Chapter : 2
Synthesis of Spiroketal Pheromones
SYNTHESIS OF SPIROKETAL PHEROMONES:

INTRODUCTION

The progress of the scientists in achieving higher food production to meet the ever increasing demands of the population has always been hampered by the destruction of the crops by insects and the diseases spread by them. As a result, insects have been a constant source of aggravation to the mankind. Inspite of the dreadful side effects, use of insecticides and pesticides continues to enjoy the prime place as the most effective method for the control of insects. However in recent years, concern over these effects is growing and hence a new protocol for insect control, free from any side effect is urged. One promising method to suit these requirements would be the use of naturally occurring compounds that influence the chemosensory organs of the insects. While studying the physiology of the insects, it has become clear that phenomena like aggregation and mating are governed by the chemical substances known as pheromones secreted by the insect body; to trigger the chemosensory organs of other individual.

The use of pheromones to control insect growth is becoming popular day by day. The remarkable potency of these substances is demonstrated by the minute amounts required to attract a large number of insect pests. The number of insects trapped within the specified time by this false stimulation serves as a probe to the degree of overall infestation in the crop. Pheromones also have been used in a 'confusion technique' where the normal mating behaviour of the insects is disrupted by premating the atmosphere with synthetic sex attractants. As a result, use of pheromones has become important tool in the integrated pest management by employing which the blanket spraying programmes of insectisides over the entire season could be reduced with obviation of their attendant hazards.
Due to limited availability of natural pheromones from insects (usually less than several milligrams) the synthetic approach has been very important in pheromone research. The syntheses of these substances not only provide these pheromones in multigram quantities, but also enable the confirmation of the pheromone structure with its stereochemistry and also helps in establishing structure-activity relationship. Thus it ensures the use of pheromones in agriculture and forestry. The established pheromone structures are scattered among the various types of volatile compounds ranging from alkanes to the nitrogen heterocycles. The fact that spiroketals constitute important structural features of insect pheromones and that they are also an integral part of several biologically active compounds like milbemycins and avermectins, prompted us to undertake their synthesis. Consequently programme for their synthesis using readily available reagents and starting materials was planned.

This chapter describes the synthesis of three spiroketal compounds; components of pheromone of olive fruit fly, using dianion alkylation of the Tosyl methyl isocyanide (TosMIC) as the key step. The chapter is divided into the two parts.
PART I: Review of synthetic methods with special reference to the
target compounds described in the part - II.

PART II: Synthesis of
i) 1,7-dioxaspiro[5,5]undecane (1)
ii) (2S,6R,8S),2,8-dimethyl-1,7-dioxaspiro[5,5]undecane (2)
iii) (2S,6R)-2 methyl 1,7-dioxaspiro[5,6]dodecane (3)

PART I

Since 1980, numerous strategies for the synthesis of spiroketal moieties
have been developed which have also been reviewed from time to time.
For the sake of comparison this part reviews the synthetic methods developed
only for the pheromones described in the part II of this chapter.

A. Synthesis of 1,7-dioxaspiro[5,5]undecane:

This is the simplest class of spiroketal compounds available whose
synthetic aspects have been reviewed below briefly.

H. Stetter (Chem Ber 1958)

Stetter and coworkers were the first to demonstrate the synthesis
of spiroketals by keto diol approach which became the most popular one
during the course of time. The ketodiol (6) was obtained through the reduction
of ketodiester (5) which in turn was obtained by the alkylation of 1,3-cyclo-

Scheme 1

H. Stetter (Chem. Ber 1958)
hexane dione. With -bromo ethyl propionate followed by acid catalysed opening of resulting compound (4).

**Micovic (Tetrahedron 1969)**

Micovic's group characterised the presence of 1,7-dioxaspiro unit in the products of oxidation of 1,9-nonane diol (7) with lead tetraacetate in refluxing benzene.

**SCHEME 2**

**Micovic (Tetrahedron 1969)**

\[
\text{HO} - \text{CH}_2-(\text{CH}_2)_7-\text{CH}_2\text{OH} \xrightarrow{\Delta} \text{LTA}, \text{C}_6\text{H}_6
\]

**SCHEME 3**


Two molecules of -valerolactone were condensed by sodium ethoxide catalysed reaction to obtain \(\alpha,\beta\)-unsaturated lactone (9). Compound 9 on treatment with refluxing acid underwent intramolecular cyclization with decarboxylation to give the spiro undecane (1).

**Deslongchamps (Can J Chem. 1981)**

A four carbon unit in the form of compound 10 was added on -valerolactone to obtain the key intermediate 5-oxo-1,9-nonyne diol. This on treatment with acid followed by hydrogenation furnished the target compound (1).
Ireland (Chem. 1981)

Ireland and coworkers developed a general convergent route to the synthesis of spiroketals through a hetero-Diels Alder reaction between an exocyclic enol ether (12) and an α,β-unsaturated compound. Hydrogenation of the double bond in the compound 13 such obtained, furnished the required spiroketals.

Gamill (JOC 1983)

Hetero-Diels Alder reaction between diene 14 and a carbonyl compound followed by intramolecular Michael addition on the enone 16 had been exploited by Gamill and coworkers. Thus enone 16 was obtained as depicted in the scheme 6. This on further treatment with AcOH, followed by alumina, underwent intramolecular 1,4-addition to produce the spiroketal compound 17.
Wittig-Horner reaction was used by Ley and coworkers\textsuperscript{13} to synthesize cyclic hydroxy enol ethers from compound 18 and several hydroxy aldehydes.

**SCHEME 7**

**Ley (Tetrahedron Lett., 1984)**

\[
\begin{array}{c}
\text{Ph}_2\text{P} - \text{OHC} - \text{LDA} - 78^\circ C \\
\text{O} - \text{H} - \text{OHC} - \text{Ph}_2\text{P} - \text{OHC}
\end{array}
\]

These on further treatment with acid produced spiroketal compounds of type 20.

**Brinker (Angew Chem Int Ed Engl, 1985)**

Insertion of carbenes into C-H bonds had been exploited by Brinker and coworkers\textsuperscript{14} for synthesizing spiroketal. Addition of dibromomethane

**SCHEME 8**


\[
\begin{array}{c}
\text{O} - \text{O} - \text{CHBr}_3 \\
\text{MeLi}
\end{array}
\]

to the compound 21 produced dibromocyclopropane 22. This on further treatment with methyl lithium formed the intermediate 23 which underwent insertion reaction with adjacent equatorial C-H bond of the tetrahydropyran ring. The resulting tricyclic intermediate 24 on hydrogenation produced the target compound along with some other spiroketal.
Ley (Tetrahedron Lett, 1985)

Ley and coworkers in another approach for spiroketals alkylated cyclic sulphones with bromohydrins\textsuperscript{15}. The alkylated product on treatment with acid produced the spiroketals.

\textbf{SCHEME-9}

Deshong (JACS, 1988)

Synthetic potential of furan derivatives as 1,4-dicarbonyl compounds had been utilized by Deshong and coworkers\textsuperscript{16} in their strategy for spiroketals. Thus the diol 27 prepared from furan as shown in the scheme 10, on treatment with mCPBA followed by acid produced the dioxaspiro enone (28). It was then converted to target compound as shown in the above scheme 10.

K Mori (Tetrahedron, 1985)

Mori's group in their chiron approach for the spiroketals\textsuperscript{17} exploited S-malic acid as the starting material. Iodide 31 obtained in several steps
from Malic acid, when dialkylated with Corey-Seebach reagent produced compound 33. This on treatment with CuCl$_2$ underwent Spiroketalization to give dihydroxy spiroketal 34 in optically pure form. This on de-oxygenation as shown in the scheme 11 produced 1.

**B Synthesis of 2,8-dimethyl-1,7-dioxaspiro[5,5]undecane.**

Giese (Liebig's Ann Chem, 1987)

The spiroketals were synthesized as the racemates by Giese and coworkers via a radical addition. The radical precursors were alkyl mercurals (36) which were prepared by solvomercuration of olefins. The compound 36 undergoes 1,4-addition to divinyl ketone to produce ketodiol derivative 37. This on treatment with sodium methoxide followed by acid produced the spiroketal (scheme 12).
Mori's group exploited biochemical reduction of ethylaceto acetate to fix the optical centres in the spiroketal molecule. Ethylaceto acetate was reduced enzymatically by Baker's yeast to get (R)-3-hydroxy ethyl butanoate. It was then converted to iodide by the sequence depicted in scheme 13. Two molecules of were condensed on ethylaceto acetate to produce ketoester. This was further converted in to target compound via decarboxylation followed by acid catalysed cyclization.

The chiral building block obtained from S-malic acid and the one obtained from enzymatic reduction of ethylaceto acetate (scheme 13) were combined to obtain keto trihydroxy ester which was converted to opti-
C. Synthesis of 2-methyl-1,7-dioxaspiro[5,6]dodecane

Only one report of the synthesis exists in the literature by K. Mori in 1984. This report available on the synthesis of compound 3 makes use of compound 42 obtained from ethylacetoacetate which was alkylated with THP ether of 4-chlorobutanol. Compound 49 thus obtained on further treatment with refluxing methanolic KOH followed by acid, furnished the target compound 3.
PART II: Synthesis of spiroketal pheromones.

In the various strategies described in the part I towards the synthesis of spirolketals, it could be seen that the spirolketals are formed mainly by the intramolecular ketalization of the 'Keto-diol' unit. The ketone functionality in this ketodiol is present either as the free carbonyl group or in the masked form such as enol ethers, dithiane or other sulphur derivatives etc.

Thus a general retrosynthetic analysis of the spiroketal system may be represented as shown in the diagram. Hence any attempt to synthesize the spiroketals should be directed towards the synthesis of this 'Keto-diol unit'. It is apparent from the retrosynthesis that alkylation of the masked formaldehyde unit by 4-haloalkanol derivatives should eventually lead to the desired synthons for spiroketet systems.

Tosylmethyl isocyanide (TosMIC) a masked formaldehyde unit is best suited to our requirements for the following reasons.

i. Two powerful electron withdrawing groups (tosyl and NC) in the TosMIC render the two remaining protons very much acidic and hence the generation of the anion with milder bases like sodium hydroxide is possible.
Ample amounts of TosMIC can be prepared using simple procedures and using readily available materials like tosyl chloride, formaldehyde and formamide.

By changing the base employed to generate anion, the mode of alkylation could be altered giving rise to unsymmetrical or symmetrical, monoalkylated or dialkylated TosMIC respectively.

Based on these facts a general synthetic strategy for the spiroketal (1) was drawn as shown in the scheme 16. In accordance with the above strategy the synthesis of three spiroketal pheromones (1 to 3) have been achieved which are described below.

1,7-Dioxaspiro[5,5]undecane (1) a major component of the pheromone of olive fruit female fly Dacus oleae has been synthesized in its racemic form, while (2S,6R,8S)-2,8-dimethyl-1,7-dioxaspiro[5,5]undecane (2) a major constituent of pheromone of fly Andrena willikela and (2S,6R)-2-methyl-
1,7-dioxaspiro[5,6]dodecane (3) a constituent of pheromone of *Andrena haemorrhhoa-F* have been synthesized in their optically pure forms using the chiron approach.

1,7-Dioxaspiro[5,5]undecane:

This structurally simplest unit was synthesized by dialkylation of the TosMIC by 4-bromo-1-tetrahydropyranoyloxybutane and then its treatment with acid (scheme 17). Thus the reaction of TosMIC with two equivalents of sodium hydride in DMSO-Et₂O followed by addition of 1-bromo-4-tetrahydropyranoyloxybutane produced the symmetrical dialkylated TosMIC i.e. 5-Tosyl-5-isocynato-1,9-di-tetrahydropyranoyloxy nonane (51a) in 80% yield. The infrared spectrum showed strong absorption at 2150 cm⁻¹ characteristic for -N=C grouping. The PMR showed the presence of THP ethers and two o-coupled doublets from 7.5-7.8 for Tosyl group. This compound on treatment with dil.sulphuric acid in methanol underwent three transformations as expected namely deprotection of masked carbonyl, deprotection of hydroxyls and the intramolecular ketallization in one pot to furnish the desired spiroketal in 60% yield. The analytical sample could be obtained by distillation of the compound under reduced pressure. IR of this compound displayed no absorptions for -N=C or -OH groups. PMR showed two sets of protons one centred at 3.8 ppm and the other at 1.8 ppm confirming the structure of the molecule.
(2S,6R,8S)-2,8-Dimethyl-1,7-dioxaspiro[5,5]undecane

In dealing with the synthesis of such optically pure compounds having three asymmetric centres; only the stereochemistry at C-2 and C-8 needs to be specifically addressed since the correct configuration at C-6 would be derived by these two centres at C-2 and C-6 based on the established reasons as follows:

1) Phenomenon of anomeric effect fixes two oxygens in the mutually diaxial orientation
2) The tendency of the groups on the remaining carbon atoms remains towards acquisition of the equatorial orientation to avoid 1,3-diaxial interactions.

Thus recalling the retrosynthesis of the target compound, it could be seen that the desired optically active ketodiol unit could be synthesized from the (S)-lactic acid.

Accordingly a strategy for its synthesis from (S)-ethyl lactate, a readily available material was visualized (Scheme 18). The optically pure 1-bromo-4-tetrahydropyranyloxy pentane (60) needed for dialkylation of the TosMIC to prepare the masked ketodiol unit was prepared as follows: The free hydroxyl group of S-ethyl lactate was protected as the tetrahydro pyranyl ether by treatment with dihydropyran in the presence of acid in almost quantitative yield. Here -THP had been used as the protecting group
as it allows its removal at the final stage in the acid-medium, enabling one pot spiroketalization. The compound 55 on treatment with diisobutyl aluminium hydride at -78°C, produced volatile and unstable aldehyde which therefore was treated in C-2 with the carbethoxytriphenylphosphorane to produce the corresponding \( \alpha,\beta \)-unsaturated ester (56). The PMR spectrum of this compound displayed characteristic \( \alpha \)-protons of this ester at 6.8-7.1 ppm and a multiplet centered at 6.5 ppm. Infrared spectrum showed the absorbions characteristic of \( \alpha,\beta \)-unsaturated ester at 1730 cm\(^{-1}\) confirming the structure of the compound. Direct reduction of this ester (56) to the saturated alcohol (58) was an inconsistat reaction, sometimes showing the partial reduction of the double bond as judged by the PMR analysis. Hence the stepwise reduction of 56 to 58 was achieved first by reducing the unsaturation under \( \text{H}_2 \) atmosphere in the presence of Rhodium on alumina as the catalyst. The compound 57 thus obtained was treated with lithium aluminium hydride to furnish the alcohol (58) in 71% yield from 56. IR showed the characteristic \( \alpha \)-OH stretchings at 3550 cm\(^{-1}\) and 3300 cm\(^{-1}\) and
the absence of any unsaturation and ester functionality. The alcohol \(58\) was converted to the bromide \(52/53\) via its mesylate \(59\) using the normal procedures in 62% yield. The IR spectrum showed absence of the hydroxyl absorption and PMR displayed all characteristic signals. The alkylation of the TosMIC with two equivalents of this bromide \(52/53\) using sodium hydride as the base produced \((2S,10S)-2,10\)-ditetrahydropyranyloxy-5-isocyno-5-tosyl undecane \((51b)\) in 75% yield. The compound \(61\) was characterised again by PMR and IR spectra. Treatment of the compound \(51b\) with dilute sulphuric acid in methanol for 24 h produced the desired spiroketal with \((2S,6R,8S)\) configuration in 70% yield. The \(\left[\alpha\right]_D\) was \(-61^\circ\) which was in agreement with the reported\(^{19-20}\) value. PMR spectrum displayed characteristic doublet at 1.1 ppm and amultiplet at 3.7 ppm; confirming the structure of the compound.

\((2S,6R)-2\)-Methyl-1,7-dioxaspiro[5,6]dodecane

For the synthesis of spiroketals like \((3)\) wherein two rings are of different sizes; the alkylation of the TosMIC with two different halides was a prerequisite. This was achieved by first mono alkylation the TosMIC under phase transfer conditions\(^{22}\) and then further alkylation was effected by sodium hydride with different desired halide.

Thus in the synthesis of the title compound; TosMIC was subjected to monoalkylation with 1-bromo-5-tetrahydropyranyloxy pentane using aqueous sodium hydroxide as the base in the presence of tetrabutyl ammonium bromide as a phase transfer catalyst. The reaction produced 1-tosyl-1-isocynato-
6-tetrahydropyranlyoxy hexane (52b); the monoalkylated TosMIC in 55% yield. It was characterised by its PMR and IR spectra. This compound on further treatment with sodium hydride followed by halide (52/53) produced the unsymmetrical dialkylated TosMIC (10S)-6-isocyanato-6-tosyl-1,9-ditetrahydropyranlyoxy undecane in 79% yield. After its characterization in the usual manner it was subjected for the acid treatment to furnish the target spiroketal in its optically pure form in 52% yield. PMR and IR spectra were in accordance with the structure and the \([\alpha]_D^{+99}\ C=1.5\), pentane was in good agreement with the reported value confirming the structure and the stereochemistry of the compound synthesised.

Thus in conclusion it can be said that the sequential alkylation of the TosMIC with suitable bromohydrin derivatives and further the treatment of the dialkylated TosMIC with the acid is a simple and versatile method for synthesizing spiroketals in good yields.
EXPERIMENTAL

5-Tosyl, 5-isocyano, 1,9-bis-tetrahydropyranoyloxy nonane 51a

A solution of TosMIC 49 (1.99 g, 10 mmol) in DMSO (2 ml) was added dropwise with stirring at 0°C to a suspension of prewashed sodium hydride (460 mg, 20 mmol) in ether (30 ml). Mixture was brought to the room temperature to complete the anion formation and again cooled to 10°C. A solution of 1-bromo-4-tetrahydropyranoyloxy butane (52/53a) 4.8 g (20.1 mmol) in ether (30 ml) was slowly to the anion at 10°C. After stirring for 1 h, mixture was poured in ice water, organic phase was separated and aqueous phase was once extracted with ether (30 ml). Combined organic phases were diluted with ether, washed with water, brine, dried (Na₂SO₄) and evaporated to get the crude 51a (4.0 g, 80%). The analytical sample is obtained by chromatography on neutral alumina as a colourless viscous liquid.

IR(νmax, Film): 3000, 2150, 1595, 1495, 1330, 1220 etc.
PMR(CDCl₃): δ 1.5-2.0 (m, 2H), 2.3 (s, 3H), 3.1-3.9 (m, 10H), 4.5 (bs, 2H), 7.3 (d, 2H, J=7 Hz), 7.75 (d, 2H, J=9 Hz).

Analysis: C₂₇H₄₁O₆S

1,7-Dioxaspiro[5,5]undecane (1)

Crude 51a (4.0 g, 7.8 mmol) obtained as above was dissolved in methanol (15 ml) and to it was added 10% aqueous sulphuric acid (60 ml) with stirring at 0°C. Mixture was allowed to attain the room temperature and stirred for 24 h. It was diluted with water (100 ml) and extracted with Et₂O (4x20 ml). Combined extracts were washed with water, brine and dried (Na₂SO₄) and then evaporated to get crude 1 (1.07 g, 80%) as a colourless liquid which was distilled under reduced pressure to get pure 1 (2.8 g) b.p.: 100°/50 mm. Lit¹⁷ 76-80°/30 torr.

IR(νmax, Film): 2960, 2870, 1460, 1380, 1280, 1100-1000 cm⁻¹.
NMR(CDCl₃): δ 1.00-2.30 (m, 12H), 3.3-3.9 (m, 6H).
Mass: m/z 156 (15%), 128, 116, 101, 100, 98 etc.
Analysis for C₉H₁₆O₂: Observed: C, 69.0; H, 10.5. Expected: C, 69.19; H, 10.32%.

(4S)-Ethyl-4-tetrahydropyranoyloxy-2-pentenoate (56)

A 20% solution of diisobutyl aluminium hydride in toluene (21.5 ml, 30 mmol) was added dropwise to the solution of (2S)-ethyl-2-tetrahydropyranyloxy propionate (6.06 g, 30 mmol) in methylene dichloride (30 ml) with stirring under nitrogen at -78°C. After stirring for 1 h at -78°C, methanol (5 ml) was added and then carbethoxy methylene triphenylphosphorane (10.44 g, 30 mmol) was added and the mixture is allowed to attain the room temperature. After 1 h, saturated solution of sodium potassium tartarate (50 ml) was added and it was further stirred for 30 min. After diluting further the mixture with CH₂Cl₂ (100 ml), organic phase was separated, washed with water, dried and evaporated to give a residue which was purified on silica gel column eluting with hexane and 10% EtOAc to furnish pure compound 56 as a mixture of cis and trans isomers (4.4 g, 65% from 54).

IR(ν max, Film): 1715, 1600 cm⁻¹.

PMR(CDCl₃): δ 1-1.2 (one doublet and one triplet merged, 6H, H₃C-O and COOCH₂CH₃), 1.2-1.7 (m, 6H), 3.2-3.85 ((m, 2H, -CH₂-CH₂-O-CH-O), 4.0 (broad quartet, 2H, -COOCH₂CH₃), 4.5 and 4.8 (two broad singlets, 1H, -CH₂-O-CHR-O), 5.3 (q, 1H, J=6 Hz), 5.5-6.9 (m, 2H, vinylic protons).

Mass: m/e 228 (5%).

Analysis: C₁₂H₂₀O₄: Observed: C, 63.0; H, 8.9. Expected: C, 63.13; H, 8.83%. 

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(4S)-4-Tetrahydropranlyloxy pentane-1-ol (58)

A solution of compound 56 (4.4 g, 23.4 mmol) in ethanol (80 ml) was stirred with Rhodium-Alumina catalyst under hydrogen atmosphere for 24 h. An aliquot was removed, the solvent was evaporated and the compound obtained was examined for the presence of olefin. The PMR of this compound exhibited following absorptions indicating absence of olefin: 1.1 (m, 6H), 1.3-1.9 (m, 8H), 2.2 (t, 2H, J=7.5 Hz), 3.2-3.8 (m, 3H), 4.0 (q, 2H, J=7.5 Hz), 4.5 (bs, 1H). The solution of the compound thus obtained after evaporation of solvent from the filtrate of whole reaction mass, was added dropwise to a stirred suspension of lithium aluminium hydride (726 mg, 19 mmol) in tetrahydrofuran (5.0 ml) at 0°C. Mixture was quenched after its stirring at room temperature for 4 h with saturated solution of Na$_2$SO$_4$ in water (1 ml). Organic phase was separated. All lithium salts were once boiled with ethyl acetate (50 ml) and this extract was combined with previous organic layer. Combined organic layers were evaporated. The residue thus obtained was purified on silica gel using hexane-EtOAc (80:20) as the eluent. Combined eluent fractions were evaporated to get the pure compound (2.9 g, 80% from 10) as a thick colourless liquid.

IR$_{\text{max}}, \text{Film})$: 3400-3250 (b), 1460, 1150 cm$^{-1}$.

NMR(CDCl$_3$): 1.1 (two doublets, 3H), 1.3-1.7 (m, 10 H), 1.9 (s, 1H, exchangeable with D$_2$O), 3.3-3.8 (m, 5H), 4.9 (bs, 1H).

Analysis: C$_{10}$H$_{20}$O$_3$: Observed: C, 63.5; H, 10.9. Expected: C, 63.79, H, 10.79%.

(4S)-1-Tosyl-4-tetrahydropranlyloxy pentane-1-ol (59)

p-Toluene sulphonyl chloride (3.24 g, 16.96 mmol) was added to a solution of compound 58 (2.9 g, 15 mmol) in dichloromethane (35 ml) and triethyl amine (4 ml) at 0°C. After stirring for 4 h at room temperature,
reaction mixture was further diluted with dichloromethane (50 ml), washed with water (3x25 ml), dried (Na$_2$SO$_4$) and evaporated to get almost quantitatively the compound 59, pure enough to carryout further transformations.

IR($
\nu_{\text{max}}$, Film): 1620, 1470, 1360, 1270, 1150 cm$^{-1}$.

PMR(CDCl$_3$):  6 1.1 (two doublets, 3H), 3.2-3.9 (m 5H), 1.3-1.5 (m, 10H), 2.2 (s, 3H), 3.2-3.9 (m, 5H), 4.5 (bs, 1H), 7.2 (d, 2H, J=10 Hz), 7.6 (d, 2H, J=10 Hz).

(4S)-4-tetrahydropyranlyoxy-1-bromopentane (52/53b)

Lithium bromide (3 g, 34 mmol) was added with stirring to the solution of the tosylate 59 obtained in the previous reactions, with a pinch of sodium bicarbonate in solvent was evaporated under reduced pressure, water (100 ml) was added and then mixture was extracted with hexane (4x20 ml). Combined extracts were washed with water, brine, dried and evaporated to furnish the crude bromide which was purified by column chromatography on silica gel eluting with hexane. The yield of pure bromide was (2.0 g, 80%).

IR($
\nu_{\text{max}}$, Film): 1460, 1150, 600 (w) cm$^{-1}$.

PMR(CDCl$_3$): 6 1.1 (two doublets, 3H), 1.25-1.5 (m, 10H), 3.35 (bt, 2H), 3.5-3.8 (m, 3H), 4.5 (bs, 1H).

(2S,10S)-2,10-bistetrahydropyranlyoxy,6-tosyl, 6-isocyano undecane (51b)

It was prepared in a similar manner as described for compound 51a, using TosMIC (595 mg, 3 mmol), 52/53b (1.5 g, 6 mmol) and sodium hydride (144 mg, 6 mmol) in 66% yield from 49.

IR ($
\nu_{\text{max}}$, Film): 2150, 1600, 1470, 1365, 1150, 1100 cm$^{-1}$.

PMR(CDCl$_3$): 6 1.1 (m, 6H), 1.2-2.0 (m, 24H), 3.3-3.9 (m, 6H), 4.5 (bs, 2H), 7.3 (d, 2H, J=9 Hz), 7.7 (d, 2H, J=9 Hz).

(2S,6R,8S)-2,8-Dimethyl-1,7-dioxaspiro[5,5]undecane (2)

A solution of compound 51b (1.2 g, 2.2 mmol) in methanol (5 ml) was stirred with 10% aqueous sulphuric acid (25 ml) first at 0°C then at
room temperature for 24 h. Water (100 ml) was added, and it was then extracted with hexane (4x20 ml). Combined extracts after usual workup furnished the crude compound which was distilled under reduced pressure (b.p. 110°/100 mm. Lit. 89°/28 torr) to give 360 mg (66% from 49) pure title compound. [\(\alpha\)]\(_D\) -63° (c 1.2, pentane) lit \(\alpha\) -60.1°.

IR \(\nu_{\max}\), Film: 2960, 2870, 1500, 1100, 1075 cm\(^{-1}\).
PMR(CDCl\(_3\)): \(\delta\) 1.1 (d, 6H, \(J\ =\ 7\) Hz), 1.2-1.8 (m, 12 H), 3.5-3.9 (m, 2H).

Mass: m/z 184 (20%), 169, 140, 115 (100%), 97 (56%).

\(1\)-Isocyano-\(1\)-tosyl-\(6\)-tetrahydropyranoloxy hexane (50a)

Aqueous solution of sodium hydroxide (40%, 25 ml) was added dropwise with stirring at 0°C to a solution of TosMIC (1.99 g, 10 mmol), \(1\)-bromo-\(5\)-tetrahydropyranoloxy pentane (2.76 g, 11 mmol) and tetrabutyl ammonium bromide (640 mg, 2 mmol) in dichloromethane (75 ml). Mixture was stirred for 8 h at room temperature, diluted with dichloromethane (75 ml) and washed with water (3x40 ml) to remove excess sodium hydroxide. After drying and evaporation of the DCM phase, crude product obtained was purified on silica gel column to get the pure product as the pale yellow thick liquid 2.35 g (65%).

IR \(\nu_{\max}\), Film: 3000, 2120, 1590, 1150, 1070, 1020 cm\(^{-1}\).
PMR(CDCl\(_3\)): \(\delta\) 1.5-1.9 (m, 14H), 2.3 (s, 3H), 3.3-3.9 (m, 4H), 4.3-4.6 (m, 2H), 7.3 (d, 2H, \(J\ =\ 9\) Hz), 7.7 (d, 2H, \(J\ =\ 9\) Hz).

\((10R)-1,10\)-bistetrahydropyranoloxy-\(6\)-isocyano-\(6\)-tosyl-undecane (51c)

The compound was prepared employing the same conditions used for the preparation of 51a and 51b using 50c (2.3 g, 6.5 mmol) sodium hydride (1.68 g, 7 mmol) and 52c (1.6 g, 6 mmol). Compound obtained was purified as described earlier to get 51c as the thick colourless liquid (2.6 g, 85%).

IR \(\nu_{\max}\), Film: 3010, 2120, 1600, 1150, 750 cm\(^{-1}\).
PMR(CDCl₃): δ 1.1 (two doublets, 3H), 1.3-1.9 (m, ), 2.3 (s, 3H), 3.3-3.9 (m, 7H), 4.5 (m, 2H), 7.3 (d, 2H, J=9 Hz), 7.7 (d, 2H, J=9 Hz).

(2S,6R)-2-Methyl-1,7-dioxaspiro[5,6]dodecane (3)

Treatment of 51c obtained in the above experiment with methanol and aqueous sulphuric acid as described for the preparation of 1 and 2 produced the desired compound after 24 h. It was purified on silica gel column using pentane as the eluent. 3 was obtained as a colourless liquid (690 mg, 70% from 51c). Distillation under reduced pressure furnished the analytical sample.

b.p. 125°C/100 mm. Lit b.p. 100-110°C/105 torr.

IR (ν_max, Film): 2950, 2880, 1470, 1370, 1150, 1100 cm⁻¹.

NMR(CDCl₃): δ 1.15 (d, 3H, J=7 Hz), 1.2-2.1 (m, 14H), 3.5-4.0 (m, 3H).

Mass: m/z 184 (15%, M⁺), 1401, 125, 115 etc.

Analysis C₁₁H₂₀O₂. Observed: C, 71.5; H, 11.0. Expected: C, 71.69; H, 10.94%.
REFERENCES


