

TOTAL SYNTHESIS OF (+)-KAURENE AND (+)-PHYLLOCLADENE  
FROM 1-ABIETIC ACID<sup>\*1</sup>

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(Received in Japan 6 March 1973; received in UK for publication 29 March 1973)

The intramolecular carbenoid reaction of diazoketones and subsequent cleavage of the resulting cyclopropyl ring have been used as one of the methods for the formation of the bicyclo[3.2.1]octane system.<sup>1</sup> The structural system is an indispensable skeleton of the tetracyclic diterpenes. Only a similar method was used in the diterpene synthesis.<sup>1e</sup>

Now, the typical tetracyclic diterpenes, (+)-kaurene (18) and (+)-phyllocladene (19) have been synthesized by the use of this method on 1-abietic acid (1), a major component of pine rosin.

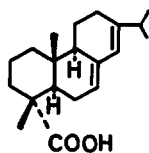
In order to make the foothold for the bridge-formation, isopropyl side chain of 1-abietic acid (1) was converted to a carboxylic group of (2).<sup>2</sup> Reduction of the C-ring (Li-11q. NH<sub>3</sub>-EtOH) and subsequent methylation (CH<sub>2</sub>N<sub>2</sub>) of the diacid (2) gave a mixture (3) of stereoisomers at C-12 in 1:1 ratio (t<sub>R</sub>(1.5% OV-17 on Shimalite W (100-120 mesh), 4 mm X 2 m, 220°) = 7.7 and 8.8 min) (GC-mass of both peaks: M<sup>+</sup> = 334; δ(mixture): 3.60 (s, COOMe), 1.13, 0.96 (s, Me)). The diester<sup>\*2</sup> (3) was partially hydrolyzed (KOH-H<sub>2</sub>O-EtOH) to give the half ester (4) (δ: 11.65 (broad s, COOH), 3.62 (s, COOMe), 1.14, 0.97 (s, Me)).

The subjective ring formation was carried out on the half ester (4). The

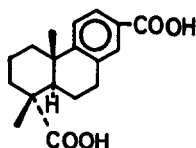
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\*1 New compounds indicated by mp gave satisfactory analytical values. NMR (60 MHz, internal reference) and IR spectra were measured in CCl<sub>4</sub>.

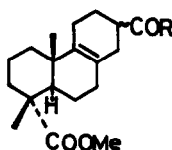
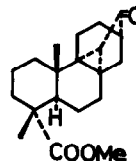
\*2 The compounds (3), (4), (5), and (6) were used as the stereoisomeric mixture in the reaction.



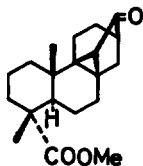
(1)



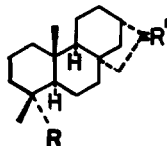
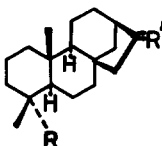
(2)

(3) R=OMe (4) R=OH  
(5) R=Cl (6) R=CHN<sub>2</sub>

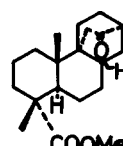
(7)



(8)

(9) R=COOMe, R'=O  
(12) R=COOMe, R'=OCH<sub>2</sub>CH<sub>2</sub>O  
(14) R=CH<sub>2</sub>OH, R'=OCH<sub>2</sub>CH<sub>2</sub>O  
(16) R=CH<sub>3</sub>, R'=O  
(18) R=CH<sub>3</sub>, R'=CH<sub>2</sub>(10) R=COOMe, R'=O  
(13) R=COOMe, R'=OCH<sub>2</sub>CH<sub>2</sub>O  
(15) R=CH<sub>2</sub>OH, R'=OCH<sub>2</sub>CH<sub>2</sub>O  
(17) R=CH<sub>3</sub>, R'=O  
(19) R=CH<sub>3</sub>, R'=CH<sub>2</sub>

(11)



diazoketone (6), produced from (4) via the acid chloride (5) (SOCl<sub>2</sub> and then CH<sub>2</sub>N<sub>2</sub>), was reacted as the intramolecular carbenoid (CuSO<sub>4</sub>, cyclohexane, reflux, 28 hr). The reaction mixture was chromatographed to separate two cyclopropyl ketones; (7), mp 114~116° (δ(100 MHz): 3.60 (s, COOMe), 1.18, 1.12 (s, Me), ν<sub>max</sub>: 1725 cm<sup>-1</sup>), and (8), mp 161~163° (δ(100 MHz): 3.62 (s, COOMe), 1.06, 1.05 (s, Me), ν<sub>max</sub>: 1725 cm<sup>-1</sup>), in about an equal ratio.

The stereochemistry and the cleavage mode of the cyclopropyl ketones attracted our attention. The latter ester (8) was cleaved ((i) Li-liq. NH<sub>3</sub>-THF-tert. BuOH, (ii) Jones reagent-Me<sub>2</sub>CO, and (iii) CH<sub>2</sub>N<sub>2</sub>) to give only one product (10), mp 170~171° (δ: 3.62 (s, COOMe), 1.12, 0.94 (s, Me), ν<sub>max</sub>: 1745, 1730 cm<sup>-1</sup>, ORD (dioxane, c = 8.5 X 10<sup>-4</sup>): [α]<sub>D</sub>(nm) = +2000°(321), +1130°(313), +1250°(309), 0°(304), -2050°(280)). However, similar treatment of the former (7) gave two isomers; (9), mp 138~141° (δ: 3.61 (s, COOMe), 1.13 (s, Me X 2), ν<sub>max</sub>: 1745, 1730 cm<sup>-1</sup>, ORD (dioxane, c = 1 X 10<sup>-3</sup>): [α]<sub>D</sub>(nm) = -1150°(324), -435°(315), -500°(312),

0° (308), +1700° (280)), and (11), mp 133~135° ( $\delta$ : 3.62 (s, COOMe), 1.18, 1.03 (s, Me),  $\nu_{\max}$ : 1725  $\text{cm}^{-1}$ ) in 5:1 ratio.

IR spectra show that (9) and (10) have a 5-membered and (11) has a 6-membered ring ketone. The stereochemistry of the 5-membered ring of (9) and (10) was assumed by comparison of their ORD ((-)-Cotton effect for (9), and (+)-Cotton effect for (10)) with norketones (16) of (+)-kaurene and (17) of (+)-phyllocladene, respectively.

In order to ascertain the structural assumption, the oxo-esters (9 and 10) were chemically converted to the respective natural diterpenes (18 and 19) having a rigid structure. The oxo groups of these esters (9 and 10) were protected as the respective ketal; (12), mp 139~140°, and (13), mp 136~137°. Subsequently, the 4-methoxycarbonyl groups of (12) and (13) were converted to methyl groups ((I)  $\text{LiAlH}_4$  and (II) (i)  $\text{CrO}_3\text{-Py-CH}_2\text{Cl}_2$ , (ii)  $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ ,  $\text{KOH}$ -diethylene glycol, and (iii) 10%  $\text{HCl-Me}_2\text{CO}$ ) to give the respective norketones; (16), mp 114~115° ( $\delta(\text{CDCl}_3)$ : 1.08, 0.87, 0.83 (s, Me),  $\nu_{\max}^{\text{KBr}}$ : 1746  $\text{cm}^{-1}$ ) and (17), mp 91.5~97° ( $\delta(\text{CDCl}_3)$ : 0.87 (s, Me X 2), 0.81 (s, Me),  $\nu_{\max}^{\text{KBr}}$ : 1744  $\text{cm}^{-1}$ ) via the corresponding alcohols; (14), mp 111.5~113°, and (15), mp 128.5~129.5°. Physical constants (mixed mp, IR, and NMR spectra) of the oxo compounds (16 and 17) were completely identical with those of the authentic samples<sup>3</sup> synthesized from the natural (+)-kaurene (18) and (+)-phyllocladene (19)<sup>\*3</sup>, respectively. Since the syntheses of the natural products (18 and 19) from the respective norketones (16 and 17) had been published<sup>4</sup>, a chemical conversion from 1-abietic acid (1) to (18) and (19) and, accordingly, their total syntheses have been accomplished.

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\*3 Authors thank Prof. A. Yoshikoshi, Tohoku University, and Prof. M. Kitadani, Kobe University, for the donation of the valuable samples (18 and 19)

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