CHAPTER III

SYNTHESIS OF GRANDISOL

[A SEX PHEROMONE OF MALE BOLL WEEVIL]
INTRODUCTION

In recent years an intensive research activity has been centred on the use of insect sex pheromones in a major programme to control the destructive pests of various commercial crops all over the world. The use of pheromones in monitoring the pest population has been accepted as a major part of integrated pest management.

The male boll weevil is a highly destructive pest of cotton crop, the insect secretes a sex pheromone comprising four components 1, 1A, 1B and 1C of which grandisol, 1 possesses relatively more complex structural features. The synthesis of 1 has been a challenging problem to organic chemists and continues to be a topic of current interest.

\[ \text{1} \quad \text{1A} \quad \text{1B} \quad \text{1C} \]

*It is estimated that about 1/3 of the total pesticide production is diverted for the control of this pest alone in United States of America.*
In view of the above considerations, we concentrated our efforts to accomplish the synthesis of 1 using, especially the methodology described in the previous chapter. It is therefore pertinent to provide a brief summary of the various syntheses of grandisol reported so far in literature. These syntheses can be classified into photochemical and non-photochemical approaches.

**Photochemical approaches:** The various syntheses so far reported in this category involved [2+2] photocycloaddition reaction in order to construct cyclobutane ring. The first synthesis of grandisol was reported by Tumilson et al. who irradiated a mixture of isoprene and methylvinylketone and obtained the stereoisomers 2 and 3 (Scheme 3.01). These ketones were separated and the cis-isomer, 2 was treated with methyl grignard to get the alcohol 4. The latter was converted to 1 by hydroboration-oxidation followed by dehydration and hydrolysis.

Zurfluh et al. used a similar approach in obtaining the initial bicyclic system and successfully eliminated the formation of the trans-isomer by using a cyclic enone in [2+2] cycloaddition. The transformation of 5 to 1 was achieved by following a sequence of reactions as shown in scheme 3.02. Gueldner et al. achieved a shorter synthesis of 1 in which the cycloaddition product 6 was treated with excess of methyl-lithium to furnish the tertiary alcohol 7. The latter on
SCHEME-3.01

[Tumilson et al]⁴

\[ \text{[Image]} \]

SCHEME-3.02

[Zurflüh et al]⁵
treatment with acetic anhydride followed by reduction with LAH yielded the required 1. However, the dehydration step was not regioselective and resulted in the isomer $\delta$ in addition to the required product (Scheme 3.03). Synthesis of 1 has been achieved by Kosugi et al. starting from 6 by following a similar approach with minor modifications.

Cargil and Wright obtained the bicyclic intermediate 9 by [2+2] cycloaddition of ethylene to substituted cyclopentenone, in good yield. The key step in their synthesis was the formation of the ozonide 10 and its subsequent cleavage to the keto acid 11 (Scheme 3.04). The latter acid was transformed to 1 by a known sequence of reactions. A novel synthesis of grandisol from eucarvone has been reported by Ayer and Browne who carried out intramolecular [2+2] cycloaddition and the bicyclic ketone thus obtained was subjected to ketone transposition and oximation (Scheme 3.05). The oxime 12 underwent an unusual Beckmann fragmentation affording 13 which was further carried on to 1 by simple transformations. However, the initial intramolecular photocycloaddition was very sluggish.

**Non-photochemical approaches:** The first and the most efficient non-photochemical synthesis of 1 was reported by Billups et al. The key step in their synthesis was the catalytic dimerization of isoprene to cis-1,2-divinylcyclobutane 14 (12-15% yield) which could be isolated by fractional
SCHEME - 3.03

\[ \text{Gueldner et al}\]^{6}

1. $\text{MeLi}$
2. $\text{O}_3$

SCHEME - 3.04

\[ \text{Cargil and Wright}\]^{8}
distillation at 0°C. Selective hydroboration of the mono-substituted double bond of 14 afforded 1 (Scheme 3.06).

Wenkert11 et al. accomplished the synthesis of 1 making an elegant use of their reaction which involved the acid-catalyzed rearrangement of α-oxycyclopropyl carbinols into cyclobutanones. These authors employed a regiospecific cyclopropanation followed by acid-catalyzed rearrangement of fused cyclopropyl ether 16 to get the bicyclic dione 17. The required cyclopropyl ether 16 was obtained in a multi-step sequence of reactions from 15. The diketone 17 was selectively protected and was transformed to the known oxime 12 (Scheme 3.07).

Stereoselective cyclization of epoxynitrile 18 was the strategy used by Stork12 to construct the cyclobutane ring of 1. Reduction of the nitrile to methyl group and elaboration of the methylcarbinol into isopropenyl group completed this synthesis (Scheme 3.08). Babler13 gained entry into the cyclobutane system by an intramolecular cyclization of chloroester 19, obtained by the sequence of reactions as depicted in Scheme 3.09. Formation of the undesired trans-isomer (35%) was the drawback of the synthesis. Treatment of the cis-derivative with methyllithium afforded 4 which was already converted to grandisol by earlier workers.

In a novel approach, Trost14 et al. used their annelation reagent, lithiocyclopropylphenyl sulfide to prepare cyclo-
**SCHEME - 3.05**

[Ayer and Browne]^{9}

\[
\begin{align*}
\text{ reactant } & \xrightarrow{1. \text{hv, 7 days}} \text{ intermediate } & \xrightarrow{1. t-\text{AmOK}, n-\text{BuONO}} \text{ product } \xrightarrow{2. \text{N}_{2}\text{H}_{4}, \text{KOH}} \text{ product }
\end{align*}
\]

**SCHEME - 3.06**

[Billups et al]^{10}

\[
\begin{align*}
\text{ reactant } & \xrightarrow{\text{Ni(Cyclooctadiene)}_{2}} \text{ intermediate } & \xrightarrow{1. \text{L} \text{BH}} \text{ product } \xrightarrow{2. \text{H}_{2}\text{O}_{2}-\text{NaOH}} \text{ product }
\end{align*}
\]
**SCHEME - 3.07**

[Wenkert et al.]^{11}

1. $\text{SeO}_2, \text{AcOH}$
2. $\text{MeLi}$
3. $\text{CrO}_3, \text{Py}$

<Chemical Structure>

$\text{MeO}$

15

$\text{MeO}$

16

$\text{H}^+$

**SCHEME - 3.08**

[Stork et al.]^{12}

$\text{i-Pr}_2\text{NLi}$

$\text{Br}$

$\text{OTHP}$

$\text{OTHP}$

$m\text{-CPBA}$

$\text{CN}$

$\text{CN}$

17

$\text{CN}$

$\text{CN}$

18

$\text{CN}$

$\text{CN}$

($^+\text{)}{1}$
butanone 20 as well as the spiroketone 21. The latter spiro derivative was transformed to 1 by a sequence of reactions as shown in Scheme 3.10. However, the product thus obtained was contaminated with the trans-isomer fragranol 22.

An isolated report of an asymmetric synthesis of (+)1 was due to Hobbs and Magnus15. The authors elegantly utilized the asymmetry present in (-)-β-pinene in their synthesis. The sequence of reactions starting from the alcohol 23 leading to the required optical isomer has been shown in Scheme 3.11. The key reactions, worthy of mention are (i) the functionalization of the required methyl group in 23 using Barton's procedure and (ii) the unusual α'-cleavage in the photolysis of the ketone 24 leading to 25.

A synthesis of grandisol starting from cyclobutane carboxylic acid involving a 1,4-addition of vinylgrignard has been reported by Clark16. In yet another synthesis, intramolecular cyclization has been utilized/form the cyclobutane ring from a derivative of geraniol17. Banerjee and Venkateswaran18 have recently reported a photolytic Wolf rearrangement of α-diazocyclopentanones to obtain cyclobutane carboxylates. One such carboxylate has been transformed into a precursor of 1.
SCHEME - 3.09

\[
\text{[Babler]}^{13}
\]

\[
\begin{align*}
\text{Cl} & \xrightarrow{\text{MgCl}} \text{CH}_2=\text{CH}-\text{CH}_2\text{Cl} \\
& \xrightarrow{1.\text{AcOH}, H^+} \text{CH}_2=\text{CH}-\text{CH}_2\text{OH} \\
& \xrightarrow{2.\text{K}_2\text{CO}_3} \text{CH}_2=\text{CH}-\text{CH}_2\text{OH}
\end{align*}
\]

\[19\]

Cis: Trans = 65:35

SCHEME - 3.10

\[
\text{[Trost et al]}^{14}
\]

\[
\begin{align*}
\text{CHO} & \xrightarrow{1.\text{Ph SH}, \text{Et}_3\text{N}} \text{PhS} \\
& \xrightarrow{2. \text{Ph Li}} \text{PhS} \\
& \xrightarrow{\text{H}^+} \text{PhS}
\end{align*}
\]

\[20\]

\[
\begin{align*}
1.\text{PyBr}_3-\text{AcOH} \\
2.\text{NaOMe}-\text{MeOH} \\
3.\text{AgNO}_3-\text{MeOH}
\end{align*}
\]

\[21\]

\[22(20\%)\]
SCHEME - 3.11

[Hobbs and Magnus]^{15}

1. Hydroboration
2. Ac_2O-Py
3. POCl_3-Py
4. CrO_3-Py

SCHEME - 3.12

1,6 bond cleavage

1,7 bond cleavage
PRESENT WORK

The foregoing brief summary on the synthesis of 1 shows that the only photoreaction utilized for the formation of cyclobutane ring is the [2+2] cycloaddition reaction. In view of the already emphasized importance of grandisol, we envisaged to utilize the methodology developed by us to construct bicyclo[3.2.0]heptane system in its synthesis. This attempt provides an example of utilizing another photoreaction (photo-VCR) in the synthesis of cyclobutane derivatives. The present chapter describes the results of various experiments directed towards the synthesis of 1 starting from 2-carene, 26.

RESULTS

Photolysis of an approximately 1% solution of 26 in petroleum ether containing toluene as a sensitizer afforded a product comprising essentially a single component (≈ 93% conversion) along with toluene and the starting material. The characterization of the product which was isolated by preparative GLC is described below.

The VCR reaction is known to involve the opening of cyclopropyl ring and the migration of the double bond with

*The work presented in this chapter has been published as a communication: Tetrahedron Lett. 2245 (1984).
The opening of 1,6-cyclopropyl bond in **26** should lead to the structure **27**, while the bornylene **28** is to be anticipated when 1,7-bond cleaves.

The compound on hand displayed a molecular ion peak at m/e 136 and analysed for C_{10}H_{16}. From this data and the above discussed modes of cleavage, the product can be represented by either of the structures **27** and **28**. The PMR spectrum of the compound (Fig.3.01) displayed three methyl singlets at 0.94, 0.97 and 1.16, in addition to a 4H multiplet between 1.56 - 1.87 and a 2H olefinic singlet at 5.38. The downfield methyl singlet at 1.16 was suggestive of the presence of a cyclobutane ring. An examination of the reported PMR spectrum of bornylene **19**, **28**, revealed that each of its olefinic protons appears distinctly; one as a doublet at 5.59 and the other as a double doublet at 5.84; the three methyl singlets appeared at 0.75, 0.80 and 1.02.

The PMR spectrum of the compound on hand was entirely different from that of bornylene and therefore structure **28** was ruled out and the compound was identified as 1,4,4-trimethyl-cis-bicyclo[3.2.0]hept-2-ene, **27**. The cis-ring junction as shown in **27** is based on the consideration that trans-fused bicyclo [3.2.0]heptene system appears to be highly strained and has not been reported so far although a few saturated analogues are known **20**.
The assignment of the structure 27 was further corroborated by an analysis of its mass spectrum which showed the molecular ion peak at m/e 136 and a base peak at m/e 93 in addition to prominent peaks at 121 and 108. A loss of methyl group (leading to m/e 121) followed by a loss of ethylene molecule (or vice versa) could rationalize the base peak. This type of fragmentation has been observed by us previously (Chapter II) and by others21 as well.

It is interesting to note that the product 27 obtained from the optically active 26 turned out to be racemic. This observation indicated a stepwise mechanism (discussed in Chapter II) probably involving a diradical intermediate as indicated in the Scheme 3.12.

A careful analysis of the structure 27 revealed that it inherently possesses essential features of the target molecule 1. The required cyclobutane ring with a methyl and a hydrogen with right cis-stereochemistry was already present. The availability of a geminally methyl-substituted carbon adjacent to the cyclobutane ring indicated its potentiality for transformation into an isopropylidene group of grandisol. Furthermore, the two-carbon unit required for the side chain of 1 was also present. This analysis enabled us to plan a sequence of reactions for the transformation of 27 into 1; a retrosynthetic analysis is depicted in Scheme 3.13.
Treatment of the bicyclic olefin 27 with diborane afforded a product in good yield. It appeared almost as single component on TLC with a variety of solvent systems while it was found to be a mixture of two components (\( \sim 30:70 \)) having close retention times (GLC), indicating their isomeric nature. The PMR spectrum (Fig.3.02) of the product mixture exhibited a 6H singlet at 0.84 and a 3H singlet at 1.19 indicating the three methyl groups of the major isomer. In addition to these signals, there appeared three 3H singlets of low intensity at 0.78, 0.98 and 1.15 suggestive of the presence of other isomer as a minor component. The methyl singlets at 1.15 and 1.19 (assignable to methyl groups on cyclobutane ring) showed a ratio comparable to the GLC distribution. The methine protons of the isomers could not be distinguished and these were observed as multiplets in the range of 3.55 - 4.29. From this PMR spectral data and certain mechanistic considerations discussed later, the major and minor components of the products have been assigned the structures 29 and 30 respectively (Scheme 3.14).

The above structural assignment was corroborated by the mass spectrum of the product mixture which exhibited a molecular ion peak at m/e 154 and major peaks at m/e 126 (base peak), 139 and 121. The base peak could easily be rationalized to have arisen from the loss of an ethylene molecule from the molecular ion; the peaks at 139 and 121 could
have derived from an initial loss of a methyl group and a further loss of a water molecule from the parent molecular ion.

Two pairs of epimeric alcohols that can be anticipated from the hydroboration of 27 are shown in scheme 3.14. The alcohols 29 and 30 are to be expected from 27 if the hydroboration occurs from the exo-face whereas the reaction from the endo-face should lead to the mixtures of alcohols 31 and 32. An examination of the molecular model of 27 revealed that the exo-face is relatively free and attack of any reagent should be anticipated to occur from that face. Such a preference has also been observed\textsuperscript{22} in comparable bicyclic systems. Based on this rationale, it was assumed that the hydroboration of 27 has resulted in a mixture of regioisomers 29 and 30, with same stereochemical disposition of the hydroxyl function. However, the above spectral data did not suffice to identify the major and minor components in terms of 29 and 30. This distinction was possible when these regioisomeric alcohols were oxidized to the corresponding ketones.

Oxidation of 29 and 30: The mixture of alcohols 29 and 30 was subjected to PCC oxidation and the product obtained therefrom was found to be a mixture of two components (GLC) in 30:70 ratio. The IR spectrum was conspicuous by the absence of hydroxyl band and the presence of an intense absorption at
1740 cm\(^{-1}\) indicative of a five-membered ring ketone. The PMR spectrum of the product exhibited a set of three 3H singlets of high intensity at 0.91, 1.04 and 1.23 and another set of three 3H singlets of much lower intensity at 0.96, 0.99 and 1.33. Comparison of this PMR spectral data with those reported\(^9\) for the expected products 33 and 34 (Scheme 3.15) confirmed their presence and also indicated that the major component was the undesired 33. In view of the fact that the required ketone intermediate 34 could not be obtained as a major product from the hydroboration of the bicyclic olefin 27, we contemplated a few more reactions to check their suitability to achieve high regioselectivity in favour of 34. One such attempt was the stereoselective epoxidation of the bicyclic olefin 27; possible regioselective opening of this epoxide was anticipated to furnish the required alcohol as a major component.

**Epoxidation of 27:** Treatment of 27 with m-chloroperbenzoic acid furnished a product which comprised two components with close retention times in a 70:30 ratio (GLC) again suggestive of an isomeric nature of the product; however, no attempts were made to separate these isomeric epoxides. The PMR spectrum of the product (Fig.3.03) displayed three methyl singlets at 0.80, 0.96 and 1.07; in addition to these, two singlets of low intensity together integrating for nine protons were noticed at 1.00 and 1.18. The singlets at
**RETRO-SYNTHETIC SCHEME 3.13**

![Scheme 3.13 Diagram](image)

**SCHEME 3.14**

![Scheme 3.14 Diagram](image)

**SCHEME 3.15**

![Scheme 3.15 Diagram](image)
1.07 and 1.18 were in a 70:30 ratio and could be attributed to the methyl groups on cyclobutane ring of the expected isomeric epoxides. The spectrum was conspicuous by its absence of olefinic protons originally present in 27 and showed a 4H multiplet between 2.80 and 3.16 which could be attributed to the epoxy protons. The GLC picture and the PMR spectral pattern showed that the product consisted of the isomeric epoxides 35 and 36 (Scheme 3.16). The major epoxide was assigned the structure 35 based on the expected preferential attack of the peracid from the less hindered exo-face of the olefin 27 as observed in similar systems.

**LAH opening of epoxides 35 and 36**: When the mixture of epoxides was treated with LAH in ether for a long duration, it was observed that the reaction was rather sluggish. However, the rate of the reaction could be accelerated when the solvent was changed to tetrahydrofuran and the reaction carried out under reflux conditions (experimental). The GLC of the product indicated it to comprise two components of close RT's in a 70:30 ratio. Its PMR spectrum showed three 3H singlets at 0.78, 0.98 and 1.15 accounting for the methyl groups of the major component. The spectrum also showed three singlets at 0.74, 0.90 and 1.20, however, of low intensity indicating the presence of a minor isomeric component. The latter and former groups of signals bore a 7:3 ratio to each other comparable to the observed GLC distribution. However, the methine protons of the
two components could not be discerned and these appeared as multiplets in the range 3.64 - 4.27. From this PMR spectral data and a few mechanistic considerations discussed later, the major and the minor components were assigned the structures 30 and 31 respectively (Scheme 3.17).

As in the case of hydroboration reaction, the same two pairs of alcohols 29, 30, and 31, 32 can in principle be anticipated from the mixture of the epoxides 35 and 36 (Scheme 3.16). In the opening of epoxides by LAH, steric factors play an important role. The opening of epoxide 35 from the endo-face leads to a mixture of regioisomers 30 and 29 with a β-oriented hydroxyl group. Similarly, opening of the epoxide 36 from the exo-face is to be expected to result in a mixture of two regio-alcohols 31 and 32 with α-stereochemistry.

As the reaction product resolved (GLC) into only two these components (instead of four), we thought that/compounds could be mostly regioisomeric alcohols. It can be recalled here that the epoxide 35 and 36 were present in a 70:30 ratio and the products obtained therefrom, were also in the same ratio. From these considerations the product could be considered to be either a mixture of 30 and 31 or 29 and 32. It is necessary to point out here that although regiodistribution of isomers is of great importance, the stereochemical disposition of the hydroxyl group is insignificant, as these functional groups were required to be transformed into ketones in the subsequent step.
Although the selection of either $30$ and $31$ or $29$ and $32$ to represent the products could not be made at this stage, this could be done easily when the alcohols were oxidized to the corresponding ketones.

**PCC oxidation of $30$ and $31$:** The mixture of $30$ and $31$ when subjected to oxidation with PCC furnished a product in high yield. This was found by GLC to comprise two components in a 70:30 ratio. It is interesting to note that the product composition although remained same, the distribution between the two ketones had widely changed in comparison with that obtained from hydroboration route. A 30:70 ratio of the previous case had clearly changed to 70:30 ratio indicating an opposite pattern of selectivity. The PMR spectrum of the oxidation product (Scheme 3.17) also confirmed this distribution. These two components were isolated by preparative GLC and the PMR spectra of the major (Fig.3.04) and minor components were identical with those reported$^9$ for $34$ and $33$ respectively. The structural assignment of $34$ to the major isomer was further confirmed by the transformation of the ketone to its well-characterized$^9,11$ oxime derivative, $12$. It can be observed here that between the two routes employed to obtain the required ketone $34$, the epoxidation route was successful.

Two other methods that we contemplated for possible selective hydroxylation of the double bond of $27$ are the Prevost reaction$^{23}$ and oxymercuration-demercuration$^{24}$. As can
be anticipated from the previously discussed mechanistic considerations, the major pathways of these two reactions should involve $37$ and $39$ (Scheme 3.18) as intermediates respectively. The intermediate $37$ on nucleophilic opening with an acetate anion leads to $38$ which on further sequence of reactions should result in the undesired ketone $33$. Similarly, the intermediate $39$, an opening with water followed by sodium borohydride reduction (to cleave C-Hg bond) and subsequent oxidation is expected to give a mixture of the ketones $33$ and $34$. Therefore, these reactions were not attempted.

An examination of the various synthetic schemes reported for grandisol (vide supra) reveals that the oxime derivative $12$ of the ketone $34$ constitutes a key intermediate in two of the schemes (3.05 and 3.07). This intermediate has been independently transformed by Ayer$^9$ and Wenkert$^{11}$ into the target molecule following the same sequence of reactions. Therefore, the present synthesis of this key intermediate $12$ constitutes a formal synthesis of grandisol, $1$.

**DISCUSSION**

It can be recalled that [2+2]cycloaddition has been the only photochemical reaction adopted so far for the construction of the cyclobutane ring of grandisol. It may be pointed out that the present synthesis offers the first example of a different photoreaction, namely, photo-VCR in the construction of a four-membered ring.
SCHEME 3.16

(+) 27 \( \xrightarrow{m\text{-CPBA}} \) \( \text{35} \) + \( \text{36} \)

SCHEME 3.17

\( \text{35} \xrightarrow{\text{LAH, THF}} 30 + 29 \)

\( \text{36} \xrightarrow{\text{LAH, THF}} 31 + 32 \)

\( 30 + 31 \xrightarrow{\text{PCC, } CH_2Cl_2} 34 \) (major) + 33 (minor) (70:30)

SCHEME 3.18

(+) 27 \( \xrightarrow{I_2, CH_3COOAg} \) \( \text{37} \xrightarrow{^{18}OAc} \text{38} \xrightarrow{\text{I}} \text{33} \)

(+) 27 \( \xrightarrow{\text{Hg(OAc)}_2} \) \( \text{39} \xrightarrow{1. \text{H}_2\text{O}} \xrightarrow{2. \text{NaBH}_4} \xrightarrow{3. \text{PCC}} \text{33 + 34} \)
Another interesting feature of the present synthesis is the utilization of 2-carene as the starting material. It is now being produced by the base-catalyzed isomerization of 3-carene, a major component of the Indian turpentine oil. In fact, the utilization of 3-carene in a worthwhile manner has been one of the challenging problems since long. As the present synthesis of 1 is carried out as an academic exercise only, its feasibility as a practical route remains to be worked out. However, in view of the ready accessibility of 3-carene as a cheap raw material in the country, it would be worthwhile to introduce certain modifications in the basic approach in order to assess its merits as a practical route.

Grandisol, as an important component of grandlure, insect sex pheromone of male boll weevil, finds application in field traps experiments designed to monitor and control the boll weevil. From this point of view, a practical method for the synthesis of grandisol* assumes importance.

*Currently, (±)grandisol is marketed at the rate of $ 35/g in USA [from Farchan, Story Chemical Corporation (USA)].
EXPERIMENTAL

General remarks remain the same as described in experimental section of Chapter II.

2-Carene, 26*: Freshly distilled over sodium, b.p. 166-170°, $[\alpha]_D^0 +96°$ (neat), lit. 25 $[\alpha]_D^0 +97.7°$ (neat), $[\alpha]_D^0 +10.2°$ (c, 0.60).

UV: $\lambda_{max}$ (methanol) 210 (ε 5450)

PMR: (60 MHz) 0.85 and 1.07 (2s, 3H each, t-CH$_3$s), 1.65 (s, 3H, -C=C-CH$_3$) and 5.48 (s, 1H, -C=CH) [Lit. 26 UV, PMR].

Photolysis of 2-carene, 26: (Scheme 3.12). A solution of 26 (4.08 g, 0.03M) in petroleum ether (40-60° range 500 ml) containing toluene (3.1 ml, 0.03N) was irradiated with lamp B using Vycor filter. The reaction was monitored by GLC (column B, 80°, 30 ml/min.) and was continued till 93% conversion (50 hr). The solvent was slowly distilled out using a vigreux fractionating column and the residue was distilled b.p. 130-140° (3.04 g). An analytical GLC of the product mixture showed it to comprise three components of RT's 1.73 (17%), 3.35 (77%) and 7.86 (6%). The first and the last components were found by GLC to be toluene and the unreacted 26 respectively. The product of RT 3.35 amounted to ~60% based on 26 consumed.

The required product was separated from toluene and 2-carene by preparative GLC (Column C, 110°, 50 ml/min.).

*We express our sincere thanks to Dr. Sukh Dev, Malti-Chem Research Centre (Nandesari), India, for a generous gift of 2-carene and 4α-hydroxy-2-carene.
1,4,4-Trimethyl-cis-bicyclo[3.2.0]hept-2-ene, 27 (RT 3.35)

IR: 2941, 2865, 2857, 1600, 1365, 1355, 1240, 1165 and 770 cm⁻¹.

PMR: (80 MHz, Fig.3.01) 0.94, 0.97, 1.16 (3s, 3H each, t-CH₃s), 1.56 - 1.87 (m, 4H, cyclobutane CH₂s) and 5.38 (s, 2H, -CH=CH).

MS: m/e 136 (M⁺, 16%), 121 (45%), 108(64%), 107(19%), 105(12%), 93 (base peak), 91(32%), 79(19%) and 77(16%).

Analysis: Found: C, 87.96; H, 11.83; C₁₀H₁₆ requires: C, 88.24; H, 11.76%.

Component (RT 7.86), unreacted 26, [α]D +6.3° (c, 0.63).

Hydroboration of the bicyclic olefin 27: (Scheme 3.14). To a solution of 27 (406 mg, 3.0 mmol) in anhydrous THF (10 ml) was added 1M solution of diborane in THF (3.0 ml) in a dropwise manner, at 0°, maintaining an atmosphere of N₂. The reaction mixture was stirred for 21 hr at room temperature, 3N aqueous sodium hydroxide (5 ml) was added followed by 30% hydrogen peroxide (5 ml), cooling the reaction mixture to about 0°. The resulting solution was neutralized with 15% hydrochloric acid, saturated with brine and thoroughly extracted with ether (20 ml x 3). The combined ether extract was washed successively with 10% sodium bicarbonate solution, water, brine and dried over anhydrous sodium sulfate. Removal of the solvent gave a colourless liquid (370 mg, 80%). GLC (column A, 130°, 30 ml/min): two components RT 3.80 (31%) and 4.68 (69%). The
mixture of major component 29 and the minor 30 showed the following spectral data.

**IR:** 3378, 2950, 2890, 1460, 1390, 1380, 1370, 1225, 1130, 1070, 1040, 1020 and 990 cm⁻¹.

**PMR:** (90 MHz, Fig.3.02) 0.84 (s, 6H, t-CH₃,s, signal of high intensity), 1.19 (s, 3H, t-CH₃, signal of high intensity), 0.78, 0.98 and 1.15 (3s, 3H each, signals of low intensity and 3.55 - 4.29 (m, 2H, -CH(OH)).

**MS:** m/e 154 (M⁺, 57%), 139 (96%), 136 (81%), 126 (base peak), 125 (39%), 123 (61%), 121 (87%), 111 (77%), 96(54%), 94)36%) and 84(41%).

**PCC oxidation of the mixture of 29 and 30:** To a suspension of PCC (860 mg, 4.0 mmol) and sodium acetate (54 mg, 0.6 mmol) in dry CH₂Cl₂ (10 ml) was added, while stirring at room temperature, the mixture of 29 and 30 (309 mg, 2.0 mmol) in CH₂Cl₂ (2 ml). The reaction mixture was stirred for 1 hr and worked up as described earlier to obtain a product b.p. 130-140°(bath)/25 mm (288 mg, 95%). The mixture (GLC: Column A, 130°, 30 ml/min) of the minor component 34 (RT 2.07, 32%) and major component 33 (RT 2.37, 68%) showed the following spectral data.

**IR:** 1740 cm⁻¹

**PMR:** (80 MHz) 0.91, 1.04 and 1.23 (3s, 3H each, t-CH₃,s, signals with high intensity) 0.96, 0.99 and 1.33 (3s, 3H each, t-CH₃,s,
signals with low intensity).

**MS:** 152 (M$^+$)

**Epoxidation of the bicyclic olefin, 27:** A solution of m-chloroperbenzoic acid (1.03 g, 6.0 mmol) in chloroform (10 ml) was slowly added at room temperature to a stirred solution of 27 (546 mg, 4.0 mmol) taken in chloroform (5 ml). The reaction was monitored by TLC and stirring was continued till the disappearance of the starting 27 (3 hr). The reaction mixture was successively washed with water, saturated sodium bisulfite solution, 10% sodium bicarbonate, water, brine and finally dried. Evaporation of solvent gave a product (511 mg, 84%). GLC (column A, 100°, 30 ml/min); two components: 35 (RT 2.59, 69%) and 36 (RT 2.95, 31%). The mixture exhibited following spectral data.

**IR:** 3003, 2976, 2874, 1470, 1455, 1400, 1360, 1265, 1100, 1020, 890, 840 and 760 cm$^{-1}$.

**PMR:** (80 MHz, Fig.3.03) 0.80, 0.96 and 1.07 (3s, 3H each, t-CH$_3$s, signals of high intensity), 1.00 and 1.18 (2s, 9H, 3$x$ t-CH$_3$s, signals of low intensity) and 2.80 - 3.16 (m, 4H, -CH$_2$-).

**Treatment of Epoxide mixture with LAH:** The mixture of 35 and 36 (455 mg, 3.0 mmol) taken in dry THF (3 ml) was added to a well-stirred slurry of LAH (570 mg, 15.0 mmol) in THF (10 ml) maintaining an atmosphere of nitrogen. The reaction mixture
was heated under reflux and was monitored by GLC (Column A, 130°, 30 ml/min.). When the starting material was absent (16 hr) the reaction mixture was worked up in a standard manner to get the product (392 mg, 85%). The GLC showed it to comprise two components: 30 (RT 3.80, 71%) and 31 (RT 4.67, 29%).

PMR: (90 MHz) 0.78, 0.98 and 1.15 (3s, 3H each, t-CH₃s, signals of high intensity), 0.74, 0.90 and 1.20 (3s, 3H each, signals of low intensity) and 3.64 - 4.27 (m, 2H, -CH(OH)).

MS: m/e 154 (M⁺).

Oxidation of the mixture of 30 and 31: The mixture of alcohols (386 mg, 2.5 mmol) taken in methylene chloride (5 ml) was added at room temperature to a stirred suspension of PCC (1.08 g, 5.0 mmol) and sodium acetate (63 mg, 0.7 mmol) in methylene chloride (5 ml). The reaction mixture was stirred for 1 hr and worked up as described previously to get the product, b.p. 130-140°(bath)/25 mm (361 mg, 95%). The components of RT 2.08 (71%) and 2.38 (29%) were separated by preparative GLC (Column C, 160°, 50 ml/min) and characterized as 34 and 33 respectively.

1,4,4-Trimethyl-cis-bicyclo[3.2.0]heptan-3-one, 34: (RT 2.08).

IR°: (Fig.3.04): 2959, 2874, 1740, 1475, 1460, 1410, 1380, 1300, 1280, 1245, 1230, 1130, 1100, 1050, 900 and 760 cm⁻¹.

PMR°: (90 MHz, Fig.3.05) 0.96, 0.99 and 1.33 (3s, 3H each,
\[ t-\text{CH}_3 \text{s} \] and 1.20 (q, \( J=19 \text{ Hz} \), 2H, \(-\text{CH}_2\text{CO}\)).

**MS:** m/e 152 (M\(^+\), 2%), 73 (70%), 67 (base peak) and 45 (90%).

**Analysis:** Found: C, 78.78; H, 10.45; \( \text{C}_{10}\text{H}_{16}O \) requires: C, 78.90; H, 10.59%.

1,4,4-Trimethyl-cis-bicyclo[3.2.0]heptan-2-one, 33: (RT 2.38).

**IR:** 1740 cm\(^{-1}\).  
**PMR:** (90 MHz) 0.91, 1.04 and 1.23 (3s, 3H each, \( t-\text{CH}_3 \text{s} \)).  
**MS:** m/e 152 (M\(^+\), 67%), 124 (30%), 109 (85%), 95 (95%), 82 (base peak), 81 (45%) and 69 (57%).

**Analysis:** Found: C, 78.98; H, 10.63; \( \text{C}_{10}\text{H}_{16}O \) requires: C, 78.90; H, 10.59%.

**Oximation**\(^{11}\) of the ketone 34: Hydroxylamine hydrochloride (330 mg, 10.0 mmol) and potassium hydroxide pellets (336 mg, 6.0 mmol) were added to a solution of the ketone (151 mg, 1.0 mmol) in ethanol (10 ml). The mixture was refluxed for three hours and then poured into 30 ml of brine solution and extracted with methylene chloride (20 ml x 3). The residue after solvent removal was crystallized from aqueous methanol to obtain 12 (85 mg, 51%), m.p. 116-118\(^\circ\).

**IR:** 3580, 3285 and 1660 cm\(^{-1}\).  
**PMR:** (90 MHz) 0.98 (s, 6H, \( 2\times t-\text{CH}_3 \text{s} \)), 1.22 (s, 3H, \( t-\text{CH}_3 \)) and 2.55 (q, \( J=19 \text{ Hz} \), 2H, \(-\text{CH}_2\text{-C=NH} \)).

**MS:** m/e 167 (M\(^+\), 19%), 152 (57%), 150 (36%), 139 (27%), 124 (base peak), 122 (46%), 109 (27%) and 81 (44%).

[\text{Lit.} 9,11 m.p., IR, PMR].
FIG. 3-01. PMR SPECTRUM OF
1,4,4-TRIMETHYL-CIS-BICYCLO(3.2.0)HEPT-2-ENE, 27
(80 MHz)
FIG 7.02 PMR SPECTRUM OF THE MIXTURE OF ALCOHOLS
FIG. 3-03. PMR SPECTRUM OF THE MIXTURE OF EPOXIDES 35 AND 36 (80 MHz)
FIG. 3.05. PMR SPECTRUM OF 1, 4, 4-TRIMETHYL-CIS-BICYCLO (3.2.0) HEPTAN-3-ONE, 34 (90 MHz)
REFERENCES


16 R.D. Clark  

17 V. Rautenstranch  

18 U.K. Banerjee and R.V. Venkateswaran  

19 L. Borowiecki and Y. Cheretien-Bessi'ere  

20 J. Meinwald, J.J. Tufariello and J.J. Hurst  

21 W.J. Leigh and R. Srinivasan  

22 R.F. Newton and S.M. Roberts  
Tetrahedron, 36, 2163 (1980).

23 C.V. Wilson  
Organic Reactions, 9, 332 (1957).

24 T.G. Traylor  

25 G. Ohloff, K.H. Schulte-Elte and W. Gierch  

26 W. Cocker, P.V.R. Shannon and P.A. Staniland  