.6	8.4	
			22(46)	5.58, 5.56	1.19		4.61				
2	7	4.0	23(77)	5.13, 5.22	1.81	3.91	5.26	5.04	10.0	10.0	
			24(17)	4.92, 5.05	1.16	4.30	4.78				
3	8	4.0	27(~100)	4.92, 5.28	0.90	4.12	5.05				
4	9	4.0	25(54)	4.98, 5.08	1.72	4.08	5.03	4.88	9.5	9.5	
			26(36)	5.08 5.33	0.90	4.08	5.08	4.60	3.0	3.0	
5	10	4.0	28(~100)	4.97, 5.40	0.91	4.17	5.08				
6	13	1.0	29(~100)	1.79	1.85	4.51	5.23	4.78	9.7	9.7	
7	14	1.0	30(95)	1.72	1.05	4.76	4.97				
8	15	4.0	31(~100)	1.97	1.84		5.23	4.72	10.0	10.0	
9	16	1.0	32(95)	1.88	1.03		4.96				
10	17	8.0	33(30)	1.16	1.86	4.27	5.31	4.96	9.0	9.0	
			34(48)	1.31	0.99	4.21	5.20	4.64	3.0	8.0	
11	20	70.0	35(93)	1.19	1.96		5.31	4.83	9.5	9.5	

the double bond formation from 5-iodogermacranolide is satisfactory carried out by heating a mixture of iodo compound and tetramethylammonium acetate in refluxing acetone in a nitrogen atmosphere.

The experiments summarized in Table 2 indicated that i) 5S-iodo- $\Delta^{10(14)}$ -, 5S-iodo-Z-9- and 5S-iodo-1,2-epoxy derivatives(7, 13, 15 and 20) produced the corresponding Z-4-germacranolides in excellent yields(Entry 2, 6, 8 and 11); ii) 5S-iodo- $\Delta^{10(14)}$ - and 5S-iodo-9,10-epoxy derivatives(6, 9 and 17) also give Z-4-germacranolides together with considerable amounts of E-5-olefin(22) or 5R-acetates(26 and 34)(Entry 1, 4 and 10); iii) 5R-iodo derivatives(8, 10, 14 and 16) exclusively afforded Z-5-germacranolides(27, 28, 30 and 32) in almost quantitative yields(Entry 3, 5, 7 and 9).

Z- configuration of the resulting Δ^4 -double bond was confirmed by the measurement of the difference spectrum⁷ which are enhanced by the nuclear Overhauser effect(H-15-H-5) and of ^{13}C - ^1H vicinal coupling constant($^3J_{\text{C-15},\text{H-5}}\sim 5\text{ Hz}$)(21, 23, 25, 33, 35 and 36).

The above experiments showed that the regio- and stereoselective introduction of Z-4-double bond into the cyclodecane ring required for the synthesis of naturally occurring Z-4-germacranolide

(heliangolide) is performed in excellent yield via 5S-iodo derivatives of Z-9-germacranolides.

Further studies on the synthesis of heliangolide type sesquiterpenoid are now in progress.

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* To whom correspondence should be addressed

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