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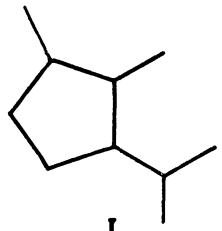
A SYNTHESIS OF (±)-IRIDOMYRMECIN FROM THE BIOGENETIC PRECURSOR

Yasuji YAMADA*, Hidenao SANJOH, and Kazuo IGUCHI
Tokyo College of Pharmacy, Horinouchi 1432-1, Hachioji, Tokyo 192-03

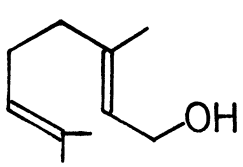
The synthesis of (±)-iridomyrmecin (1) was accomplished from the cyclization products (3) of geraniol (2) via intermediates (4)-(8). This provides a synthesis of 1 from geraniol which is recognized as the biogenetic precursor of cyclopentano-monoterpenes.

Previously we reported an olefinic cyclization of geraniol (2) with thallium(III) perchlorate giving predominantly five-membered carbocyclic products (3a) and (3b) in good yield[1]. These cyclization products involve exactly the carbon skeleton (shown as I) of cyclopentano-monoterpenes (iridoid). This finding prompted us to investigate the synthesis of iridoid starting from these cyclization products (3). Although several studies[2,3] on the synthesis of iridoid were reported in connection with the unique biological activities, the present synthesis offers the first example that iridoid can be derived chemically from their biogenetic precursor geraniol[4]. Here we wish to describe a synthesis of (±)-iridomyrmecin (1) from the cyclization products (3) of geraniol.



I

Dehydration (p-TsOH/C_6H_6, 50-60°C, 6 h) of a mixture of the epimeric alcohols (3a) and (3b) which were obtained from geraniol (2)[1] gave exclusively olefin (4)(bp 44-45°C/2 mmHg) in 72 % yield. Hydroboration of 4 followed by treatment with alkaline hydrogen peroxide gave alcohol (5) (bp 106-108°C/2 mmHg) in 76 % yield. The stereochemistry at C-4 position of 5 was strongly suggested as illustrated by the preferential attack of diborane from the less-hindered side of the cis-fused cyclopentene ring of 4. The alcohol (5) was then submitted to Jones oxidation, giving ketone (6a)[1](90 % yield, bp 89-90°C/2 mmHg). Base-catalyzed epimerization of 6a (t-BuOK/t-BuOH, reflux, 5 h) gave an equilibrium mixture in which the thermodynamically more stable epimer (6b) predominated (6a:6b = 1:4). Direct Huang-Minlon reduction of the ketone (6a) ($NH_2NH_2 \cdot H_2O$, NaOH, diethylene glycol, reflux) gave epimeric products[5] (7a)[15 % yield, NMR(CCl_4) δ 0.98(3H,d,J=7.0 Hz), 1.12, 1.14 (each 3H,s), 3.58(2H,d,J=6.5 Hz)ppm] and (7b)[63 % yield, NMR(CCl_4) δ 1.01(3H,d, J=7.0 Hz), 1.07, 1.16(each 3H,s), 3.40(1H,dd,J=9.2,2.0 Hz), 3.78(1H,dd,J=9.2,6.0 Hz)ppm]. During this reaction epimerization of 6a apparently occurred prior to the reduction of the carbonyl group of 6a. The compound (7b) involves the configurations at C-3a, -4 and -6a positions corresponding to those of the natural product (1). Cleavage of the tetrahydrofuran ring of 7b was achieved by treatment of pyri-



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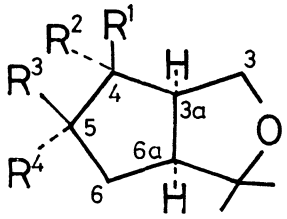
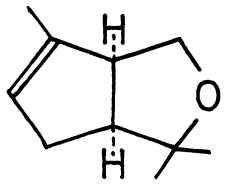


3a R^1=CH_3, R^2=OH, R^3=R^4=H
3b R^1=OH, R^2=CH_3, R^3=R^4=H
5 R^1=CH_3, R^2=R^3=H, R^4=OH
6a R^1=CH_3, R^2=H, R^3,R^4=O
6b R^1=H, R^2=CH_3, R^3,R^4=O
7a R^1=CH_3, R^2=R^3=R^4=H
7b R^1=R^3=R^4=H, R^2=CH_3



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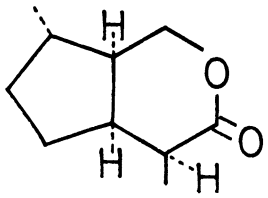

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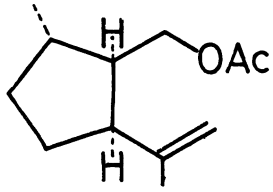

8

dine hydrochloride[6] in acetic anhydride (reflux, 2 h) giving an isopropenyl derivative (8) [IR($CHCl_3$) 1725 cm^{-1}, NMR(CCl_4) δ 1.06(3H,d,J=6.0 Hz), 1.79(3H,br s), 1.95(3H,s), 4.67, 4.78(each 1H,br s)ppm] and an isopropylidene isomer in nearly quantitative yield (the ratio, ca.1:1)[5]. The compound (8) was alternatively synthesized by Wolinsky et al.[3] and the spectroscopic data of both compounds were identical, except for the optical property. The compound (8) was transformed into (±)-iridomyrmecin (1) in 28 % yield by a known procedure[3].

REFERENCES AND NOTE

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