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THE SYNTHESIS OF ANGULAR METHYL SUBSTITUTED BICYCLIC ENONES VIA A UNIQUE REGIOSELECTIVE ENAMINE ANNULATION REACTION

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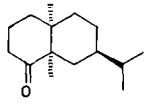
Abstract—Enamines of 2,4,4-trimethylcyclopentanone **5** and of 2,5,5-trimethylcyclohexanone **14** react with methyl vinyl ketone to afford the bicyclic enones **9** and **15** in yields up to 70%. The formation of these products bearing an angular Me group is the result of an anomalous enamine Robinson annulation reaction, due to an alkylation of the enamine in the first step at its most substituted α-position. The effect of substitution in the α- and β'-position in the cycloalkanone, its ringsize, the structure of the Michael acceptor (alkyl vinyl ketone) was illustrated in reactions of the enamines of 2,5-dimethylcyclohexanone **22**, carvomenthone **19**, menthone **26**, dihydrocarvone **28** and tetrahydroeucarvone **32** with methyl- and/or ethyl vinyl ketone.

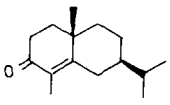
INTRODUCTION

The construction of annulated ring systems bearing at least one angular Me group is a problem which is often encountered in the total synthesis of natural products.[1]

Examples of such products in the sesquiterpenoid field are the valerane and the selinane or eudesmane skeleton. Valeranone **1** is a member of the rather rare group of valerane sesquiterpenoids. It has met considerable attention among organic chemists before the structure was definitely settled by Hikino.[2] α-Cyperone **2** is an important member of the eudesmane (or selinane) sesquiterpenoids, and obeys in contrast to valeranone **1** the well-known isoprene rule.

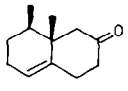


1



2

The compound **2** was first isolated from the essential oil of *Cyperus rotundus* by Hegde and Rao[3] and synthesized by Howe and McQuillin.[4] The importance of α-cyperone as a starting material for the synthesis of various other ring fused sesquiterpenoids has led to a variety of syntheses, laborious in most cases with the exception of the one given by Caine and Gupton.[5] Compounds derived from the naturally occurring sesquiterpenes by elimination of methyl and/or isopropyl groups have also been found.



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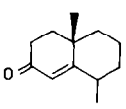


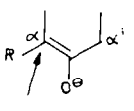
4

The octalones **3** and **4** were isolated by Maurer *et al.*[6] from the essential oil of *Vetivera zizanoides* L. in which they possibly play an important role in defining the overall odour.

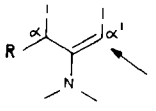
Being interested in the synthesis of important olfactive natural compounds we tried to develop simple routes leading via compounds like **3** and **4** to the more complex sesquiterpenoids like **1** and **2**.

The most direct way for the preparation of the bicyclo[4.4.0]decane sesquiterpenoid and their biogenetically related derivatives is the Robinson annulation reaction, wherein an appropriately substituted cyclohexanone is condensed with an alkyl vinyl ketone under the influence of a base.[1] Although such annulation reactions have been thoroughly studied, reviewed and applied in the synthesis of natural products, they are often low yield procedures due to polymerisation of both ketones in the basic medium. Results are influenced by the composition of the enolate anion mixture, which is altered by the nature of the base and the polarity of the solvent,[7] and therefore optimum conditions are not easily found.

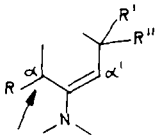
A very useful modification of this reaction is the condensation of an alkyl vinyl ketone with the enamine of the cyclic ketone. Whereas a conventional base catalysed Michael reaction favours attack at the *most* substituted α-position of the cyclic ketone, it is the *least* substituted α'-position that is attacked in the enamine derivative. This has been explained with carbanion and enamine stabilities: structure A represents the most stable enolate anion and structure B the most stable enamine. Consequently A is predominantly attacked at the *most* substituted α-position and B at the least substituted α'-position.



A



B



C

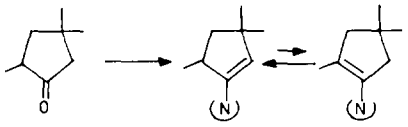
Therefore the synthesis of sesquiterpenoids and derivatives like the eudesmanes (cf. **2**) cannot be based on an enamine reaction, starting from and α-substituted cyclohexanone.

In this paper we show how this problem can be

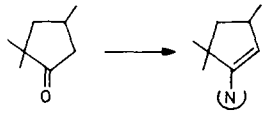
overcome by the introduction of extra steric effects (cf. formula C), thus leading to an enamine reaction (followed by ring closure) at the *most substituted α-position*. In this way angular substituted octalones were synthesized via a route, to our knowledge not described in the literature.[8]

RESULTS

The work was initiated by our study of the enamines of a commercially available 1:1 mixture of 2,4,4-trimethylcyclopentanone **5**[9] and the 2,2,4 substituted isomer **6**.[10] Refluxing of this mixture with pyrrolidine for 24 hr with removal of water afforded after distillation the unreacted trimethylcyclopentanones **5** and **6** (approximately in a ratio of 1:6), and the 1-(N-pyrrolidino)-trimethyl-1-cyclopentenes **8a** and **8b** in more than 90% yield. Under the reaction conditions the enamine **7** is not formed.†



5 **8a** **8b**



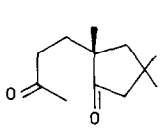
6 **7**

The enamine of **5** consists of a 3:1 mixture of **8a** and **8b**. This is easily recognized from the NMR spectrum where for **8a** a vinyl proton is observed as a broad singlet at 3.88 ppm (integrated area about 0.75 protons), and a doublet (C̲H₃CH) at 1.13 ppm (J = 7 Hz). The singlet at 1.04 ppm is due to isomer **8b**, which can exist in a rapid equilibrium with **8a** through minute traces of acid.

Although little is known about the position of the double bond in enamines of 2- and 3-alkyl substituted cyclopentanones,[8] the higher proportion of **8a** seems to be in accord with the observations of Gurowitz and Joseph[12] who stated that the pyrrolidine enamine of 2-methylcyclohexanone exists for about 90% of the trisubstituted isomer.

The same is true for Johnson's findings[13] that 2,5-dimethylcyclohexanone pyrrolidine enamine exists for less than 5% of the tetrasubstituted double bond isomer.

When methyl vinyl ketone was slowly added to a solution of the enamine mixture **8a** and **8b** in benzene at 15–20° it was completely consumed within 3 hr. Hydrolysis with acetic acid-sodium acetate buffer afforded a 1:1 mixture of the 6,8,8-trimethylbicyclo[4.3.0]non-1-en-3-one **9**, and its uncyclized precursor **10**.



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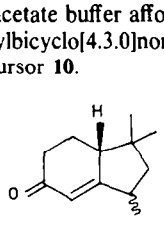


11

The latter could easily be cyclized by refluxing the crude product in 5% ethanolic potassium hydroxide. In this way **9** was obtained in 68% yield (calculated on the starting enamine).

The structure is supported by the NMR spectrum with a singlet of the angular Me group at 0.99 ppm. Formally its formation must be explained by the action of the Michael acceptor on the tetrasubstituted double bond in enamine **8b**, the minor component in the equilibrated enamine mixture. No trace of 7,7,9-trimethylbicyclo[4.3.0]non-1-en-3-one **11** could be detected. This reaction seems to be quite general, provided that certain structural requirements are fullfilled.

The same procedure with ethyl vinyl ketone and the enamine **8b** yielded the bicyclic nonenone **12** in 83%. The yield was severely diminished when alkyl vinyl ketones, substituted at the double bond, were used. This was also observed when simple enamines (e.g. cyclohexanone enamine) were used. Thus methyl isopropenyl ketone afforded only 18% of the bicyclic nonenone **13** while mesityloxide did not react at all.

In order to evaluate factors influencing the direction of this annulation reaction, the above described reaction sequence was studied with some cyclohexanones bearing a Me group in the 2-position and another alkyl group (*gem* dimethyl, isopropyl, isopropenyl, methyl) in the 5-position. The appropriate cyclohexanone derivatives were either prepared by known procedures (Experimental) or obtained commercially.

As can be seen from Table 1, the enamine of 2,5,5-trimethylcyclohexanone **14** yielded with methyl vinyl ketone a 4:1 mixture of octalones **15** and **16**, again showing that the isomer with the angular Me group is formed predominantly. Reaction of the same enamine with ethyl vinyl ketone gave an analogous result, be it that it was somewhat less selective as shown by the 3:2 ratio of the products **17** and **18**. A further decrease in selectivity was found when instead of the *gem* dimethyl group an isopropyl group as in carvomenthone **19** was present; annulation via the enamine with methyl vinyl ketone yielded **20** and **21** in a ratio of 3:7.

When the bulkiness of the substituent was diminished as in 2,5-dimethylcyclohexanone **22**, formation of about 30% of **23**, the isomer with an angular Me group was observed. The mixture of enamines of **22** with ethyl vinyl ketone gives no product with an angular Me group, **25** being the sole isomer that is isolated.

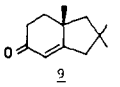
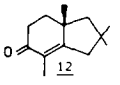
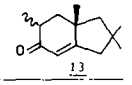
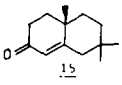
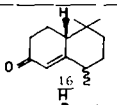
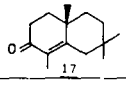
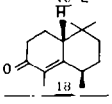
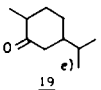
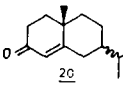
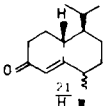
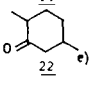
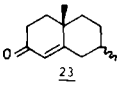
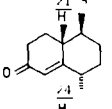
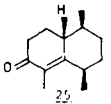
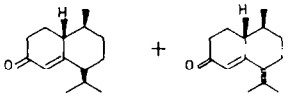
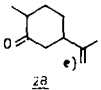
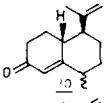
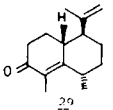
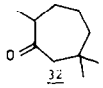
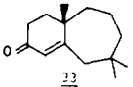
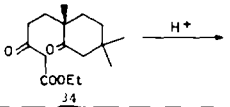
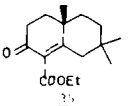
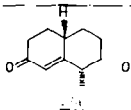
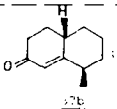
Reaction of the enamine of menthone **26** containing a bulky isopropyl group in its α-position with methyl vinyl ketone yielded the nor-cadalane system **27** exclusively. As expected in this case the "normal enamine route" leading to a product with no angular Me group is followed.

Considering the observed 3:7 ratio of condensation products obtained from carvomenthone **19** (with an isopropyl side chain) we were surprised to find that the enamines from dihydrocarvone **28** (with an isopropenyl side chain) reacted with methyl- as well as with ethyl vinyl ketone to products containing no angular Me group.

The importance of *gem*-disubstitution in the cyclic alkanone is further demonstrated by the reaction of the enamine of 2,6,6-trimethylcycloheptanone **32** with methyl vinyl ketone. This afforded the angular substituted **33** in 61% yield, as the sole product. Our procedure enables us in principle to synthesize compounds that can be very useful as precursors for natural products. For instance the enamine of **14** reacted with the Nazarov reagent to the dione **34**, which could only be cyclized with acid to the desoxy triterpene precursor **35**. Literature states[14] that

†Under the more drastic conditions, developed for this kind of reactions by White and Weingarten,[11] 1-(N-pyrrolidino)-3,5,5-trimethyl-1-cyclopentene **7** can be synthesized in about 50% yield.

Table 1

Entry	Ketone	Enamine ratio [a] α	Enamine ratio [a] α′	Vinyl-ketone [b]	Product distribution [c]	Yield [d]
1	 5	25	75	MVK	 9 (100)	66
2				EVK	 12 (100)	92
3				i-PMK	 13 (100)	74
4	 14	35	65	MVK	 15 (80)  16 (20)	60
5				EVK	 17 (60)  18 (40)	62
6	 19	10	90	MVK	 20 (30)  21 (70)	63
7	 22	10	90	MVK	 23 (30)  24 (70)	61
8				EVK	 25 (100)	69
9	 26	10	90	MVK	 27a + 27b	68
10	 28	10	90	MVK	 30 (100)	61
11				EVK	 29 (100)	72
12	 32	80	20	MVK	 33 (100)	61
13	 14	35	65		 34  35 (100)	74
14	 36	10	90	MVK	 37a  37b (100)	64

[a] Enamine ratio's (α/α') were determined from the integrated area of the enamine vinylic proton in the NMR-spectrum

[b] MVK (methyl vinyl ketone); EVK (ethyl vinyl ketone); i-PMK (i-propenyl methyl ketone)

[c] Product distribution is given in % (total 100%).

[d] Isolated yield.

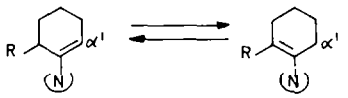
[e] Enamines of **19**, **22**, **26** and **28** consist of a mixture of *cis*- and *trans* isomers. It was not possible to estimate exactly the ratio from the NMR-spectrum, but in all cases the *cis*-isomer (60–80%) predominated.

such an annulation reaction through enamines is impossible.

DISCUSSION

The characteristic feature of the alkylation of enamines of cycloalkanones which has stimulated its tremendous development, is the selective monoalkylation. The reactivity of enamines in electrophylic reactions can be correlated with the amount of negative charge on the α'-C atom due to an overlap of the electron pair on nitrogen with the double bond. This is reflected by the position of

the vinyl proton in the NMR. In general the greater the overlap the larger the amount of the less (tri)substituted double bond and the further upfield will be the vinyl proton absorption, as is illustrated by Gurowitz[15] for a series of 2-methylcyclohexanone enamines.



B **B'**

That an overlap in **B'** is very low or absent and an overlap in **B** is only possible with an axial group R has been explained in terms of allylic strain.[16-19]

Consequently alkylation proceeds via **B**, despite 1,3-diaxial interactions,[20-22] thus leading to 2,6-dialkylated products. In literature there are a few reports mentioning 2,2-disubstitution in enamines of cyclopentanone[23] as well as cyclohexanone,[24] and a proper explanation is still absent.

From our experimental work the following facts are pertinent:

1. A substituent in the β'-position of the cycloalkanone is necessary. A large substituent favours 2,2-disubstitution. The influence of this steric factor decreases in the order: *gem*-dimethyl > isopropyl > methyl > isopropenyl.

2. The formation of angular substituted bicyclic enones is more pronounced with the 5- than with the 6-membered ring.

3. There is an influence of the nature of the alkyl vinyl ketone.

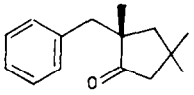
That our experimental results have to be explained through an alkylation of enamines is obvious from the following:

1. It is not a pyrrolidine catalysed Michael reaction with the 2-alkyl substituted cycloalkanones during the hydrolytic work-up with buffer, because these reaction conditions are unusually mild for formation of the required enolate anion.[25]

2. The possibility, that during the cyclization with ethanolic potassium hydroxide a reverse Michael reaction has occurred, followed by a new Michael reaction ultimately giving 2,2-disubstituted products, is also very improbable.[26] Further arguments that this process does not take place are entries 8, 9, 10 and 11, where no angular alkyl substituted products are formed.

3. The NMR spectrum of the crude product of entry 1 (Table 1) reveals before treatment with dilute base all the relevant signals of **9** (Me singlets at 0.99; 1.23 and 1.28 ppm).

4. Furthermore an alkylation experiment with the enamine of **5** (**8a** + **8b**) with benzylchloride in dimethoxy ethane yielded the 2-benzyl-2,4,4-trimethylcyclopentanone **31** as the only isolable product.



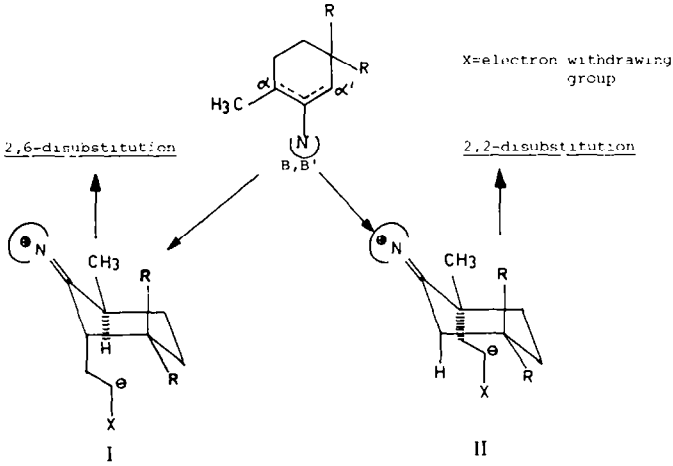
31

Our experiments were performed in benzene ($\epsilon = 2.0$) with enamine concentrations of about 1 molar. Firrell and Hickmott[25] concluded from the reaction of 1-(N-pyrrolidino)-6-methyl-1-cyclohexene and methyl acrylate and acrylonitrile that 2,2-disubstitution is favoured by moderate enamine concentration (0.1–2 molar and low dielectric constant of the solvent (dioxan $\epsilon = 2.2$). It is however difficult to understand why reaction with methyl acrylate in dioxan affords a ratio of 2:1 for the 2,6- and 2,2-disubstituted products, while the product ratio in benzene is 4:1.

The essence of the model of Firrell and Hickmott[25] is depicted in Scheme 1. When we apply their reasoning to the alkylation of the enamine of 2,5,5-trimethylcyclohexanone in an aprotic solvent, product formation takes place via intermediates I and II, both capable of stabilisation through intramolecular proton transfer. The only difference in interaction energies between II and I is a gauche butane interaction of about 1 kcal/mole.[27]

For the analogues of the 5-membered ring (alkylated enamine of 2,4,4-trimethylcyclopentanone I' and II') the difference between II' and I' can be calculated as a staggered Me–Me interaction of about 4.4–6 kcal/mole.[27,28a,28b]

When the reaction is performed in ethanol ($\epsilon = \sim 24$) it has no effect on the product distribution of the 5-membered ring (**9** is still the only product formed). But with the enamine of **14** the ratio of the products is altered from 80:20 to 43:57 for **15** and **16**. In this way Hickmotts scheme[25] suggests an unacceptable low solvent effect of 1 kcal/mole.



Scheme 1

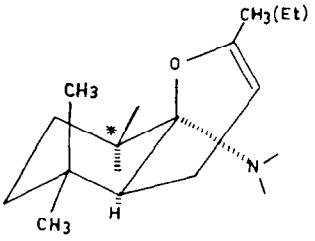
So the scheme possibly explains why the alkyl substituent in enamines of 3-alkylcyclohexanones hinders the attack at the 2-position, and gives arguments for the occurrence of α,α-disubstitution, it is generally wrong for enamine alkylation followed by an annulation reaction. This is further illustrated by the reaction of **36** with methyl vinyl ketone where under the specified reaction conditions of Firrell only **37a** and **37b**, as a result of 2,6-disubstitution were isolated. This is in agreement with the earlier observations of Stork *et al.*[22]

The reaction mechanism proves to be even more complex because the concept of intramolecular proton transfer is not strictly necessary in aprotic solvents. Because part of the intermediates are cyclized (annulation reaction) via a mechanism whereby pyrrolidine or water is formed,[29,30] both capable of intermolecular protonation.

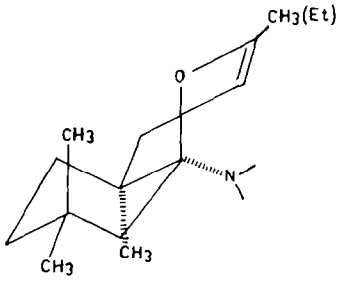
It is also possible that this kind of stabilisation is circumvented by an intramolecular charge neutralization. This is realized when the enolate anion of the introduced side chain attacks the iminium bond, yielding dihydropyrans.

The occurrence of dihydropyrans in the reaction of enamines with methyl vinyl ketone is not without precedent. Although labile and not isolable they have been proposed, i.a. based on spectroscopic evidence, as reactive intermediates.[8,31,32] The subsequent conversion of the unstable dihydropyrans to other products is promoted by small amounts of hydrolytic agents (water).

Scheme 2 illustrates this possibility for the configurations with an equatorial enamine group.



III



IV

eq. or ax methyl group

Scheme 2

From molecular models it can be seen that in III the mean distance between the axial CH_3-group and the dihydropyran ring is about 2.4 Å, while in IV it is about 1.5 times as large, thus favouring this intermediate strongly. A polar medium does not favour the neutral pyran IV, but the polar intermediates like I and II. Then, if Firrell's scheme is true, this tells us that there is a preference for 2,6-disubstitution.

However, steric effects in the cyclopentane system seems to be so stringent that the solvent has no noticeable effect.

Models also suggest that the dihydropyran intermediates are destabilized somewhat when the reaction is performed with ethyl vinyl ketone instead of methyl vinyl ketone, due to the greater alkyl interaction with the pyrrolidine ring.

Further work on the application of the above findings to the synthesis of sesquiterpenoids is in progress. It is hoped that such experimental work will also contribute to a better understanding of the precise mechanism of the annulation reactions.

EXPERIMENTAL

NMR spectra were measured on a Varian Associates A-60A instrument, using TMS as internal reference; unless stated otherwise spectra were measured of 10% v/v CCl_4 solns. Chemical shifts are given in ppm (δ) downfield from the internal standard, coupling constants (J) are given in Hz.

IR spectra have been recorded on a Perkin Elmer model 457 spectrophotometer, and were taken on CCl_4-solns, unless stated otherwise. Combined GLC-Mass spectra have been obtained on a Varian MAT CH 5 mass spectrometer coupled with a Varian Aerograph model 1200 gaschromatograph. Preparative separations were carried out on a Varian Aerograph model 1520, modified by us with a glass injector and equipped with a 2 m glass column, packed with a stationary phase of 10% DEGS on Embacel 80–100 mesh.

Starting materials. Solvents and reagents were reagent grade and were used without further purification.

2,4,4-*Trimethylcyclopentanone* **5**. was prepared according to a procedure of House[7] from isophoroneoxide, or from a 50/50 mixture of **5** and **6** purchased from VEBA Chemie A.G. by effective distillation.

2,5,5-*Trimethylcyclohexanone* **14**. was prepared by the following procedure: Dimedone was methylated[33a,33b] with MeI, the resulting methyldimedone was treated with iBuOH under the influence of a catalytic amount of *p*-toluenesulphonic acid.[34] The obtained keto enolether was reduced with LAH and treated with cold H_2SO_4 soln.[35] Finally the α,β-unsaturated ketone was hydrogenated to the desired **14**, b.p. 76–82°/18 mm.

5-*Isopropyl*-2-*methylcyclohexanone* (carvomenthone) **19** was prepared by catalytic hydrogenation of dihydrocarvone **28**, b.p. 89–90°/10 mm.

2,5-*Dimethylcyclohexanone* **22** was prepared by chromic acid oxidation of 2,5-dimethylcyclohexanol, purchased from Swiss Explosive Works Ltd (SSF), Switzerland.

2,6,6-*Trimethylcycloheptanone* (tetrahydro eucarvone) **32** was prepared according to known procedure[37] from carvone **26**.

Preparation of the pyrrolidine-enamines (General procedure). The enamines were prepared by azeotropic removal of water from a mixture of the cycloalkanone and excess of pyrrolidine in boiling benzene, using a Dean-Stark water separator. When reaction was slow, the water separator was filled with molecular sieves and p-TsOH was added to the reaction mixture as a catalyst[22] (Method A). Alternatively the reaction was carried out according to the procedure of White and Weingarten[11] (Method B).

2,4,4-*Trimethylcyclopentanone pyrrolidine-enamine* **8**. Method A, yield 95%, b.p. 61–64°/3 mm; IR: 1625 cm^{-1} (strong band, trisubstituted isomer) and 1665 cm^{-1} (weak, tetra-substituted isomer); NMR: 3.88 (1 H, broad s).

2,5,5-*Trimethylcyclohexanone pyrrolidine-enamine*. Method A, 82%, b.p. 110°/9 mm; IR: (neat) 1630 cm^{-1}; NMR: 3.91 (1 H, s).

5-*Isopropyl*-2-*methylcyclohexanone pyrrolidine-enamine*. Method A, 54%, b.p. 80–90°/0.4 mm; IR: (neat) 1632 cm^{-1}; NMR: 3.97 (1 h, d, J = 2 Hz) assigned to the *cis* isomer[13] 4.21 (1 H, d, J = 3 Hz) assigned to the *trans* isomer.[13]

2,5-*Dimethylcyclohexanone pyrrolidine-enamine*. Method A, 53%, b.p. 84–90°/5 mm; IR: (neat) 1630 cm^{-1}; NMR: 3.95 (1 H, d, J = 2 Hz) assigned to the *cis* isomer[13] 4.11 (1 H, d, J = 3.5 Hz) assigned to the *trans* isomer.[13]

2-Isopropyl-5-methylcyclohexanone pyrrolidine-enamine. Method B, 52%, b.p. 70–80°/0.2 mm; IR: (neat) 1634, 1636, 1654 (sh) cm $^{-1}$; NMR: 4.38 (1 H, d, J = 2 Hz) assigned to the *cis* isomer[13] 4.31 (1 H, d, J = 3 Hz) assigned to the *trans* isomer.[13]

5-Isopropenyl-2-methylcyclohexanone pyrrolidine-enamine. Method A, 48%, b.p. 96°/0.5 mm; IR: 1627 cm $^{-1}$ (enamine band), 1642 cm^{-1} (C=C); NMR: 3.05 (1 H, d, J = 2 Hz) assigned to the *cis* isomer[13] 4.09 (1 H, d, J = 3 Hz) assigned to the *trans* isomer.[13]

2-Methylcyclohexanone pyrrolidine-enamine **32**. Method A, 50%, b.p. 91–92°/6 mm; IR: (neat) 1636 cm $^{-1}$; NMR: 4.14 (=CH, t, J = 3.5 Hz).

2,6,6-Trimethylcycloheptanone pyrrolidine-enamine. Method B, 41% b.p. 86–87°/0.5 mm; IR: (neat) 1624, 1648, 1655 (sh) cm $^{-1}$; NMR: 3.97 (=CH, s, ~0.2 proton).

Synthesis of the bicyclic enones (General procedure). To 0.23 mole of the pyrrolidine enamine dissolved in 100 ml dry benzene was added dropwise a soln of 0.23 mole of alkyl vinyl ketone in 25 ml dry benzene. After stirring, in an atmosphere of dry N_2 for several hr at a temp. between 35 and 75° (the course of the reaction was monitored by NMR) the mixture was hydrolyzed with 50 ml of a soln made up of 25 ml AcOH, 25 ml water and 12.5 g NaOAc, by vigorous stirring and refluxing for 1–2 hr. Separation of the layers and extraction of the aqueous layer with benzene and washing the combined extracts with water and then with sat. $NaHCO_3$aq, gave after removal of the solvent under reduced pressure a mixture of cyclized and uncyclized product. The residue was dissolved in 150 ml of a 5% alcoholic KOH (unless stated otherwise), and refluxed for 1–2 hr. After cooling, neutralizing with AcOH and pouring into water, the mixture was extracted with pentane. The combined extracts were washed with water, dried on $MgSO_4$, concentrated *in vacuo* and distilled to give the bicyclic enone in yields up to 83%.

Whenever necessary a part of the distillate was separated into its components by means of preparative GLC.

No attempts were made to optimize the yields.

6,8,8-Trimethyl-bicyclo[4.3.0]*non*-1-*en*-3-*one* **9** was prepared by the reaction of the enamine of **5** with but-3-en-2-one. Yield: 68%, b.p. 65–66°/0.3 mm; IR: 1638 cm $^{-1}$ (w), 1674 cm $^{-1}$; NMR: 0.99 (3 H, s), 1.23 (3 H, s), 1.28 (3 H, s), 5.63 (1 H, m); Mass: 178 (M^+, 29%), 163 (28%), 150 (97%), 136 (100%), 135 (52%), 121 (31%) 107 (57%), 93 (25%), 91 (25%), 79 (39%), 41 (34%). An identical product was formed when a protic solvent was used. In methanol the yield was 9%.

2,6,8,8 - Tetramethyl - bicyclo[4.3.0]*non - 1 - en - 3 - one* **12** was prepared by the reaction of the enamine of **5** with pent-1-en-3-one. Yield: 83%, b.p. 85–87°/1 mm; IR: 1654 cm $^{-1}$ (sh), 1666 cm^{-1}; NMR: 1.00 (3 H, s), 1.24 (3 H, s), 1.27 (3 H, s), 1.63 (3 H, s); Mass: 192 (M^+, 26%), 177 (39%), 164 (31%), 150 (100%), 135 (42%), 121 (58%), 93 (49%), 55 (32%), 41 (52%).

4,6,8,8 - Tetramethyl - bicyclo[4.3.0]*non - 1 - en - 3 - one* **13** was prepared by the reaction of the enamine of **5** with 3-methylbut-3-en-2-one. Yield: 18%, b.p. 77–79°/0.6 mm; IR: 1649 cm^{-1} (w), 1674 cm $^{-1}$; NMR: 0.98 (3 H, s), 1.07 (3 H, d, J = 7 Hz), 1.23 (3 H, s), 1.30 (3 H, s), 5.62 (1 H, m); Mass: 192 (M^+, 12%), 150 (100%), 136 (15%), 135 (29%), 107 (24%), 93 (11%), 91 (14%), 41 (17%).

6,9,9 - Trimethyl - bicyclo[4.4.0]*dec - 1 - en - 3 - one* **15** and *7,7,10 - trimethyl - bicyclo*[4.4.0]*dec - 1 - en - 3 - one* **16** were formed from the enamine of **14** with but-3-en-2-one in a ratio of 4:1. Yield: 60%, b.p. 84–87°/0.4 mm; IR: 1620, 1677 cm $^{-1}$.

Compound **15**. NMR: 0.87 (3 H, s), 1.05 (3 H, s), 1.24 (3 H, s), 5.57 (1 H, d, J = 1.5–2 Hz) Mass: 192 (M^+, 64%), 177 (65%), 150 (63%), 149 (44%), 135 (57%), 124 (87%), 79 (57%), 69 (78%), 55 (43%), 41 (100%).

Compound **16**. Mass: 192 (M^+, 29%), 135 (13%), 124 (100%), 107 (15%), 95 (29%), 93 (17%), 91 (15%), 79 (23%), 77 (15%), 69 (58%), 55 (17%), 41 (55%). The same compounds **15** and **16** were formed, but in a ratio of 3:4 when the reaction was performed in EtOH as a solvent, yield 43%.

2,6,9,9 - Tetramethyl - bicyclo[4.4.0]*dec - 1 - en - 3 - one* **17** and *2,7,7,10 - tetramethyl - bicyclo*[4.4.0]*dec - 1 - en - 3 - one* **18** were formed from the enamine of **14** with pent-1-en-3-one in a ratio of 3:2. Yield: 62%, b.p. 94–96°/0.5 mm. The isomers were obtained by preparative GLC.

Compound **17**. IR: 1421, 1430, 1431, 1447, 1455 cm $^{-1}$ (medium bands), 1611, 1668 cm^{-1} (strong bands), shoulders at 1460, 1461 and 1670 cm^{-1}; NMR: 0.85 (3 H, s), 1.07 (3 H, s), 1.22 (3 H, s), 1.68 (3 H, d, J = 1.4 Hz); Mass: 206 (M^+, 81%), 191 (77%), 164 (48%), 149 (65%), 138 (64%), 91 (48%), 69 (46%), 55 (53%), 41 (100%).

Compound **18**. IR: 1422, 1453, 1474 cm^{-1} (medium bands), 1604, 1673 cm $^{-1}$ (strong bands) and shoulders at 1437, 1459 and 1677 cm^{-1}; NMR: 0.80 (3 H, s), 1.03 (3 H, s), 1.10 (3 H, d, J = ~6.5 Hz), 1.74 (3 H, d, J = 2.0 Hz), 2.7–3.3 (1 H, m); Mass: 206 (M^+, 24%), 138 (100%), 109 (24%), 69 (54%), 55 (16%), 41 (39%).

9 - Isopropyl - 6 - methyl - bicyclo[4.4.0]*dec - 1 - en - 3 - one* **20** and *7 - isopropyl - 10 - methyl - bicyclo*[4.4.0]*dec - 1 - en - 3 - one* **21** were formed in a ratio of 2:5 by the reaction of the enamine of **19** with but-3-en-2-one. Yield: 69%, b.p. 98–108°/0.1 mm. The products were separated by preparative GLC.

Compound **20**. IR: 1419, 1434, 1456, 1460, 1466, 1617 cm $^{-1}$ (medium bands) 1677 cm^{-1} (s), shoulder at 1450 cm $^{-1}$; NMR: 0.7–1.0 (6 H), 1.27 (3 H, s), 5.58 (1 H, s, $W_{1/2}$ = 3 Hz); Mass: 206 (M^+, 41%), 178 (39%), 163 (74%), 135 (49%), 121 (98%), 96 (46%), 93 (51%), 91 (57%), 82 (59%), 79 (69%), 55 (65%), 43 (48%), 41 (100%).

Compound **21**. IR: 1421, 1457, 1465 cm^{-1} (medium bands), 1615 cm $^{-1}$ (w), 1677 cm $^{-1}$ (s), shoulders at 1444, 1452 and 1687 cm $^{-1}$; NMR: 0.83 (3 H, d, J = 6.5 Hz), 0.96 (3 H, d, J = 6.5 Hz), 1.11 (3 H, d, J = 6.5 Hz), 5.70 (1 H, $W_{1/2}$ = 3.5 Hz); Mass: 206 (M^+, 37%), 135 (58%), 124 (100%), 121 (31%), 107 (29%), 93 (31%), 82 (32%), 79 (42%), 55 (40%), 41 (63%).

6,9 - Dimethyl - bicyclo[4.4.0]*dec - 1 - en - 3 - one* **23** and *7,10 - dimethyl - bicyclo*[4.4.0]*dec - 1 - en - 3 - one* **24** were formed in a ratio of 2:5 by reaction of the pyrrolidine enamine of **22** with but-3-en-2-one. Yield: 61%, b.p. 96–103°/0.6 mm. The products were separated by preparative GLC.

Compound **23**. This could not be obtained in a pure state. IR: (neat) 1420, 1430, 1455 (m); 1462 cm^{-1} (sh), 1679 (s), 1685 (sh), 1709 (w) cm^{-1}; Mass: 178 (M^+, 86%), 150 (97%), 136 (100%), 135 (78%), 121 (95%), 93 (67%), 69 (72%), 41 (74%), 39 (67%).

Compound **24**. IR: (neat) 1420, 1451, 1456 (medium bands), 1468 (sh) cm $^{-1}$; (CCl_4): 1614, 1621 cm $^{-1}$ (weak bands), 1682 (s) and shoulders at 1678, 1675 cm^{-1}; NMR: 1.07 (3 H, broad s), 1.12 (3 H, d, J = 6 Hz), 5.68 (1 H, s, $W_{1/2}$ = 3.5 Hz); Mass: 178 (M^+, 87%), 150 (67%), 135 (80%), 108 (78%), 107 (68%), 93 (62%), 69 (92%), 55 (64%), 41 (100%), 39 (78%).

2,7,10 - Trimethyl - bicyclo[4.4.0]*dec - 1 - en - 3 - one* **25** was formed from the reaction of the enamine of **22** with pent-1-en-3-one. Yield: 69%, b.p. 90–92°/0.5 mm; IR: 1422, 1605 cm^{-1} (weak bands), 1452, 1463 cm $^{-1}$ (medium bands), 1670 cm $^{-1}$ (s); NMR: 1.05 (3 H, broad s), 1.11 (3 H, d, J = 7 Hz), 1.72 (3 H, d, J = 1.7 Hz), 2.7–3.4 (1 H, m); Mass: 192 (M^+, 100%), 136 (83%), 121 (43%), 107 (45%), 93 (59%), 79 (42%), 77 (39%), 55 (44%), 41 (73%).

10 - Isopropyl - 7 - methyl - bicyclo[4.4.0]*dec - 1 - en - 3 - one* **27** was prepared by reaction of the enamine of **26** with but-3-en-2-one. Yield: 60%, b.p. 103–107°/0.5 mm; The two epimers **27a** and **27b** were formed in a ratio of 4:1 and were separated by preparative GLC.

Compound **27a**. IR: 1420, 1450, 1455, 1618, 1679 cm^{-1}, shoulders at 1462, 1467, 1682, 1685 cm^{-1}; NMR: 0.79 (3 H, d, J = 6 Hz), 0.98 (3 H, d, J = 6 Hz), 1.03 (3 H, broad s), 5.67 (1 H, $W_{1/2}$ = 2.5 Hz).

Compound **27b**. IR: (neat) 1422, 1451, 1468 cm^{-1}; IR: 1619, 1675, 1678, (sh), 1687 cm^{-1}; NMR: 0.92 (3 H, d, J = 6.5 Hz), 1.00 (3 H, d, J = 6.5 Hz), 1.05 (3 H, broad s), 5.69 (1 H, s, $W_{1/2}$ = 3.0 Hz). The mass spectra of diastereoisomers **27a** and **27b** were almost identical. Mass: 206 (M^+, 37%), 164 (100%), 149 (36%), 122 (33%), 121 (31%), 91 (36%), 79 (30%), 55 (27%), 43 (45%), 41 (55%).

2,10 - Dimethyl - 7 - isopropenyl - bicyclo[4.4.0]*dec - 1 - en - 3 - one* **29** was formed as the only product from the reaction of the pyrrolidine enamine of **28** with pent-en-3-one. Yield: 72%, b.p. 104–105°/0.25 mm, solidifies at room temp. IR: 1423, 1440, 1450, 1454, 1608, 1645 cm $^{-1}$ (medium weak bands), 1462 cm^{-1} (sh), 1672 cm $^{-1}$ (s); NMR; 1.12 (3 H, d, J = 7 Hz), 1.71 (3 H, m), 1.75 (3 H, s), 4.65–4.80 (2 H, m); Mass: 218 (M^+, 48%), 203 (37%), 161 (28%), 136 (37%), 119 (27%), 109 (82%), 105 (36%), 93 (49%), 91 (55%), 82 (54%), 81 (100%), 79 (53%), 77 (44%), 67 (52%), 55 (43%), 53 (41%), 41 (100%).

7 - Isopropenyl - 10 - methyl - bicyclo[4.4.0]*dec - 1 - en - 3 - one*

30. These epimers were formed from the pyrrolidine enamine of **28** with but-3-en-2-one, in a ratio of 1:2. Yield: 61%, b.p. 110–114°/0.5 mm. The diastereoisomers could not be separated. IR: 1421, 1450, 1458, 1618, 1625, 1645 (medium weak), 1444 cm^{-1} (sh), 1680 cm^{-1} (s); NMR: 1.10 (3 H, d, J = 6.5 Hz), 1.19 (3 H, d, J = 7 Hz), 4.7–4.85 (2 H, m), 5.6–5.8 (1 H, m); Mass: 204 (M^+, 86%), 189 (16%), 162 (97%), 147 (53%), 105 (66%), 95 (58%), 91 (75%), 81 (59%), 79 (74%), 77 (50%), 67 (42%), 55 (43%), 53 (54%), 41 (100%), 39 (61%).

2-Benzyl-2,4,4-trimethylcyclopentanone **31**. 0.15 Mole of the enamine of **5** and 0.165 mole of benzyl chloride, dissolved in 100 ml of dry dimethoxyethane (there was no reaction in benzene) was heated at 85° for 20 hr. The mixture was hydrolized with acetate buffer soln and was extracted with pentane. The pentane extract was washed to neutral, dried, concentrated and distilled. Yield: 10%, b.p. 92°/0.6 mm; IR: 1496, 1583, 1602 cm^{-1} (medium weak bands), 1741 cm^{-1} (s); NMR: 0.93 (3 H, s), 1.07 (3 H, s), 1.15 (3 H, s), 2.66 (CH_2, AB part, J = 13 Hz), 6.9–7.4 (5 H, m).

10-Methyl-bicyclo[4.4.0]dec-1-en-3-one **37a** and **37b** was the only product formed from the reaction of **36** with but-3-en-2-one in a ratio of 2:1. Yield: 64%, b.p. 82–84°/0.25 mm, solidifies at room temp. IR: 1421, 1450, 1460 (medium weak bands), 1680 cm^{-1} (s); NMR: 1.08 (3 H, d, J = 7.5 Hz) assigned to **37a**, 1.18 (3 H, d, J = 6.5 Hz) assigned to **37b**, 5.68 and 5.71 (1 H, s).

1,5,5-Trimethyl-bicyclo[5.4.0]undec-7-en-9-one **33** was formed from **32** with but-3-en-2-one. Yield: 61%, b.p. 101°/0.2 mm, solidfies at room temp. IR: (CCl_4): 1417, 1438, 1449, 1451, 1612 cm^{-1} (medium weak bands), 1470 cm^{-1} (sh), 1670 cm^{-1} (s); NMR: 0.85 (3 H, s), 1.03 (3 H, s), 1.18 (3 H, s), 1.59 (1 H, s); Mass: 206 (M^+, 19%), 124 (100%), 109 (24%), 107 (18%), 91 (18%), 82 (43%), 79 (23%), 77 (17%), 55 (36%), 41 (42%), 39 (26%).

2-Carbethoxy-6,9,9-trimethyl-bicyclo[4.4.0]dec-1-en-3-one **33**. A soln of 0.043 mole **14** and 0.043 mole ethyl acryloylacetate[36] in 25 ml dry benzene was heated for 1 hr at 65°. The mixture was hydrolyzed with 10 ml of the acetate buffer soln by stirring at 70° for 1 hr. After the usual work-up the crude alkylated product **34** was cyclized by dissolving it into 200 ml EtOH, saturated with dry HCl gas and standing for a weekend at room temp. The soln was poured into 400 ml ice cold saturated brine and extracted 4 times with 100 ml chloroform. The extracts were washed to neutral, dried and concentrated. The residue was distilled and the distillate crystallized from hexane. Yield: 38%, m.p. 97–99°; Lit.[14]: 42%, m.p. 97.5–98.5°; IR: (neat) 1418, 1425, 1443, 1454, 1462, 1619 cm^{-1} (medium weak bands), 1680, 1735 (s); NMR: 0.87 (3 H, s), 1.03 (3 H, s), 1.19 (3 H, s), 1.21 (3 H, t, J = 7 Hz), 4.20 (2 H, q, J = 7 Hz).

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