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Synthetic Study of Akaterpin: Determination of the Relative Stereochemistry of the Upper Decalin Moiety with Disulfated Hydroquinone

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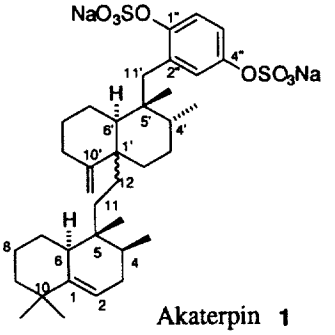
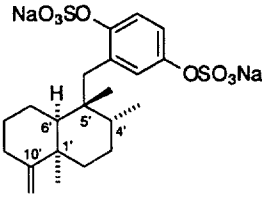
Abstract: *In order to establish the stereochemistry of akaterpin, a specific inhibitor of PI-PLC, synthesis of cis-decalin 2 and trans-decalin 3 was carried out. Comparison of NMR spectra of 2 and 3 with that of akaterpin indicated that the upper decalin has a cis-fused structure.*

Keywords: akaterpin; cis-decalin ; trans-decalin ; intramolecular Diels-Alder reaction; reductive alkylation.

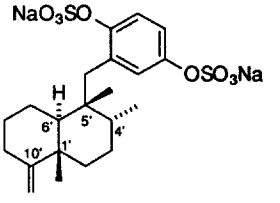
Akaterpin[2] (**1**) was isolated by Umezawa *et al.* in 1997 as a specific and most potent inhibitor of phosphatidylinositol-specific phospholipase C (PI-PLC). PI-PLC hydrolyzes PIP_2 into diacylglycerol (DG) and inositol-1,4,5-triphosphate (IP_3). Further, PI-PLC is considered to be the rate-limiting enzyme of PI turnover;[3] therefore, a selective inhibitor of PI-PLC is quite useful as a tool for the investigation of signal transduction. The planer structure of akaterpin containing two decalin rings and a hydroquinone disulfate moiety was determined, although the stereochemistry has remained unknown.[4] Moreover, even the relative configuration of the upper decalin has not yet been established. In order to determine the stereochemistry as well as to clarify the structure-activity relationships of akaterpin,[6] we became interested in the synthesis of *cis*-decalin **2** and *trans*-decalin **3**. Here we would like to describe the synthesis and representative NMR data of **2** and **3** which strongly indicate the *cis*-configuration for the upper decalin moiety of akaterpin.



Akaterpin **1**



2



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Our synthetic strategy for *cis*-decalin **2** and *trans*-decalin **3** is shown in Scheme 1. Thus, we envisaged that β,γ-unsaturated ketone **5** might undergo regio- and stereoselective alkylation under particular conditions to afford *cis*-decalin **4**. Unsaturated ketone **5**, in turn, might be derived from trienal **6** through an intramolecular Diels-Alder reaction.[7] For the synthesis of *trans*-decalin **3**, we expected that 4',5'-*trans* dimethyl derivative **7** might be obtained by hydrogenation of the known methylene *trans*-decalin **8**[8] derived from homologated Wieland-Miescher ketone **9**.

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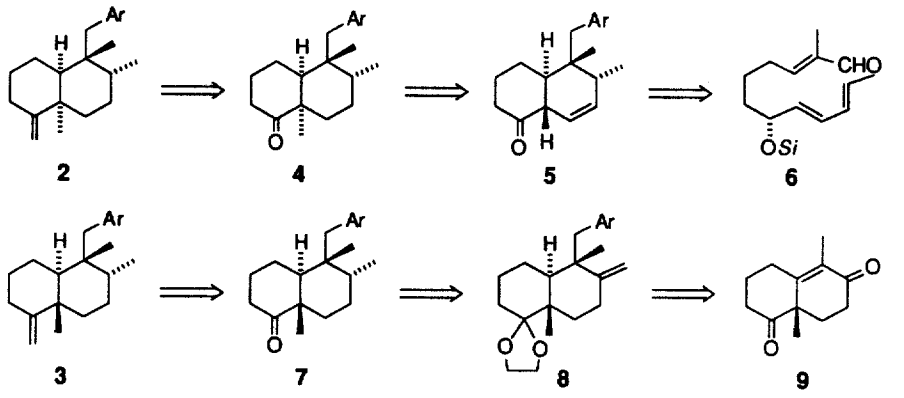
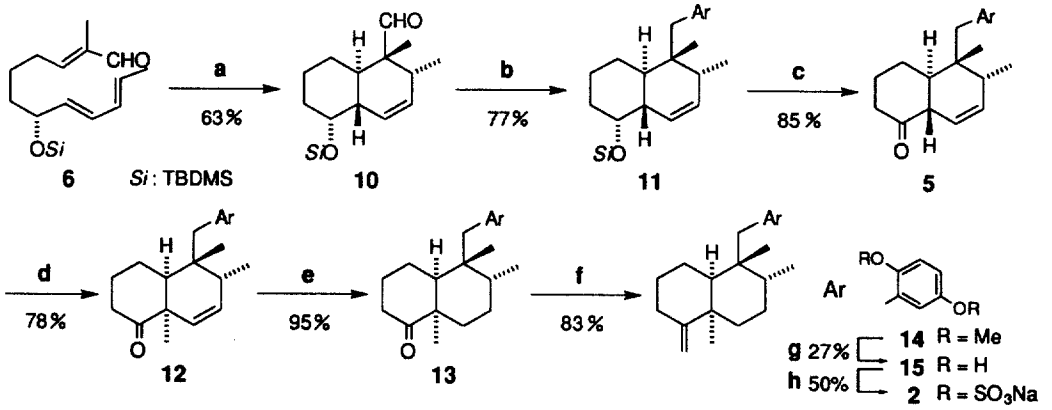
Scheme 1



The synthesis of the *cis*-decalin **2** is summarized in Scheme 2. According to the procedure reported by Marshall,[7] trienal **6**, prepared from 2,4-hexadienal in 6 steps, was treated with Et_2AlCl to obtain **10** in 63% yield. After introducing the aromatic moiety by Grignard reaction, benzylic alcohol was reduced with Et_3SiH and CF_3CO_2H[9] to give **11** in good yield. The TBDMS group in **11** was cleaved with HF, and the resulting alcohol was oxidized with PCC to obtain the key intermediate **5**. After a number of experiments, regio- and stereoselective methylation was accomplished by the treatment of **5** with $NaN[Si(CH_3)_3]_2$ as a base and MeI. It should be noted that the choice of base and the order of addition are critical in the present methylation.[10] Hydrogenation of **12** was next examined. Conventional hydrogenation using a Pd catalyst under H_2 atmosphere afforded **13** and its epimer at C-4'[11,12] (*ca* 5:1). Finally, we found that Raney-Ni hydrogenation proceeded without accompaniment of the undesirable epimerization, giving **13** in 95% yield. The *cis*-decalin structure of **13** was confirmed by N.O.E. between benzylic methylene and the newly introduced angular Me. Exomethylenation of **13** was carried out using CH_2Br_2-Zn-$TiCl_4$[13] to obtain **14**.

Scheme 2

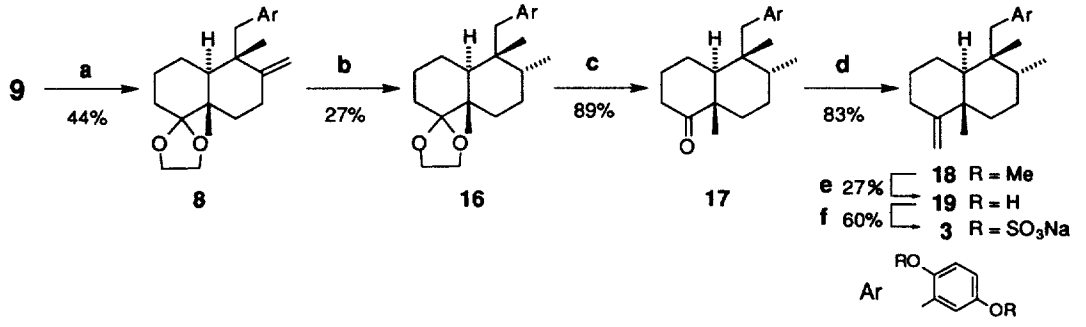


Reagents and conditions: **a** Et_2AlCl/CH_2Cl_2, -78 to -15 °C, 63%. **b** (i) Mg, 2,5-$(MeO)_2C_6H_3Br$/THF-Et_2O, 0 °C, 96%. (ii) Et_3SiH, CF_3CO_2H/CH_2Cl_2, r.t., 8 h, 80%. **c** (i) aq. HF/CH_3CN, r.t., 6 h, 89%. (ii) PCC, MS-3A/CH_2Cl_2, r.t., 0.5 h, 95%. **d** $NaN[Si(CH_3)_3]_2$, CH_3I/THF, r.t., 10 h, 78%. **e** Raney-Ni, H_2/EtOH, r.t., 12 h, 95%. **f** CH_2Br_2, Zn, $TiCl_4$/THF-CH_2Cl_2, r.t., 0.5 h, 83%. **g** (i) CAN/CH_3CN, r.t., 12 h, 36% (ii) $Na_2S_2O_4$/THF, r.t., 0.5 h, 76%. **h** SO_3•pyridine/pyridine, 60 °C, 3 h, then Na_2CO_3, 50%.

Demethylation of **14** was carried out with CAN[5b,8b,11], and the resulting quinone was reduced with $Na_2S_2O_4$ to give hydroquinone **15**. Finally, **15** was reacted with an SO_3•pyridine complex[14] in pyridine at 60°C, followed by treatment with Na_2CO_3 to complete the synthesis of *cis*-decalin **2**.

Scheme 3 shows the synthesis of *trans*-decalin **3**. Methylene *trans*-decalin **8** was prepared from Wieland-Miescher ketone analog **9** by the reported procedure.[8] Although hydrogenation of **8** was reported to produce the 4',5'-*cis* dimethyl isomer predominantly,[8] we attempted the hydrogenation of **8** under various conditions to achieve the reversal of stereoselectivity. However, the desired 4',5'-*trans* isomer **16** was best obtained in 27% yield by the treatment with Raney-Ni under H_2 atmosphere in EtOH. The major product (57% yield) was an isomeric 4',5'-*cis* isomer. After deprotection of ethylene ketal in **16**, the resulting ketone **17** was converted to *trans*-decalin **3** by a similar procedure to that for *cis*-decalin **2**.

Scheme 3



Reagents and conditions: **a** (i) 2-ethyl-2-methyl-1,3-dioxolane, D-CSA/ethylene glycol, 60 °C, 3 h, 79%. (ii) Li, NH_3, 2,5-$(MeO)_2C_6H_3CH_2Br$/THF, -35 °C, 3 h, 80%. (iii) Ph_3P-CH_3Br, *n*-BuLi/dioxane, 110 °C, 24 h, 70%. **b** Raney-Ni, H_2/ EtOH, r.t., 10 h, 27%. **c** 1*N* HCl/THF, r.t., 1 h, 89%. **d** (i) CH_2Br_2, Zn, $TiCl_4$/THF-CH_2Cl_2, r.t., 0.5 h, 83%. **e** (i) CAN/CH_3CN, r.t., 12 h, 37% (ii) $Na_2S_2O_4$/THF, r.t., 0.5 h, 75%. **f** SO_3•pyridine/pyridine, 60 °C, 3 h, then Na_2CO_3, 61%.

We were thus able to synthesize both *cis*-decalin **2** and *trans*-decalin **3** in a stereochemically unambiguous manner.[15] ^{1}H-NMR (500 MHz, CD_3OD) spectra of **2** and **3** were then compared with that of akaterpin. As shown in Table 1, differences in chemical shifts of the exomethylene protons (10'-CH_2) are most diagnostic. These data strongly indicate the *cis* configuration of the upper decalin of akaterpin.

Table 1

Position	Akaterpin	*cis*-decalin **2**	Δδ	*trans*-decalin **3**	Δδ
4'-Me	1.15 d	1.13 d	-0.02	1.17 d	+0.02
5'-Me	1.03 s	0.96 s	-0.07	0.89 s	-0.14
10'-CH_2	4.76 br s	4.75 br s	-0.01	4.52 br s	-0.24
	4.73 br s	4.67 br s	-0.06	4.46 br s	-0.27
11'	3.32 d	3.26 d	-0.06	3.34 d	+0.02
	2.40 d	2.53 d	+0.13	2.33 d	-0.07
3"	7.30 d (2.4 Hz)	7.31 d (3.0 Hz)	+0.01	7.34 d (3.0 Hz)	+0.04
5"	7.09 dd (2.4, 8.5 Hz)	7.08 dd (3.0, 8.9 Hz)	-0.01	7.08 dd (3.0, 8.9 Hz)	-0.01
6"	7.38 d (8.5 Hz)	7.38 d (8.9 Hz)	0.00	7.38 d (8.9 Hz)	0.00

In summary, we were able to synthesize both *cis*- and *trans*-decalins, **2** and **3**, and determine the relative stereochemistry of the upper decalin moiety of akaterpin. Studies toward total synthesis and determination of the absolute structure are now in progress, and will be reported in due course.

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References and Notes

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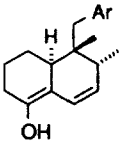
10. The desired **12** was obtained only by the following procedure; $NaN[Si(CH_3)_3]_2$ in THF was added to the solution of **5**, followed by the addition of MeI. Reverse addition of **5** into a THF solution of a base resulted in the isolation of dienol **A**, and the formation of **12** could not be detected on TLC. Use of other bases such as LDA, $KN[Si(CH_3)_3]_2$, *t*-BuOK was unsuccessful due to the isolation of dienol **A** or production of a complex mixture.



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11. The minor compound is an intermediate for the first enantioselective synthesis of (+)-arenarol by Terashima; Kawano, H.; Itoh, M.; Katoh, T.; Terashima. S. *Tetrahedron Lett.* **1997**, *38*, 7769-7772.
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15. *Cis*-decalin **2** was synthesized as a racemate, and the synthesis of *trans*-decalin **3** started from (+)-**9**.