General Approach to Total Synthesis of Patchoulane Sesquiterpenes

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A general synthetic approach to the patchoulane system has been developed using as the target compounds the sesquiterpenes patchoulenone (**9**) and epipatchoulenone (**53**). The key steps in the synthesis involve construction and copper-catalyzed thermal cyclization of the diazo ketone **15** to the cyclopropyl ketone (**17**) and acid-catalyzed cleavage of the latter ketone to deliver the bicyclic ring system **21**. The group R is an electron-withdrawing substituent to direct ring opening and acts as a handle for introducing the fused five-membered ring. Studies on ring opening of substituted cyclopropyl ketones of type **17** and the effect of substituents on the mode of cleavage are elaborated. Diazo ketones of type **15** were found to undergo direct Lewis acid-catalyzed cyclization to the bicyclic ketones **21** in significantly better yields than the two-step process **15** → **17** → **21**. This cyclization reaction, which represents the first reported example of an acid-catalyzed addition of a diazo ketone to an olefin has general application for the synthesis of the bicyclo[3.2.1]octane skeleton.

Three basic patchoulane skeletons occur in nature—α-patchoulane (**1**), β-patchoulane (**2**), and patchouli alcohol (**3**) (Figure 1). The chief natural source of these sesquiterpenes is the perfume essential oil, patchouli oil (from *Pogostemon patchouli*), which has representatives of each of the above three classes: α-patchoulene (**4**) (Tsubaki *et al.*, 1967), β-patchoulene (**5**) (Tsubaki *et al.*, 1967), patchouli alcohol (**3**) (Büchi *et al.*, 1961; Büchi and Erickson, 1956; Dobler *et al.*, 1963), and seychellene (**6**) (Tsubaki *et al.*, 1967; Wolff and Ourisson, 1968). (The last compound is derived formally, albeit not experimentally, from patchouli alcohol by a 1,2-methyl migration.) The compounds **3, 4, 5,** and γ-patchoulene (**7**) have been isolated from Indian valerian root oil (from *Valeriana wallichii*) (Narayanan *et al.*, 1964); β-patchoulene (**5**) is present in minor quantity in guaiac wood oil (from *Bulnesia sarmienti*) (Bates and Slagel, 1962a); while cyperene (**8**) (Trivedi *et al.*, 1964b), patchoulenone (**9**) (Motl *et al.*, 1963; Trivedi *et al.*, 1964a), cyperotundone (isopatchoulenone, cyperenone) (**10**) (Hikino *et al.*, 1965, 1966, 1967b; Naves and Ardizio, 1954; Couchman *et al.*, 1964; Nerali *et al.*, 1965), patchoulenol (**11**) (Nerali and Chakravarti, 1967), cyperenol (**12**) (Nerali *et al.*, 1965), sugeonol acetate (**13**) (Hikino *et al.*, 1968a), and sugetriol triacetate (**14**) (Hikino *et al.*, 1967a) have been isolated from the oils of tuber of nutgrass (*Cyperus rotundus*) and tuber of cyperus (*Cyperus scariosus* and *Cyperus articulatus*) (Figure 1).

In spite of the widespread occurrence of the patchoulanes in nature, evaluation of the odor and flavor properties of these sesquiterpenes has been limited due to the lack of practical synthetic means for attaining working quantities of these compounds. Although syntheses of individual α-patchoulanes have been recorded (Bates and Slagel, 1962b; Büchi *et al.*, 1964; Büchi and MacLeod, 1962; Danishefsky and Dumas, 1968; Hikino *et al.*, 1968c; Piers *et al.*, 1969; Schmalzl and Mirrington, 1970), it was the objective of our work to develop a general synthetic approach which would be adaptable to all of the sesquiterpenes in this series. Such a general approach is described here.

Our initial overall strategy for the synthesis of the patchoulane skeleton involved the construction and copper-catalyzed thermal cyclization of the diazo ketone **15** (*via* the carbene **16**) to the cyclopropyl ketone **17** and acid-catalyzed cleavage of this ketone to deliver products derived from the bicyclo[3.2.1]-octyl cation **18** (formed by 2,7 bond scission, Figure 2) or the bicyclo[2.2.2]octyl cation **19** (formed by 1,7-bond scission). By suitable variation in the group R from an electron-withdrawing substituent (which should retard formation of the cation **19**) to a substituted alkyl substituent (which should favor formation of **19**), one should be able to direct the course of cleavage. The R group also provides a handle for introducing the fused five-membered ring.

In practice, then, cleavage of a tactically substituted 1-alkyl tricyclo ketone **17** in a suitable medium might be expected to yield a bicyclo[2.2.2]octanone derivative of type **20** which, *via* appropriate transformations, could be cyclized ultimately to patchouli alcohol (**3**). On the other hand, Lewis acid-catalyzed cleavage in a nonnucleophilic solvent of a tricyclic ketone **17** containing an electron-withdrawing R group should lead principally to the bicyclo[3.2.1]octanone **21**, which should be homologated readily to the endione **54**. Aldol cyclization of **54** before reduction of the double bond would yield the dienone **55**, which, by classical processes, should be transformed easily to α-patchoulene (**4**) or sugetriol triacetate (**14**). Reduction of the double bond of **54** first and subsequent cyclization would yield patchoulenone (**9**), which should be transformed readily by classical reductive means to patchoulenol (**11**). Facile methods have been described for the conversion of: α-patchoulene (**4**) to β-patchoulene (**5**), γ-patchoulene (**7**), and patchouli alcohol (**3**) (Büchi *et al.*, 1961); patchoulenol (**11**) to cyperene (**8**) (Nerali and Chakravarti, 1967); cyperene (**8**) to cyperotundone (**10**) (Nerali *et al.*, 1965); and cyperotundone (**10**) to sugeonol [and hence sugeonol acetate (**13**)] (Hikino *et al.*, 1968b). Obvious variations in the homologation of the R group also would allow the synthesis of cyperenol (**12**). This approach, then, would permit the acquisition of each of the presently known naturally occurring

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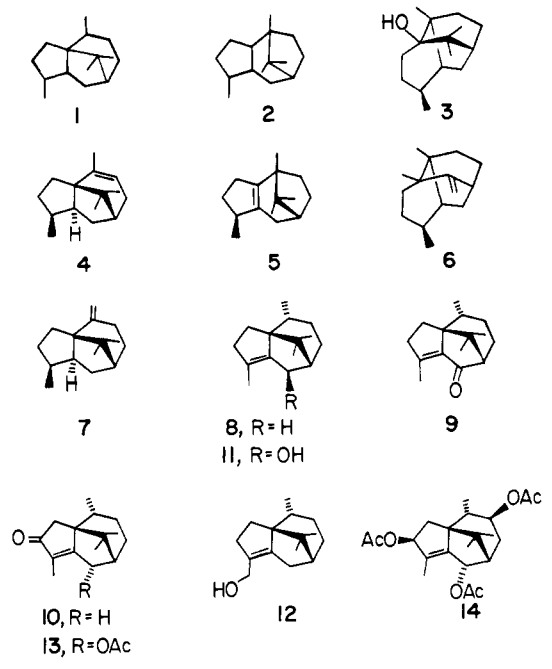

Figure 1. Naturally occurring patchoulanes

patchoulane type sesquiterpenes. We will focus our attention here on the route leading to patchoulenone (**9**).

To gain a better understanding of the limitations of the proposed approach to the patchoulanes, a cursory study of the acid cleavage of two model tricyclic ketones was made. House and coworkers (House *et al.*, 1965) have shown that the parent tricyclo[3.2.1.$0^{2,7}$]octan-6-one (**22**) undergoes rather facile cleavage on exposure to hydrogen bromide at room temperature with the exclusive formation of the bromobicyclo-

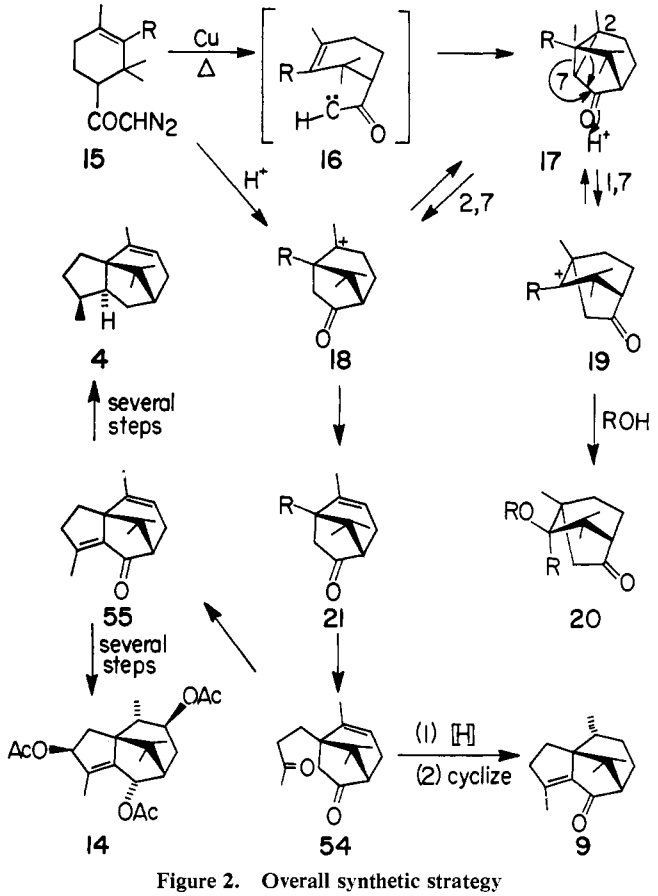

Figure 2. Overall synthetic strategy

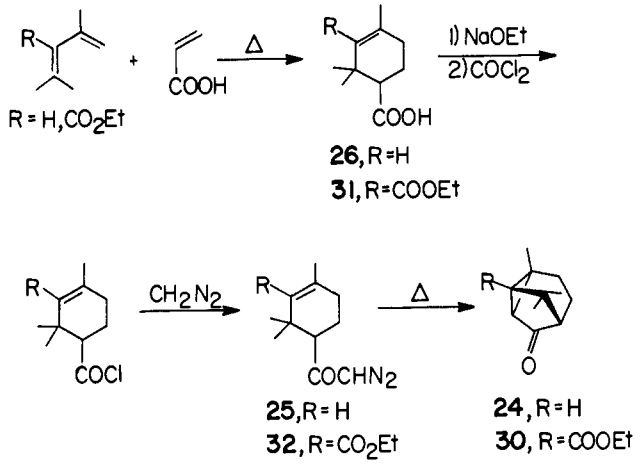

Figure 3. Synthesis of tricyclo[3.2.1.$1^{2,7}$]octanones

[2.2.2]octanone (**23**). The inclusion of a methyl group at the C-2 position would be expected to alter the direction of cleavage. To test this hypothesis the tricyclic ketone **24** was synthesized. The diazo ketone **25**, prepared from the acid **26** (Erman *et al.*, 1968; Jitkow and Bogert, 1941) by classical means (outlined in Figure 3), was decomposed in refluxing cyclohexane in the presence of copper to the ketone **24** (65% overall yield). Surprisingly, when **24** was treated with hydrogen bromide for extended periods, no bond scission occurred and starting ketone was recovered unchanged. Cleavage of **24** was effected only under rather drastic conditions. By the action of 10% boron trifluoride etherate in acetic acid (118° C, 3 hr) **24** was converted to a mixture of the bicyclo[3.2.1]octenones **27** (51% yield) and **28** (*ca.* 1% yield) and the bicyclo[2.2.2]octanone **29** (31% yield) (Figure 4). The ketoacetate **29** on treatment with boron trifluoride etherate under the same conditions produced a small quantity of the tricyclic ketone **24** (*ca.* 7%) but less than 3% of the keto olefin **27**, while **27**, in fact, was stable to these reaction conditions. The products, therefore, are those of kinetic rather than thermodynamic control.

It became apparent at this point that an electron-withdrawing group would be required at the C-1 position to direct

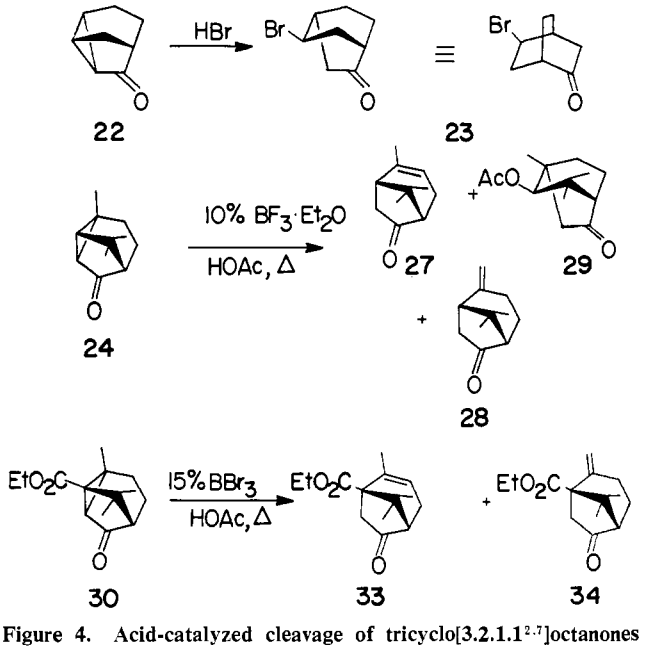

Figure 4. Acid-catalyzed cleavage of tricyclo[3.2.1.$1^{2,7}$]octanones

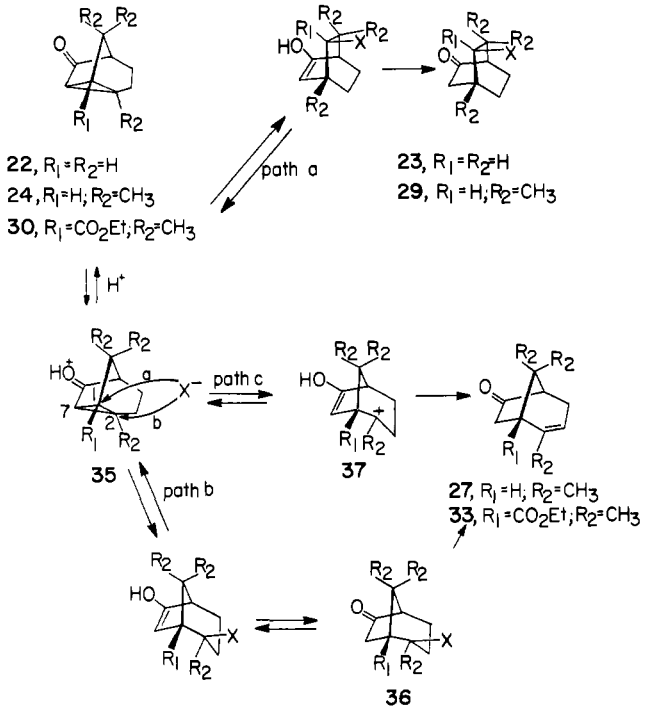

Figure 5. Mechanism of acid-catalyzed cleavage reactions

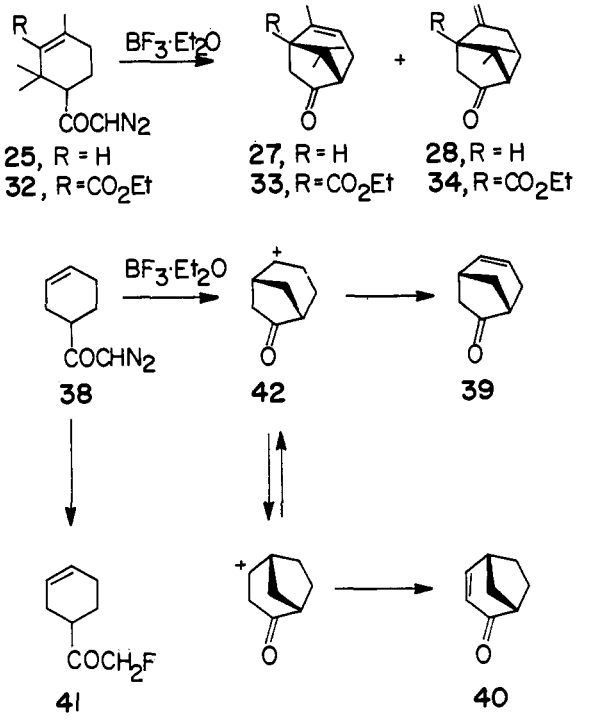

Figure 6. Lewis acid-catalyzed cyclization of diazo ketones

cleavage of **24** completely to the bicyclo[3.2.1]octenone skeleton. For this purpose the 1-carbethoxy tricyclic ketone (**30**) was prepared as outlined in Figure 3. Diels–Alder condensation of 3-carbethoxy-2,4-dimethyl-1,3-pentadiene [prepared by a variation in the procedure of Alkonyi and Szabo (1967)] with acrylic acid afforded the acid **31** (41% yield) whose acid chloride was converted with ethereal diazomethane to the diazo ketone **32** in 72% overall yield. Copper-catalyzed thermal decomposition of **32** produced the cyclopropyl ketone **30** in 16% yield. Even more drastic conditions (15% boron tribromide in refluxing acetic acid, 15 hr) were required to effect cleavage of **30.** In this instance, only the bicyclo[3.2.1]-octenones **33** and **34** (ratio **33**:**34** = 96:1) were obtained, but the combined yield of these ketones was only 54%.

It is worthwhile to note at this point that only a single epimeric bromide **23** is obtained from the cleavage of **22** and a single acetate **29** from the cleavage of **24.** Although the stereochemistries of the bromo and acetate groups of these compounds have not been elaborated, most likely these groups are oriented trans to the keto function in both **23** and **29.** This hypothesis is based on the assumption that the rate determining step in the conversion of the cyclopropyl ketones to the bicyclo[2.2.2]octanone derivatives involves the addition of nucleophilic reagent to the C-1 position of the protonated cyclopropyl ketone **35** concerted with cyclopropane bond scission (path a, Figure 5) *i.e.*, the process is viewed formally as an acid-catalyzed Michael-type addition reaction.

This mechanistic proposal is consistent with the observation that ketone **24** requires considerably more drastic conditions for conversion to ketone **29** than is required for transformation of **22** to **23** (*supra*). The C-2 and C-8 methyl substituents of the *O*-protonated derivative of **24** should offer greater hindrance to approach of nucleophiles to the C-1 site than should the corresponding hydrogen substituents of the *O*-protonated derivative of **22.** This would lead to a lower rate of conversion of **24** to **29** relative to the rate of conversion of **22** to **23.** Preferential cleavage of the 1,7-bond of the *O*-protonated derivative of **22** may reflect the differences in strain relief in proceeding to the bicyclo[2.2.2]octane system relative to the bicyclo[3.2.1]octane system.

The conversions of the cyclopropyl ketones **24** and **30** to the bicyclo[3.2.1]octenones **27** and **33,** respectively, may also be treated as concerted reactions (path b, Figure 5). The initially formed axially oriented tertiary acetate group of **36** must be assumed to undergo rapid elimination to olefin under the conditions of the reaction. Quite possibly, however, a discrete carbonium ion, *i.e.*, **37** (path c, Figure 5), is involved in these transformations and the nucleophile is not involved in the rate-determining step. The fact that keto ester **30** requires more drastic conditions for cleavage than the ketone **24** may be attributed to the inductive effect of the carbethoxy function. These proposals, of course, are speculative and further work will be required to unravel the mechanistic intricacies of these transformations.

The low overall yield (8%) of the keto ester **33** from the diazo ketone **32** impelled us to investigate other means for this conversion. The observation of Closs and coworkers (1966) that phenyl diazomethane undergoes an acid-catalyzed ionic addition to tetramethylethylene prompted us to consider the direct Lewis acid-catalyzed cyclization of **32** to **33.** Indeed, exposure of **32** to boron trifluoride etherate (2% in 1,2-dichloroethane) for a period of only 3 hr at mild temperatures (0–27° C) delivered the ketones **33** and **34** in *ca.* 30 and 3% yields, respectively (Figure 6).

This reaction, *which represents the first reported example of the acid-catalyzed addition of a diazo ketone to an olefin*, has general application for the synthesis of bicyclo[3.2.1]octenones. The ketone **27,** for example, was obtained in 56% yield accompanied by a small quantity of **28** (6% yield) by the action of boron trifluoride etherate on the diazo ketone **25** (Figure 6). In comparison, the two-step process **25** → **24** → **27** proceeded in only 33% overall yield. The parent 3-cyclohexenyl diazomethyl ketone (**38**) undergoes boron trifluoride etherate catalyzed cyclization to ketones **39** and **40** (ratio of **39**:**40** = 1:3), although in poor yield. The fluoro ketone **41** is a major side product of the reaction. Apparently, in this instance, the

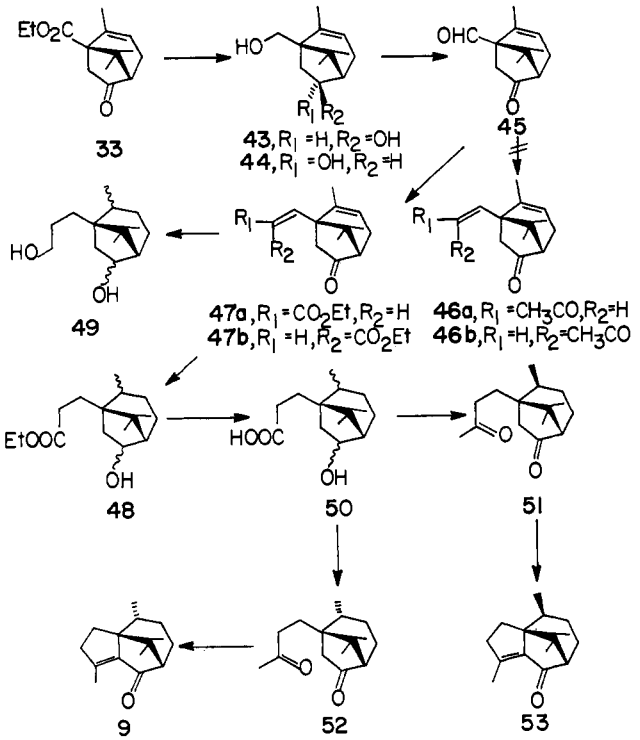

Figure 7. Annelation of the five-membered ring

olefin **39** or the intermediate carbonium ion **42** undergoes rearrangement to **40.** Significantly, bicyclo[2.2.2]octanone derivatives which might have arisen by initial addition of the diazo ketone to the C-4 position of the cyclohexyl ring (*i.e.*, from a cation of type **19**), were not observed as products of the boron trifluoride-catalyzed cyclizations of **32, 25,** or **38.**

With a convenient synthesis of the keto ester **33** in hand, introduction of the five-membered ring was pursued (Figure 7). Lithium aluminum hydride reduction of **33** provided an inseparable mixture of the epimeric alcohols **43** and **44** (82% yield) in a ratio of 55:45. Oxidation of **43** with dipyridine–chromium trioxide reagent (Collins *et al.*, 1968) produced the aldehyde **45** in 69% yield. Attempts to condense **45** with acetone or with diethylphosphonoacetonate over extended periods failed to yield the desired diketone **46.** However, condensation of **45** with one equivalent of sodium triethylphosphonoacetate led to a mixture of the E and Z unsaturated esters **47a** and **47b** (52% yield), which was easily resolved by preparative gas chromatography (ratio **47a**:**47b** = 10:1 to 14:1). A side product of the reaction was the ketone **27** (2%) which probably was formed by thermal homolytic decarbonylation of **45.** Hydrogenation of an ethanol solution of a 10:1 mixture of **47a** and **47b** in the presence of W-5 Raney nickel (Billica and Adkins, 1955) produced a mixture of epimeric hydroxy esters (**48**) (50–93%) and diols (**49**) (5–40%). (The relative yields of hydroxy esters and diols varied with the period of storage of the W-5 Raney nickel.) The free acids (**50**) were separated readily from the diols after saponification of the esters **48** with 10% methanolic potassium hydroxide. Treatment of **50** with three molar equivalents of ethereal methyllithium provided a mixture of epimeric ketols which was converted directly to a mixture of the diketones **51** and **52** in 40% yield (ratio **51**:**52** = 9:1) upon treatment with standard chromate solution in acetone (Bowden *et al.*, 1946). The epimer **51** was separated by recrystallization and cyclized to *dl*-epipatchoulenone (**53**) in 92% yield by the action of potassium *tert*-butoxide in *tert*-butyl alcohol. The ketone **53** has not been isolated from natural sources and we have not been able to detect its presence in essential oils.

Similar treatment of **52** with potassium *tert*-butoxide afforded *dl*-patchoulenone (**9**) in 70% yield. The infrared and nmr spectra of our specimen of *dl*-**9** were identical in all major aspects with the infrared (Trivedi *et al.*, 1964a; Hikino *et al.*, 1968c) and nmr (Trivedi *et al.*, 1964a) spectra of natural patchoulenone.

ACKNOWLEDGMENT

We thank Hiroshi Hikino, Pharmaceutical Institute, School of Medicine, Tohoku University, Sendai, Japan, for kindly sending us the infrared spectrum of patchoulenone. We gratefully acknowledge the interest and support of our work on patchoulenone chemistry by E. A. Schwoeppe, D. K. Brain, and E. J. Matre of the Procter and Gamble Co.

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Received for review February 8, 1971. Accepted May 13, 1971. Presented at the Division of Organic Chemistry, 161 Meeting, ACS, Los Angeles, California, March–April 1971.