

Synthesis and Odor Characteristics of New Gem-Dimethylcyclohexane Derivatives

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Searching for cyclic analogs of the insect juvenile hormones, we synthesized a series of new compounds containing the cyclogeraniolene system.¹ This system can be considered as a cyclic form of acyclic terpenes, such as dihydrocitronellol, dihydrogeraniol, and menthocytronellol. The isoprenoid chain in these compounds is rolled to form the cyclohexane ring by connection of the carbon atoms C-7 and C-10 (figure 7). As compared with the classical cyclic systems of the cyclogeraniol type, the compounds obtained by us contain the gem-dimethyl groups in the 3-position in relation to a chain with the functional group.

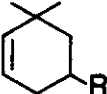
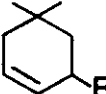
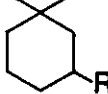
A series of our compounds exhibited interesting odor properties, which was not a surprise because many other odoriferous compounds from the gem-dimethylcyclohexane derivatives group are known.²

Materials and Methods

The starting materials for synthesis of these compounds were the easily available terpenic component, (+)-3-carene (1)³ and commercial dimedone (12). The key compound for synthesis of final products with the (Z)-menthocytronellyl skeleton, ester 11A, was obtained by the multi-step synthesis from 1, presented in figure 2.

In the first step of the synthesis, 1 was converted into keto aldehyde 2 by ozonolysis in the usual manner.⁴ Product 2 was transformed by modified intramolecular condensation in 1-acetyl-3,3-dimethyl-1,4-cyclohexadiene (3)⁵ which formed saturated ketone 4C after hydrogenation over Pd/C. Monocyclic ketone 3 was selectively reduced with zinc dust in 25% aqueous KOH to give 1-acetyl-5,5-dimethyl-3-cyclohexene (4A) which was then degraded to 5,5-di-

Table I

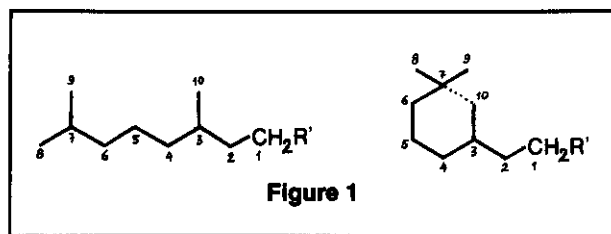
R			
-COCH ₃	<u>4A</u> C ₁₀ H ₁₆ O intensive, penetrating, herb-fruity with note of <i>Achillea millefolium</i> L. flowers	---	<u>4C</u> C ₁₀ H ₁₈ O medium-intensive, herb-fruity with note of <i>Tanacetum vulgare</i> L. flowers, thujone-like
-CH ₂ CN	<u>9A</u> C ₁₀ H ₁₅ N intensive, penetrating, chemical	---	<u>9C</u> C ₁₀ H ₁₇ N intensive, penetrating, chemical
-CH ₂ CO ₂ Et	<u>11A</u> C ₁₂ H ₂₀ O ₂ medium-intensive, fruity with cuminic note	<u>11B</u> C ₁₂ H ₂₀ O ₂ intensive, fruity with rum note	<u>11C</u> C ₁₂ H ₂₂ O ₂ less intensive than <u>11B</u> , fruity with rum note
-CH ₂ CH ₂ OH	<u>23A</u> C ₁₀ H ₁₈ O intensive, penetrating, a little fruity with wild-pear note	<u>23B</u> C ₁₀ H ₁₈ O fresh, a little chemical with cuminic note	<u>23C</u> C ₁₀ H ₂₀ O medium-intensive, chemical, with cuminic note
-CH ₂ CHO	<u>24A</u> C ₁₀ H ₁₆ O intensive, penetrating, very fresh, fatty-fruity with ozone note	<u>24B</u> C ₁₀ H ₁₆ O very intensive, penetrating, fresh fruity-floral with grape-fruit note	<u>24C</u> C ₁₀ H ₁₈ O intensive, penetrating, fruity with chemical note
-CH ₂ CH ₂ OAc	<u>25A</u> C ₁₂ H ₂₀ O ₂ intensive, fruity, fairly penetrating, fresh with pear note	<u>25B</u> C ₁₂ H ₂₀ O ₂ agreeable, medium-intensive, fruity-floral, sweet, with marked wild-strawberry note	<u>25C</u> C ₁₂ H ₂₂ O ₂ intensive, sharp, fruity-floral with desiccated-pears note
-CH ₂ CH ₂ CH ₂ Ac	<u>28A</u> C ₁₃ H ₂₄ O intensive, agreeable, fruity with apricot note	<u>28B</u> C ₁₃ H ₂₄ O medium-intensive, fruity with marked note of China quince fruit	<u>28C</u> C ₁₃ H ₂₆ O less intensive than <u>28B</u> , fruity with note of China quince fruit

methyl-3-cyclohexenoic acid (5), a yield of about 70%, by the reaction with sodium hypobromide. Acid 5 was then reduced with lithium aluminium hydride (LAH) to alcohol 6 which was converted into 5,5-dimethyl-3-cyclohexenyl/acetonitrile (9) via tosylate 7 and bromide 8 (overall yield ca. 90%). Hydrolysis of nitrile 9 afforded acid 10 with ten carbon atoms which was esterified with ethanol to ethyl 5,5-dimethyl-3-cyclohexenyl/acetate (11A).

The isomer of this ester, compound 11B, dif-

fering in position of the double bond, and the product of its hydrogenation, ester 11C, were obtained starting from dimedone (12). The scheme of this synthesis is given in figure 3.

Dimedone (12) was converted by reaction with ethanol in the presence of p-toluenesulfonic acid into ethoxyketone 13, which gave by reduction with LAH unsaturated ketone 14⁶ in the first step and 5,5-dimethyl-2-cyclohexen-1-ol (15) by further reduction. α , β -Unsaturated alcohol 15 formed ethyl 5,5-dimethyl-2-cyclohexyl/acetate



(11B)⁷ by the Claisen rearrangement with ethyl orthoacetate in the yield of ca.80%. Ester 11B was utilized for further syntheses of odoriferous compounds containing the 3,7-dimethyl-4-octene system, and its hydrogenation product, ethyl 3,3-dimethyl + cyclohexyl/acetate (11C), was applied for syntheses of cyclic dihydrocitronellyl analogs.

The hydrogenation product of ketone 14, 3,3-dimethylcyclohexanone (16), was converted by the modified Wittig-Horner reaction with diethyl phosphonoacetate (W-I)⁸ into a mixture of ethyl (E) and (Z)-3,3-dimethylcyclohexylidenyl/ace-

tate (17 a,b)* in the 70% yield. Both pure isomers of ester 17 were isolated from a mixture by means of preparative column chromatography. The ester with the (Z)-configuration is a cyclic compound with the dihydrogeranyl system, and the (E)-isomer has the dihydroneryl system. These separated isomers were reduced with diisobutylaluminum hydride (*i*-BAH) to give primary alcohols 18a and 18b, respectively, and, after their oxidation with active MnO₂, corresponding aldehydes 19a and 19b (yield ca. 55%). Alcohols 18a and 18b afforded with acetyl chloride corresponding acetates 20a and 20b. Ketone 16 was also utilized for syntheses of α , β -unsaturated nitriles 21a, b by the Wittig-Horner⁹ reaction with diethyl cyanomethylphosphonate (W-II) with a yield of about 70%. A mixture of the (Z)- and (E)-isomers obtained was not separated but hydrogenated to one saturated nitrile 9C (figure 3) in the presence of deactivated Raney-nickel.

* b : 2Z-isomer, a : 2E-isomer

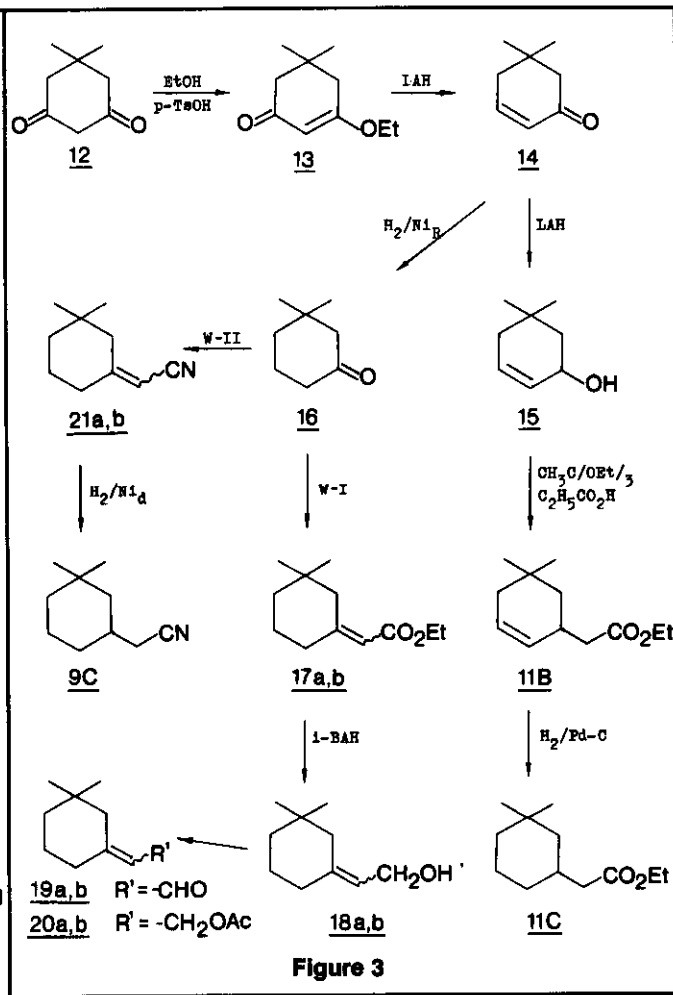
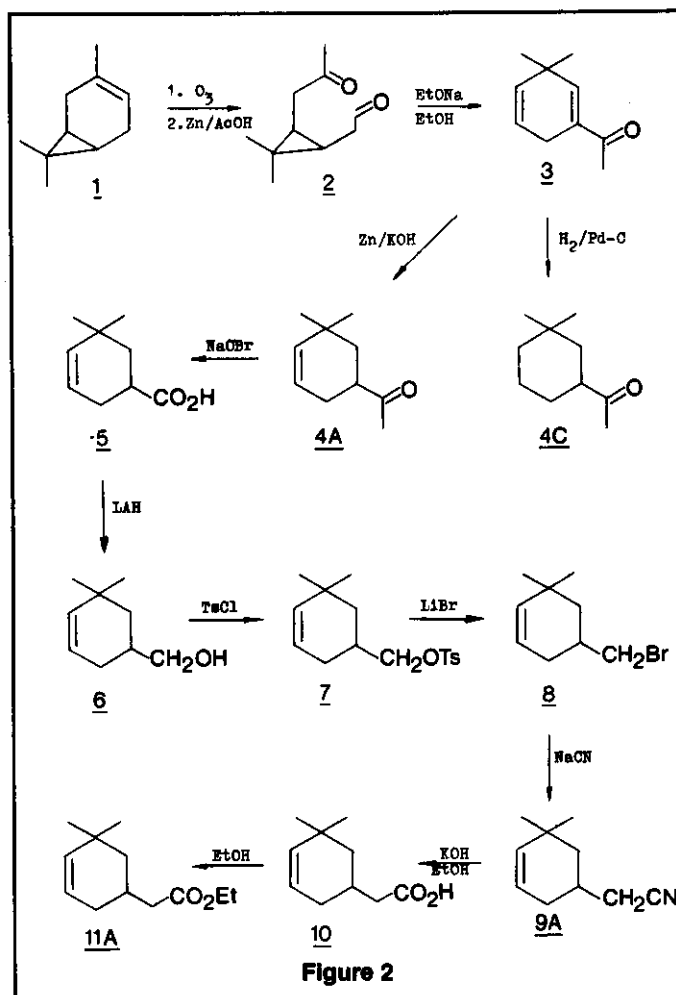
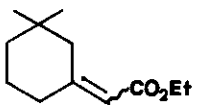
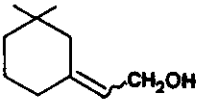
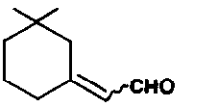
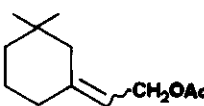
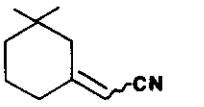


Table II

 $C_{12}H_{20}O_2$	E	<u>17a</u> medium-intensive, fruity with note of China quince fruit
	Z	<u>17b</u> weak, chemical, uninteresting
 $C_{10}H_{18}O$	E	<u>18a</u> medium-intensive, floral, sweet with sweet-pea note
	Z	<u>18b</u> medium-intensive, penetrating like odor of humus soil
 $C_{10}H_{16}O$	E	<u>19a</u> intensive, more penetrating than <u>19b</u> , fatty-floral with woody note
	Z	<u>19b</u> intensive, penetrating, fatty-floral with woody note
 $C_{12}H_{20}O_2$	E	<u>20a</u> medium-intensive, agreeable, sweet, fruity-floral with wild-strawberry and apricot note
	Z	<u>20b</u> little intensive, sweet, fruity
 $C_{10}H_{15}N$	E + Z	<u>21a,b</u> intensive, penetrating, nicotine-like

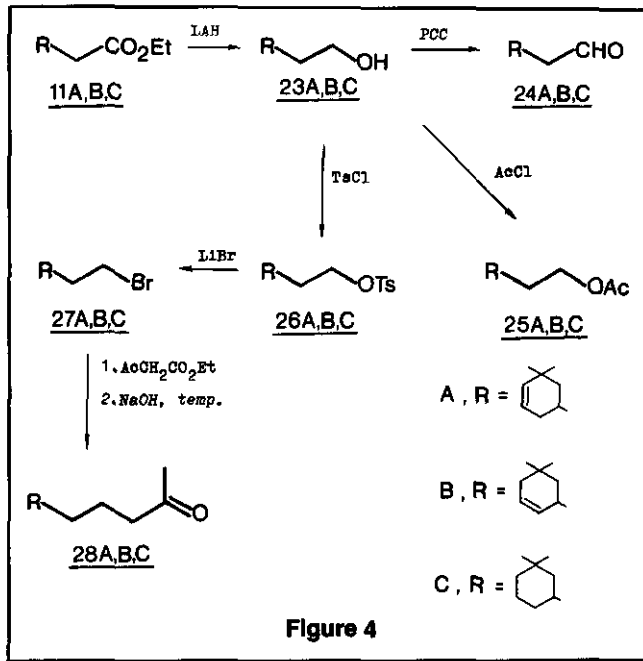
The odor characteristics of the gem-dimethylcyclohexane derivatives with the functional groups at the exocyclic double bond are presented in Table I.

From esters *11A, B, C* (figures 2 and 3) obtained by us, exhibiting interesting odor properties, further oxygen derivatives were synthesized according to the reaction sequence presented in figure 4.

Esters *11A, B, C* were reduced with LAH to give alcohols *23A, B, C* which were then oxidized by the Corey method¹⁰ with pyridinium chlorochromate (PCC) to corresponding aldehydes in different yields (*24A*—57%, *24B*—51%, *24C*—76%). Alcohols *23A, B, C* were esterified with acetyl chloride to afford acetates *25A, B, 11C*. Bromides *27A, B, C* were obtained from alcohols

23A, B, C by the Mori method¹² via tosylates *26A, B, C*. The bromides were utilized for elongation of the carbon chain by further three carbon atoms by alkylation of ethyl acetoacetate. Alkaline hydrolysis and subsequent decarboxylation of intermediate keto esters gave three derivatives of 5-cyclohexyl-2-pentanone (*28A, B, C*) in the yield of 77%. Some of the compounds mentioned were obtained earlier (alcohols *18A, B, 25C*, aldehydes *19a, b, 13 24C*¹⁴) but their odor properties were not described.

The course of all reactions and purities of products were controlled by means of GLC and TLC. The structures of compounds obtained were confirmed by the IR and NMR spectra.¹ Odor characteristics of these compounds are given in Table II.



Results

Synthesis of twenty-eight compounds containing the cyclohexenyl skeleton, differing with position of the double bond and with kind of the functional group (ester, carbonyl, al-

cohol, nitrile) allowed us to recognize some relationships between structure and odor.

Generally it can be ascertained that passage from the 3,7-dimethyloctene system to that of the cyclohexenyl influences markedly the change of odor of compounds. It concerns especially the group of alcohols, aldehydes, and nitriles. The sharp, penetrating, a little cuminic odor of cyclic alcohols 23A, B, C contrasts with the pleasant, rose-floral odor of acyclic alcohols (dihydrocitronellol, menthocytronellol, dihydrogeraniol, and dihydroneol). The exception is an (*E*)-isomer of alcohol 18a exhibiting the pleasant sweet odor of blooming sweet pea. A much less distinct change of odor is observed for acetates 25A, B, C of cyclic alcohols in question which are characterized by a pleasant fruity-floral odor.

Aldehydes 24A, B, C, containing the cyclohexenyl system, exhibit, in comparison with their acyclic analogs gifted with the citrus odor, the much more intensive, strongly penetrating odor with the fruity-floral or fatty-floral character and only aldehyde 24B exhibits a citrus (grapefruit) note. Noteworthy are intensive fruity odors of cyclic ethyl esters 11A, B, C, herb-fruity odors of the ten-carbon ketones 4A and 4C and fruity ones of 13-carbon ketones 28A, B, C.

Gem-Dimethylcyclohexane Derivatives

Conclusion

Summarizing the above remarks on the relationship between structure and odor, it can be observed that passage from the chain 3,7-dimethyloctene system to the 1,3,3-trisubstituted cyclohexane system indicates an essential effect on the interaction of this group of compounds with odor receptors. The known cyclic odoriferous substances (cyclogeraniol, cyclocitral, ionones, and irones) which are tetra- or penta-substituted derivatives of cyclohexane, have the gem-dimethyl group in the 2-position in relation to a chain with the functional group. These compounds have one or two methyl groups more in the cyclohexane ring. Comparing the compounds mentioned with those obtained by us, one can notice that the latter have the gem-dimethyl grouping in the 3-position in relation to a chain with the functional group and they have no other methyl groups in the cyclohexane ring. The differences in structures are probably the cause of decay or limitation of "sensoric impressions" associated with pleasant odors, characteristic of acyclic terpenoids and their tetra- and pentasubstituted cyclic isomers. On the other hand, a more distinct, sharp, penetrating odor note appears in our cyclic analogs containing the alcohol, aldehyde or nitrile group.

References

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