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SYNTHESIS OF (-)-WARBURGANAL AND 4α-METHOXYCARBONYL CONGENER FROM l-ABIETIC ACID

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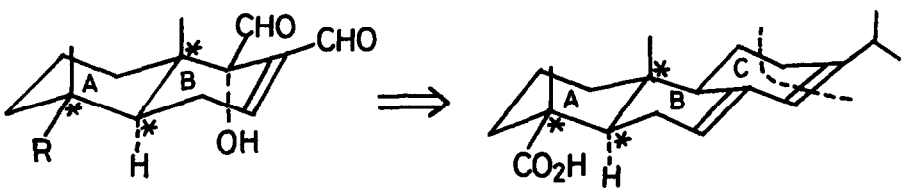
Summary: Natural warburganal (1b) and 4α-methoxycarbonyl congener (1a) were efficiently synthesized from l-abietic acid (2) by selective and oxidative cleavage.

Since its isolation in 1976[1], warburganal (1b) has attracted a great deal of synthetic study[2] because of their unique structure and interesting biological activity including insect antifeeding, plant growth regulation, cytotoxic, antimicrobial, molluscicidal, and anticomplemental properties. However, all of them lead to racemic warburganal and racemic congeners modified on the ring B. We wish to report here an efficient and first synthesis of natural warburganal (1b) and 4α-methoxycarbonyl congener (1a) first modified on the ring A starting from l-abietic acid[3] (2) easily available as a main component of pine resin. As shown in Scheme I, l-abietic acid was considered to be a good chiral synthon for the elaboration of warburganal skeleton, since the three chiral carbons of 2 can be utilized into 1 by selective and oxidative cleavage of the ring C as shown with a dotted line.

Scheme I



1a R=CO_2Me
1b R=Me

2 l-Abietic acid

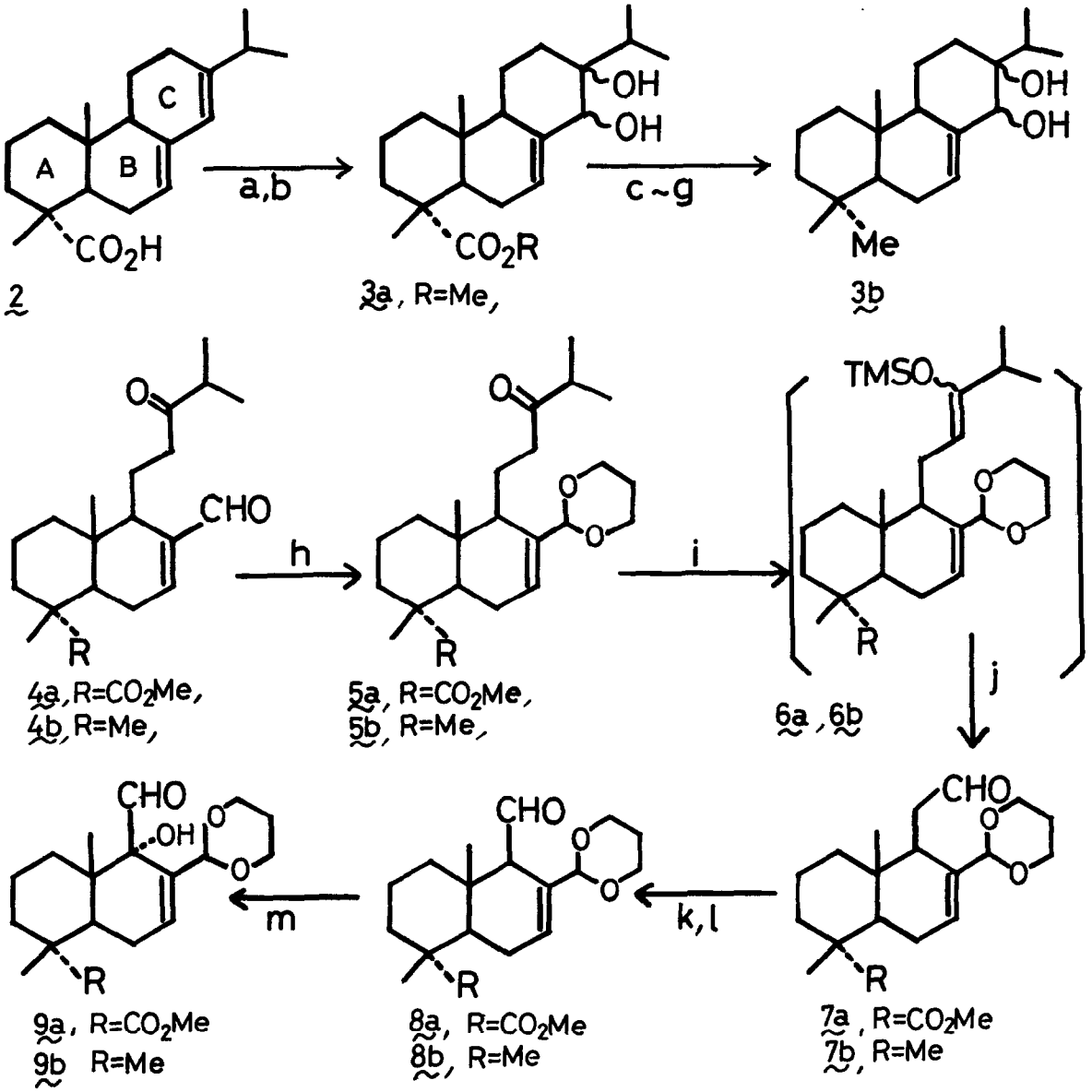
The synthesis of 4α-methoxycarbonyl congener 1a was first completed in the following way. (Scheme II) Regioselective osmylation on the double bond[4] of the ring C of 2 was remarkably improved by the application of Matteson's procedure[5], [OsO_4(catalytic)-$Me_3N{\to}O$(1.36 equiv)-pyridine(little) in aq. t-BuOH

under reflux, 20h] to afford a mixture of β- and α-diol acids 3 (R=H of 3a) in a total yield of 86%[6]. Since the stereochemistry of the glycols is destroyed in the next step, the diols were directly converted to the corresponding methyl ester 3a with CH_2N_2 quantitatively. The diol methyl esters 3a were subjected to oxidative cleavage with $Pb(OAc)_4$, affording a single product 4a (oil M^+, 348, $[\alpha]_D^{21}$+36.5°(c 1.31, $CHCl_3$) in 90% yield. The aldehyde group of 4a was selectively protected with trimethylene glycol to yield a ketoacetal 5a (oil, M^+ 406, $[\alpha]_D^{22}$+24.5° (c 1.22, $CHCl_3$) in 83% yield.

The regioselective cleavage of the ketone 5a is necessary for the most straightforward formation of an aldehyde group at C-9 position, a direct precursor to 1. A combination of silyloxyalkene formation followed by ozonolysis was considered to be best for that purpose. However, silyloxyalkene formation of 5a with LDA at -78°C in DME proceeded in non-regioselective manner, affording two expected products in about equal amount. The key step was solved by employing HMPA as a co-solvent in the reaction. Thus, the resulting reaction mixture was worked up with $NaHCO_3$ and extracted with AcOEt. The organic layer was directly subjected to selective ozonization of the silyloxyalkene linkage[7] in 6a at -78°C, after work up with dimethyldisulfide and chromatography on silica gel, an aldehyde 7a was obtained in 68% yield from 5a. (mp 97-98°C; $[\alpha]_D^{21}$ -28.3 (c 0.840, $CHCl_3$); M^+ 350) Further silyloxyalkene formation from the aldehyde 9 followed by ozonolysis gave the desired aldehyde 8a in 41% yield (mp 104-105°C; $[\alpha]_D^{26}$+29.2°(C 1.10, $CHCl_3$); M^+ 336), after the usual work up. Introduction of the tertiary hydroxy group at C-9 position was effected with MoO_5-Py-HMPA stereoselectively[2a] to afford 9a in 77% yield. Removal of the protective group of 9a with CH_3COCH_3-TsOH followed by chromatography on silica gel afforded 4α-methoxycarbonyl congener 1a in 82% yield (mp 104-105°C; $[\alpha]_D^{21}$ -132° (c 1.11, $CHCl_3$); M^+ 294).

Next, l-abietic acid (2) was successfully converted to natural warburganal (1b). Thus, gem-dimethyl β-glycol 3b[6] (mp 169-172°C; $[\alpha]_D^{20}$ -43.4° (c 0.894, $CHCl_3$; M^+ 306) was obtained in 50% overall yield by successive treatments of 3a (protection of the glycol 3a with DHP; reduction with LAH, COOMe→CH_2OH; oxidation with PCC, CH_2OH→CHO; removal of the THP group; and Wolff-Kishner reduction, NH_2NH_2/KOH, at 210°C). The diol 3b was now subjected to the same selective and oxidative cleavage as in the case of the congener 1a, affording 9b in 7 steps as shown in Scheme II (oxidation with $Pb(OAc)_4$, 3b→4b, 95% yield; protection of the aldehyde group, 4b→5b, 91% yield; selective silyloxyalkene formation and ozonolysis, 7b through 6b, 60% yield; further silyloxyalkene formation and ozonolysis, 7b→8b, 45% yield; treatment with MoO_5-Py-HMPA, 8b→9b, 96% yield). Finally, warburganal (1b) was obtained in 80% yield by removal of the protective group with CH_3COCH_3-TsOH, showing mp 107-108°C, M^+ 250, $[\alpha]_D^{21}$ -263° (c 0.380, $CHCl_3$), Rf 0.26 (C_6H_6: Et_2O=9:1). The synthetic warburganal was confirmed to be identical with natural sample in all respects including the optical rotation ($[\alpha]_D^{21}$ -260° (c 0.350, $CHCl_3$)).[9] The synthetic sequence developed here can also be adapted to the synthesis of muzigadial and other drimane sesquiterpenes[2a], either directly or by chemical modification of intermediates at varying levels

Scheme II



2

3a, R=Me,

3b

4a, R=CO_2Me,
4b, R=Me,

5a, R=CO_2Me,
5b, R=Me,

6a, 6b

7a, R=CO_2Me
7b, R=Me

8a, R=CO_2Me
8b, R=Me

9a, R=CO_2Me
9b R=Me

a)OsO_4, $Me_3N{\to}O$, b)CH_2N_2, c)DHP, TsOH, d)LAH, e)PCC, f)acetone-TsOH, g)NH_2NH_2, KOH, h)HO∿∿OH, TsOH, i)LDA, HMPA, TMSCl, Et_3N, j) O_3, Me_2S k)LDA, HMPA, TMSCl, Et_3N, l) O_3, Me_2S, m)LDA, $MoO_5{\cdot}Py{\cdot}$HMPA

of functional and structural developments. These studies and the biological study are currently under investigation.

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References and Notes

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4. Osmylation of 3 with OsO_4 in pyridine lead to preferential attack on the double bond of the ring C, but the product was shown to be a complex mixture to afford the diol 3 in about 40% yield. B. E. Cross and P. L. Myers, J. Chem. Soc. (C), 1969, 711.
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6. The ratio of β- and α-glycols was determined to be 11 to 1 by column chromatography on silica gel, and characterization of each diol was carried out of the methyl ester 5.[4]
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8. All compounds in warburganal and the congener series were purified by column chromatography on silica gel and well characterized by spectroscopic analysis and combustion data. 4b; oil, $[\alpha]_D^{25}$-4.38° (c 0.866, $CHCl_3$), M^+ 304: 5b; oil, $[\alpha]_D^{25}$-6.14° (c 1.41, $CHCl_3$), M^+ 362: 7b; oil, $[\alpha]_D^{25}$-68.4° (c 1.91, $CHCl_3$); 8b, oil, $[\alpha]_D^{25}$+13.4° (c 1.04, $CHCl_3$), M^+ 292: 9b; mp 92-93°C, $[\alpha]_D^{25}$-53.2° (c 0.596, $CHCl_3$).
9. This sample was supplied by Prof. Nakanishi and purified by column chromatography on silica gel, and the optical rotation of the purified material was determined on a JASCO DIP-140 polarimeter.

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