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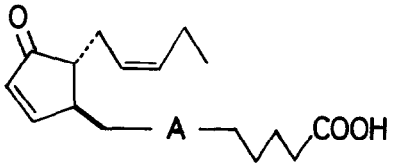
TOTAL SYNTHESIS OF (±)-DICRANENONES, NOVEL CYCLOPENTENONYL FATTY ACIDS

Kunikazu Sakai,* Tamotsu Fujimoto, Mitsuo Yamashita, and Kiyosi Kondo
Sagami Chemical Research Center
Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan

Abstract: Dicranenones **1** and **2** have been synthesized from the intermediate **12**, which was either derived from methyl jasmonate **7** or prepared by the intramolecular ring formation of diazo compound **14**.

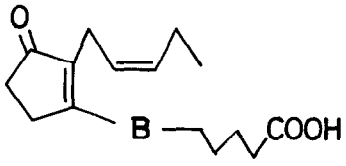
Dicranenones (**1-6**) are a series of cyclopentenonyl fatty acids isolated from Japanese mosses.[1] Although **1** and **2** have been isolated on the basis of antimicrobial activities,[2),3] they are expected to have other useful biological activities, as they are structurally similar to jasmonoid, and prostanoid. However, as only a small amount of them could be collected from mosses, establishment of an easy synthetic method is required in order to supply a sufficient amount of samples for further biological activity tests. We wish to report here a practical synthesis of dicranenone A's (**1** and **2**).

In designing the synthetic routes, the cyclopentanone **12** was considered to be a key intermediate , because it would easily be converted to **1** and **2** by regiospecific introduction of a double bond in the five-membered ring, followed by transformation of the hydroxymethyl group in lower side chain to carboxylic acid. The cyclopentanone **12** could be obtained by two routes. First, preparation of **12** from a structurally similar natural perfume, methyl jasmonate (**7**), will be described. The protected aldehyde **8** was obtained from **7** in three steps, by protection of ring carbonyl group as ethylene ketal (ethylene glycol/p-TsOH, benzene, reflux: 70%), hydride reduction ($LiAlH_4$, ether, reflux: 70%), and oxidation of the resultant alcohol to the aldehyde **8** (pyridinium chlorochromate/$NaOCOCH_3$, CH_2Cl_2, rt; 84%). Elongation of six-



1 A = C≡C

2 A = CH_2-CH_2



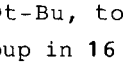
3 B = CH_2-C≡C

4 B = CH=C=CH

5 B = CH_2-CH=CH(Z)

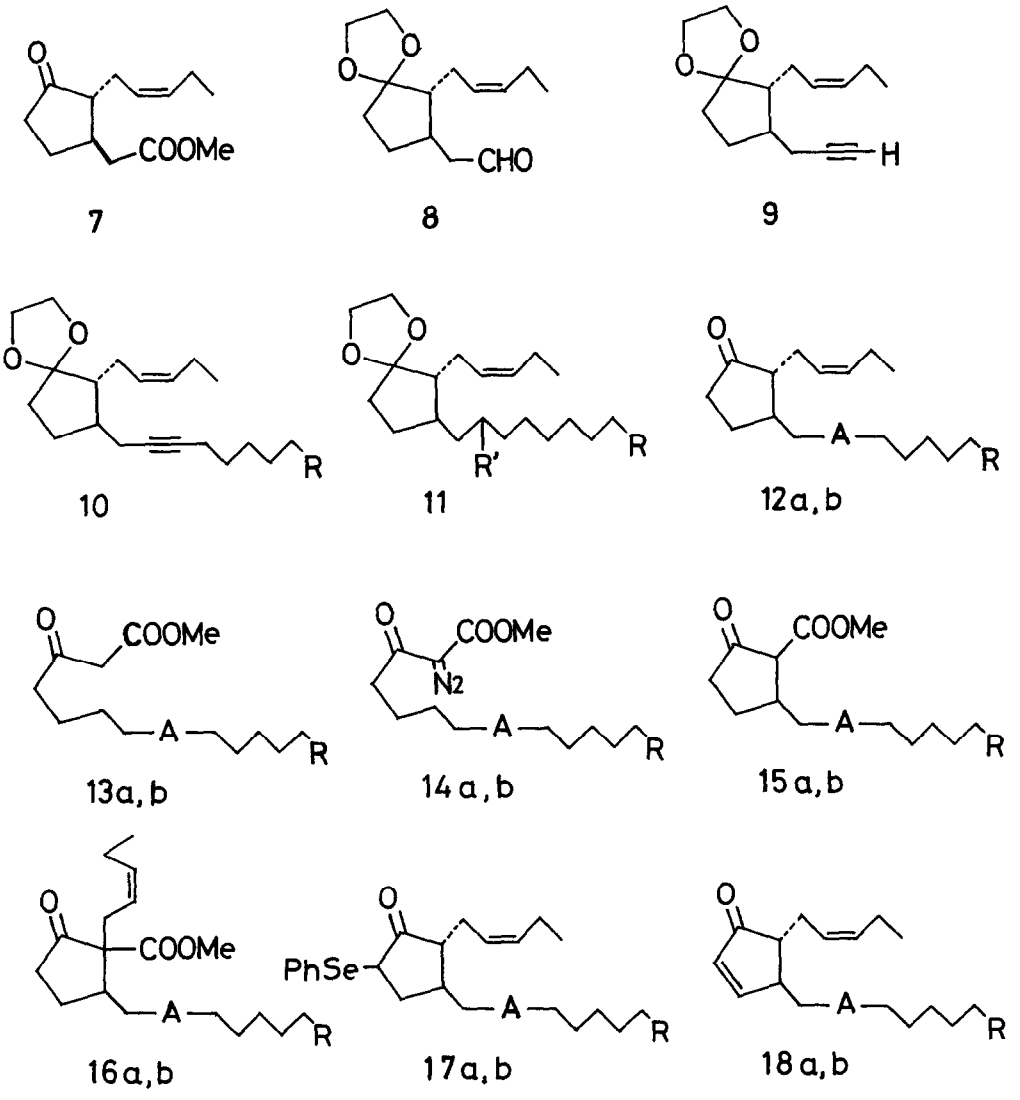
6 B = CH_2-CH_2-CH_2

carbon chain including an acetylenic bond was conducted in two stages. Firstly, **8** was condensed with bromomethylene triphenylphosphonium ylide to afford the one-carbon extended acetylene **9** ($Ph_3PCH_2Br \cdot Br$/2eq. KOt-Bu, THF, -78°C: 65%).[5] Unexpectedly, the terminal acetylenic carbon in **9** was considerably inert toward alkylation. For example, alkylation with protected 5-hydroxypentyl halides or sulfonates under various conditions failed to afford the desired compound. The only one successful route to **10** from **9** was the reaction with tri[5-(2-tetrahydropyranyloxy)pentyl]borane followed by oxidation with iodine (i n-BuLi, THF, 0°C; ii $B[(CH_2)_5OTHP]_3$, THF; iii I_2, ether, -78°C: 61%).[6),7] On the other hand, elongation of saturated six-carbon unit could smoothly be carried out by treatment of **8** with a Grignard reagent to give **11** (R'=OH) ($BrMg\text{-}C_6H_{12}OTHP$, THF, reflux: 85%), sulfonation with methanesulfonyl chloride to afford **11**($R'=SO_3CH_3$) (CH_3SO_2Cl/pyridine, CH_2Cl_2, rt: 83%), and then, reductive removal of sulfonate to produce **11**(R'=H) ($LiAlH_4$, ether, reflux: 84%). Deprotection of carbonyl and hydroxy groups in **10** and **11**(R'=H) and reprotection gave **12a** and **12b**,[8] respectively (i $CH_3COOH\text{-}H_2O\text{-}THF$= 6.5:2.5:1.0, 45°C; ii dihydropyran/p-TsOH, CH_2Cl_2, rt: 80% from **10** and 84% from **11**(R'=H)).

An another route to **12** was achieved as follows. The β-ketoester **13**, prepared by alkylation of the dianion of acetoacetic acid methyl ester with C_{10}-chain bromide[9] (2eq. $\ominus CH_2COCH\ominus COOMe$, THF-HMPA, 0°C: **13a** 72%, **13b** 71%), was used as the starting material. Diazo transfer to active methylene in **13** by the reaction with tosyl azide afforded the diazo β-ketoester **14**, and ring formation by decomposition of **14** using rhodium(II) acetate[10] as a catalyst provided the cyclopentanone **15** (i $p\text{-}TolSO_2N_3/NEt_3$, CH_3CN, rt; ii 1-3%$Rh_2(OAc)_4$, CH_2Cl_2, rt: **15a** 74%, **15b** 87%).[11] Introduction of 2(Z)-pentenyl group into **15** was most effectively performed with potassium t-butoxide as a base to give **16** (1.5eq.  /KOt-Bu, toluene, reflux: **16a** 68%, **16b** 85%). Removal of the methoxy carbonyl group in **16** was achieved under mild conditions using sodium cyanide (2eq. NaCN, HMPA, 75°C: **12a** 67%, **12b** 75%).[12] The resulting products **12a** and **12b**[8] were completely identical with the products derived from methyl jasmonate.

Final steps toward dicranenones were performed as follows. Regioselective phenylselenylation[13] of **12** afforded **17** (i LDA, THF, -78°C; ii PhSeCl) and oxidation of the crude selenide **17** with hydrogen peroxide induced smooth removal of phenylselenic acid yielding **18** with a double bond on the required position in the ring (35% H_2O_2/pyridine, CH_2Cl_2, rt: **18a** 55% from **12a**, **18b** 65% from **12b**). After removal of THP-group, **18** was converted to dicranenone A's (**1** and **2**) by oxidation with Jones reagent (i p-TsOH, CH_3OH, rt; ii $CrO_3\text{-}H_2SO_4$, acetone, -20°C: **1** 82%, **2** 94%). The synthesized racemic dicranenone A (**1**) and tetrahydrodicranenone A (**2**) were confirmed to be identical with natural products, by comparison of their NMR, IR, and MS spectra, as well as their retention times on HPLC.

Pharmacological activity tests of the obtained racemic products showed



7 8 9

10 11 12a,b

13a,b 14a,b 15a,b

16a,b 17a,b 18a,b

a, A=C≡C ; b, A=CH_2-CH_2 : R=OTHP : R'=OH, OMs or H

that they were moderately active as an antihypertensive agent.

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References and notes

1) Dicranenone A (1) was isolated from Dicranum Scoporium, Dicranum japonicum, and Dicranum scabrum.[2),3)] Tetrahydrodicranenone A (2) was isolated from Leucobryum scabrum[3)] and also from a kind of chrysathemum,

Chrumolaema morii.[4] Dicranenone B (**3**) was isolated from Dicranoloma scabrum and Dicranum majus.[3] Dicranenone B_1 (**4**) was isolated from Dicranum japonicum and Dicranoloma scabrum.[2),3] Dihydrodicranenone B (**5**) was isolated from Dicranoloma scabrum.[3] tetrahydrodicranenone B (**6**) was isolated from Leucobryum scabrum.[3]

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8) Compound **12a:** δ 0.96(t,3H), 1.25-2.60(m), 3.26-4.10(m), 4.59(bs,1H), 5.38(m,2H); νcm^{-1} 3020, 2950, 2880, 1740, 1140, 1120, 1075, 1030, 730; m/z 360(1.7%,M^+), 277(46.4%), 276(82.0%), 231(10.9%), 208(100%), 189(14.0%), 151(88.7%).
Compound **12b:** δ 0.95(t,3H), 1.10-2.40(m), 3.24-4.06(m), 4.54(bs,1H), 5.08-5.56(m,2H); νcm^{-1} 3020, 2925, 2850, 1740, 1460, 1450, 1200, 1150, 1070, 1030, 960, 730; m/z 364(7.0%,M^+), 280(36.6%), 260(13.7%), 212(95.8%), 151(100%),137(6.2%).

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