

SYNTHESIS OF INSECT SEX PHEROMONES

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ABSTRACT

The traditional use of insecticides continues to be practised in the control of insect populations, the newer methods such as the application of pheromones in the crop protection have gained prominence in the recent years. Since the pheromones have to be made available synthetically for the application in fields, their synthesis has attracted considerable attention and played a vital role in their overall development in the integrated pest management. Various approaches have successfully been made for the preparation of different pheromones and in this process a number of new methodologies have also been worked out.

INTRODUCTION

INSECTS form an integral part of the biological system. They destroy crop and often serve as a constant source of aggravation by spreading disease. Application of the chemicals like chlorinated hydrocarbons, organophosphates, carbamates and more recently synthetic pyrethroids have played an important role in their control. However, unrestricted use of these insecticides has caused several problems which include resurgence and resistance in pest populations, destroying useful parasites, predators and pollinators, causing thereby imbalance in our ecological system and also causing severe environmental pollution.

One promising method which would avoid these factors would be the use of naturally occurring compounds that influence insect chemosensory behaviour (attractants, repellants, stimulants, etc.). The behavioural patterns of many insects are controlled by chemicals, called pheromones. Pheromones are non-toxic chemical substances (like sex attractants) secreted by one insect and received by other insects of the same species. They are widely used as a communication system and this property has been used for trapping the insects and thus giving definite information on the amount of insecticides to be used for the destruction. Pheromones, therefore, constitute an important tool in controlling the insect populations which can be achieved by trapping the harmful insects and killing them selectively, disrupting their mating instincts and monitoring their population so that indiscriminate insecticidal application can be avoided.

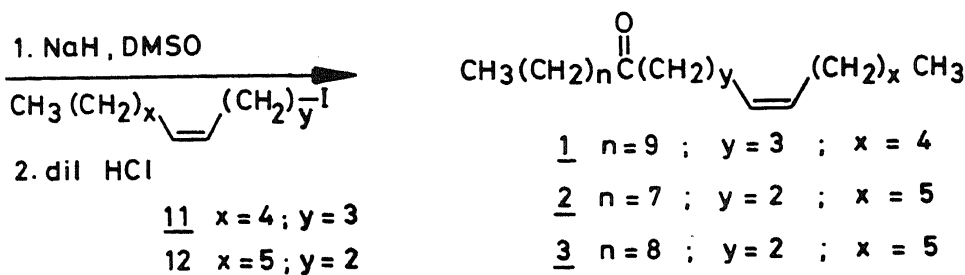
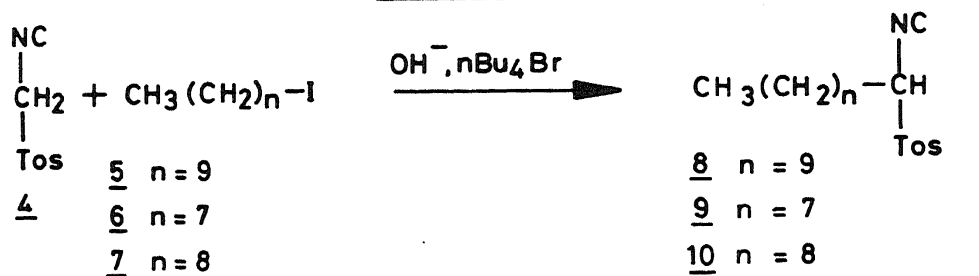
RESULTS AND DISCUSSION

From the beginning, the synthetic approach was very important in pheromone research because of the limited availability of natural pheromones from insects (usually of the order of few nanograms) and also in view of the fact that as more and more pheromones are being used for trapping insects, there is an increasing demand for particular pheromones. Chemical synthesis thus ensures ample supplies and facilitates their practical application in agriculture¹⁻⁴. The work incorporated in the present article illustrates our efforts in the synthesis of various pheromones during the last five years. The pheromones discussed here, have been grouped based on their morphological features. Our contribution in each category is described.

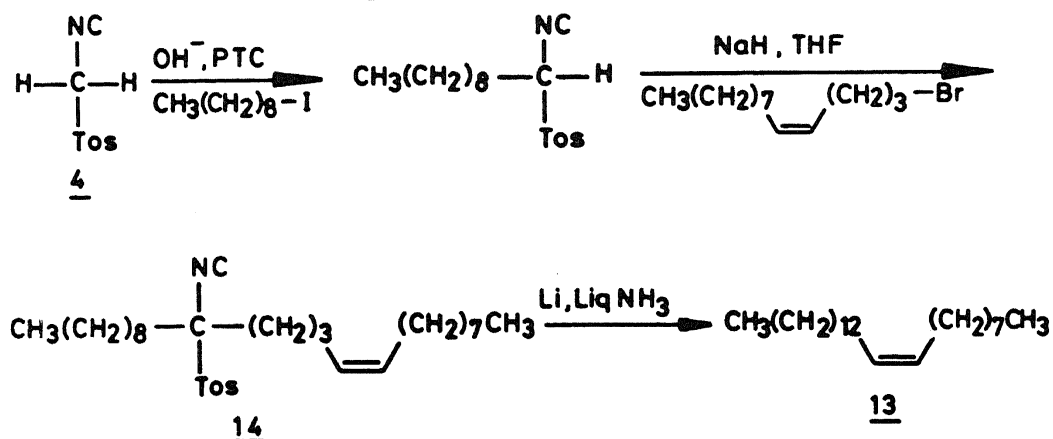
Monoolefinic pheromones

The attractancy of the majority of pheromones particularly those belonging to the Lepidoptera (moths and butterflies) is associated with the functional moieties (acetate, alcohol, ketone or aldehyde), the double bonds (position, number and configuration) and length of the carbon chain. In our initial efforts in controlling the aliphatic chain length, creation of carbonyl functionality, position of double bond, etc. tosylmethyl isocyanide (TosMIC) (4) as a conjunctive reagent was used extensively. Its successive alkylations by the use of phase transfer catalyst for monoalkylation and sodium hydride for dialkylation is indeed very useful. The dialkylated TosMIC can be hydrolysed with an acid to generate an unsymmetric ketone

Scheme - 1



Scheme - 2

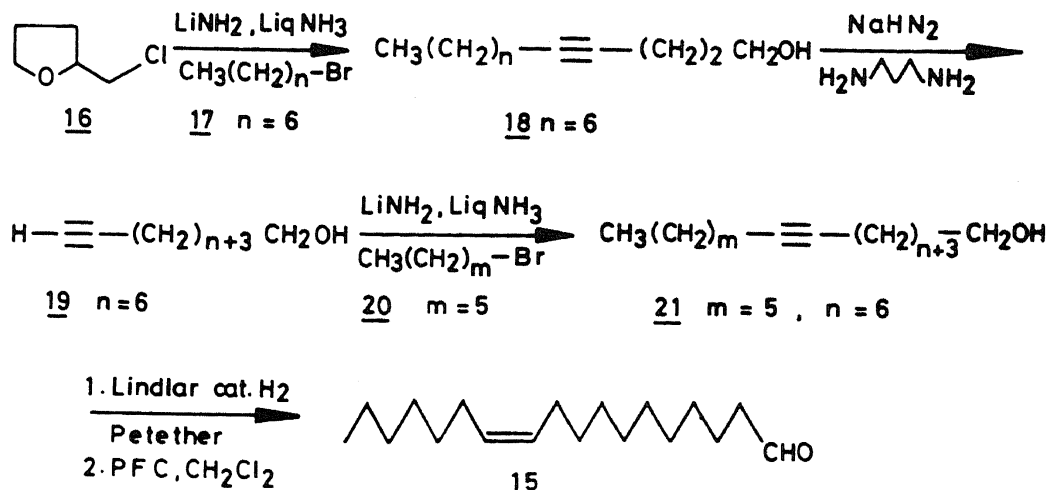
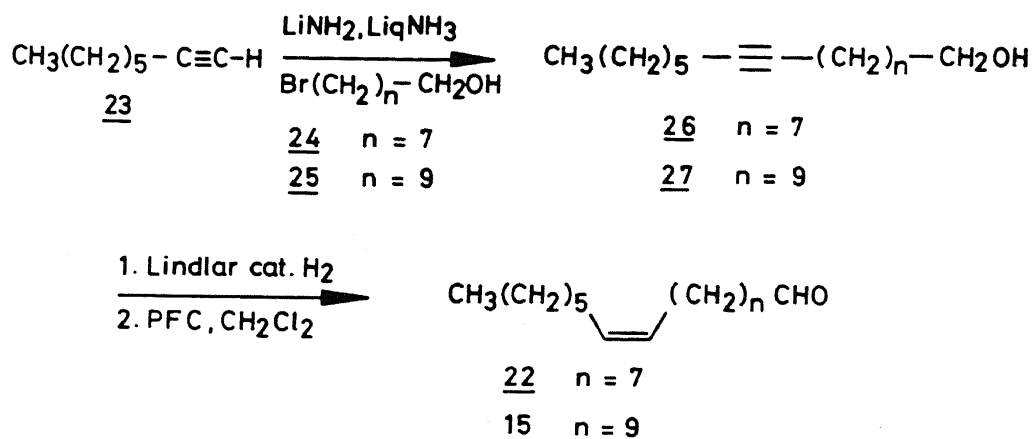


derivative. The utility of TosMIC has been illustrated in the synthesis⁵ of (Z)-5-undecen-2-one (1) a sex pheromone of Douglass-Fir Tussock Moth *Orgyia pseudotsugata* which is a severe defoliator of fir forest of western North America⁶, (Z)-7-Nonadecen-11-one (2) and Z-(7)-Eicosen-11-one (3) the pheromones of peach fruit moth *Carposina niponensis* Walsingham, a major economic pest of apple peach and other fruits of Japan⁷ which is described⁸ in scheme 1.

In addition, a new methodology has been developed⁹ for chemoselective reduction of the dialkylated TosMIC to the corresponding hydrocarbons without disturbing the functionalities such as acetylenic, aromatic, ketals, olefins, etc. The utility of this approach has been demonstrated in the synthesis of pheromones, plant growth regulators (*n*-triacantanol) and other biologically active compounds

(*L*-factor). As an illustrative example (Z)-9-tricosene (13) the pheromone of common house fly was prepared¹⁰ (scheme 2) in which the dialkylated TosMIC (14) was conveniently reduced⁹ with lithium in liquid ammonia.

In controlling the different parameters in the pheromone synthesis an innovative method in which 4-pentyn-1-ol is utilized¹¹ as a key synthon, derived from tetrahydrofurfuryl chloride (16). Thus, tetrahydrofurfuryl chloride on treatment with lithium amide in liquid ammonia provides a dianion of 4-pentyn-1-ol which *in situ* reacts with suitable alkyl halides. The disubstituted acetylenic alcohols thus obtained on treatment with sodamide in 1,3-diamino-propane furnish ω -acetylenic alcohols which can further be alkylated with saturated or unsaturated alkyl halides as desired. The acetylenic triple bond can be utilized for the introduction

Scheme - 3Scheme - 4

of double bonds with E or Z configuration using suitable reducing agents.

To illustrate the power of this method the synthesis of Z-11-octadecenol (15) a pheromone of usser wax moth *Achroia grisella* from the wing glands of the moth¹² and also a pheromone of spotted bollworm *Earias vitella* is described^{13,14} (scheme 3).

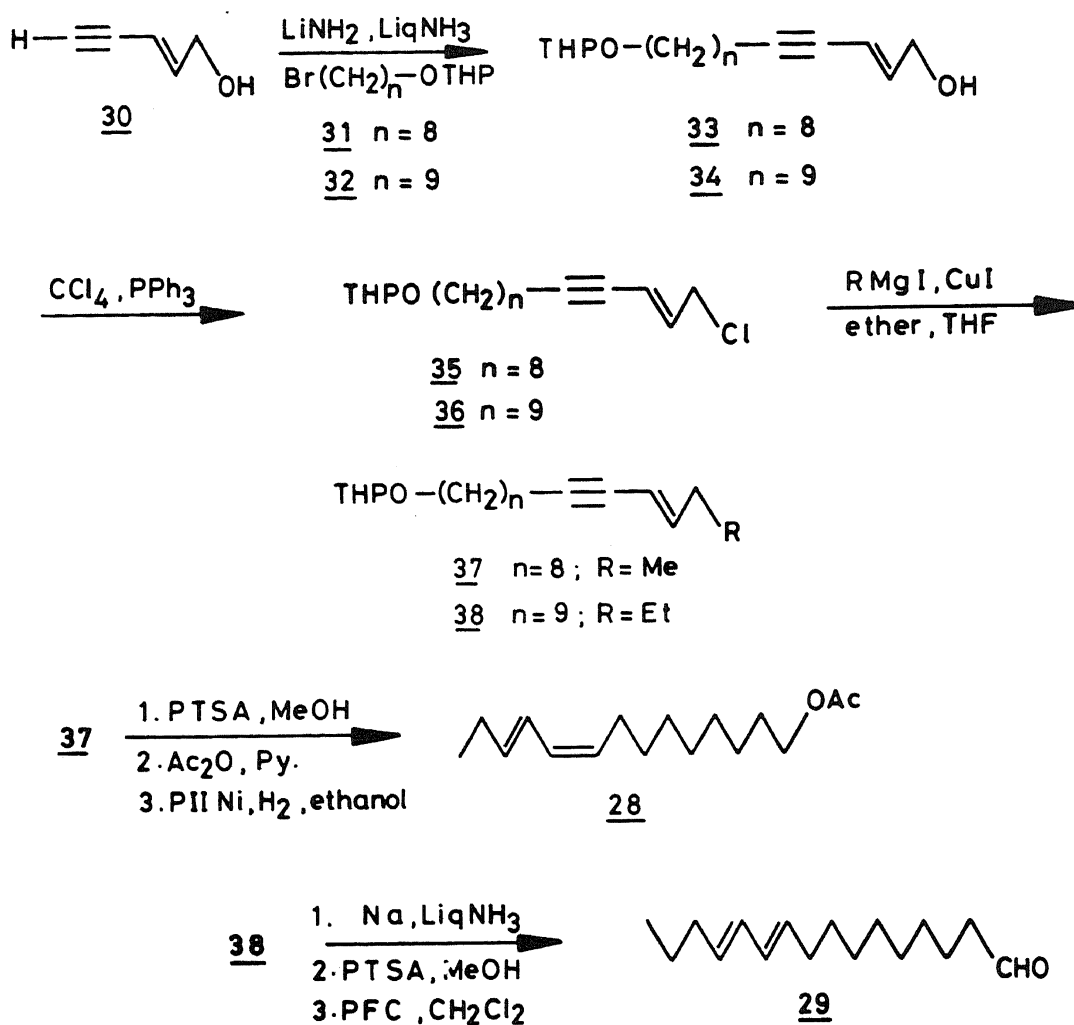
In another highly efficient and practical approach for the synthesis of monoolefinic pheromones the octyne is alkylated with ω-bromo alcohols in the presence of lithium amide in liquid ammonia and further elaboration afforded the pheromones. Thus, (Z)-9-hexadecenal¹⁵ (22) and (Z)-11-octadecenol (15), the pheromones of cotton pests

(scheme 4) are synthesized¹⁶ using the above strategy.

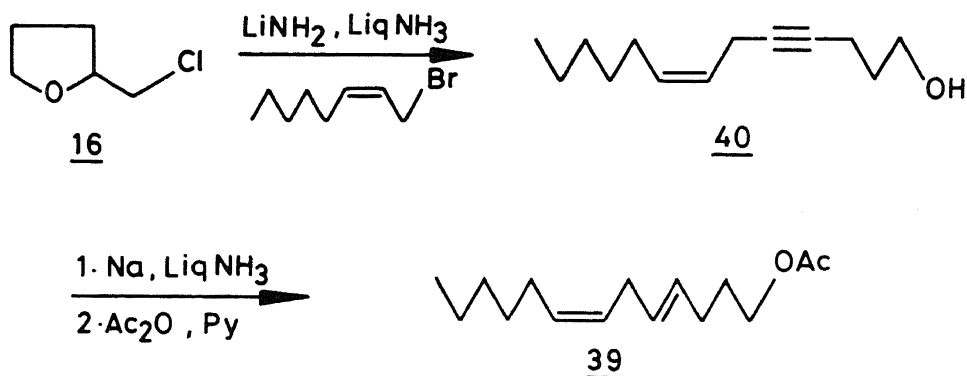
Diolefinic pheromones

A common method developed, for the preparation of (Z,E)-9,11-tetradecadienyl acetate (28), a pheromone of armyworm¹⁷ and (E,E)-10,12-hexadecadienyl acetate (29), a pheromone of bollworm¹⁸, the two pests commonly encountered in cotton crop, takes¹⁹ advantage of the bifunction present at both the ends of the (E)-2-penten-4-yn-1-ol (30) (scheme 5). The acetylenic functionality in 30 was utilised for C-C bond formation with alkyl bromide using lithium amide in liquid ammonia, while the

Scheme - 5



Scheme - 6

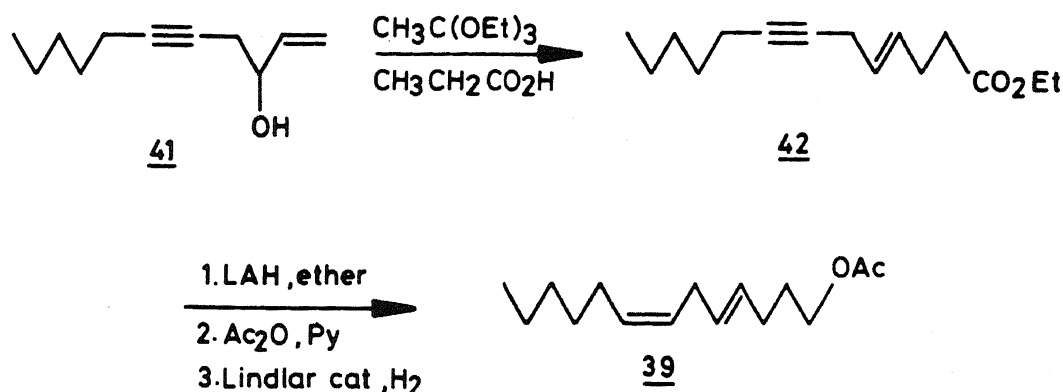


hydroxy functionality was later converted to chloride which was then coupled with suitable Grignard reagent in the presence of cuprous iodide to result in the formation of system. The en-yne system is

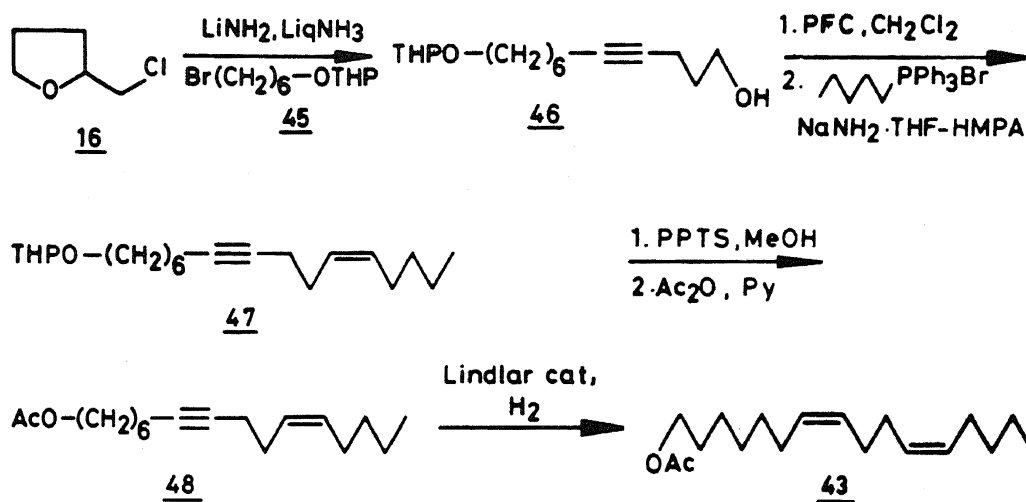
further stereoselectively converted to (E,Z) or (E,E) dienes, by choosing suitable reducing agents.

In the preparation of non-conjugated diene-pheromones, the procedure earlier reported, viz.,

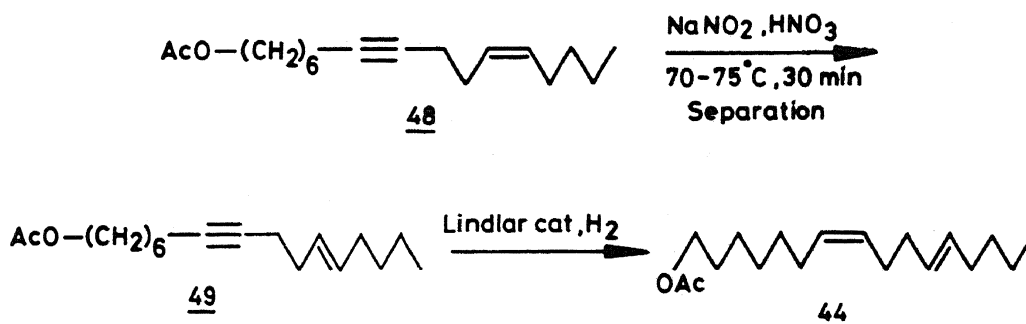
Scheme - 7



Scheme - 8



Scheme - 9

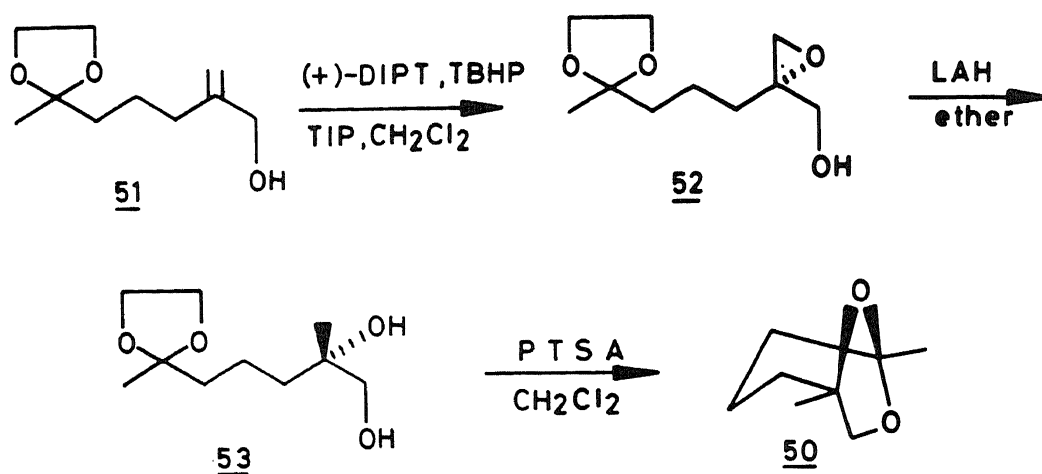


in situ alkylation 4-pentyn-1-ol made from tetrahydrofurfuryl chloride (16) has been used extensively. Thus, (E,Z)-4,7-tridecadienyl acetate (39) a pheromone of female potato tuberworm moth²⁰ was prepared²¹ starting from tetrahydrofurfuryl chloride (16) as shown in scheme 6. Alternatively, pheromone 39 was also prepared²² from acetylenic

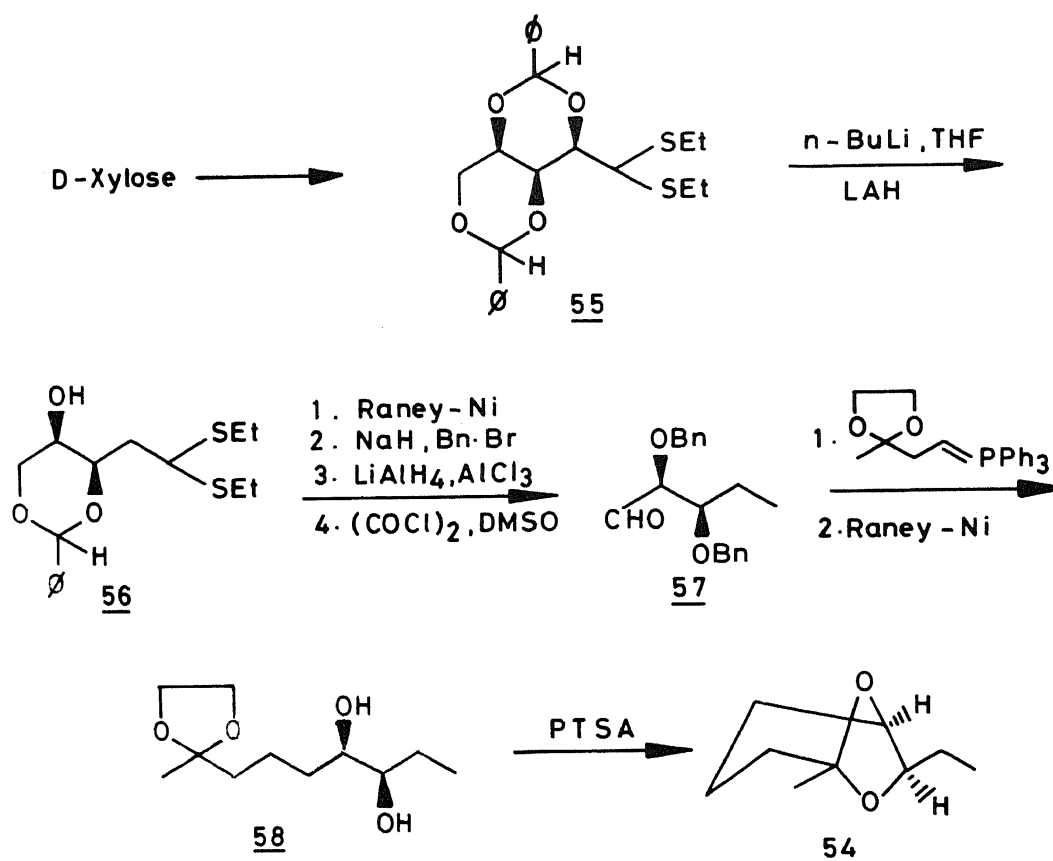
precursors using Claisen rearrangement as a key step (scheme 7). Thus allylic alcohol 41 on Claisen rearrangement with triethyl orthoacetate gave 42 which was later elaborated to pheromone 39.

In the synthesis of (Z,Z) and (Z,E)-7,11-hexadecadienyl acetate (43 and 44), the pheromones of pink bollworm moth *Pectinophora gossypiella* (saun-

Scheme - 10



Scheme - 11



ders), a destructive pest of cotton²³, the *in situ* alkylation of 4-pentyn-1-ol made from tetrahydrofurfuryl chloride was successfully exploited²⁴ (scheme 8). Thus, tetrahydrofurfuryl chloride (16) on opening with THP-ether of 6-bromohexanol (45) gave acetylenic alcohol (46) which on oxidation, stereoselective Wittig olefination and further elaboration afforded 48, a common synthon for the

preparation of both the pheromones 43 and 44. Compound 48 on hydrogenation over Lindlar catalyst afforded pheromone 43. Alternatively, compound 48 was isomerized (scheme 9) using sodium nitrite and nitric acid and further separation afforded the major trans isomer (49). Compound 49 was later partially hydrogenated to give pheromone 44.

Pheromones with an intramolecular ketal linkage

Some of the bark beetles such as *Dendroctonus frontalis*, *Dendroctonus brevicomis* utilize (-) frontalin (**50**), (+) exo-brevicomin (**54**) as their aggregation pheromones respectively³. Data on field test using optically pure isomers of these molecules indicate that the activity is associated with only one isomer. The urge to prepare these compounds in enantiomerically pure form has culminated in a short and efficient synthesis of (-) frontalin (**50**), a pheromone of western pine beetles of the western coast of North America²⁵.

The basic strategy involved in the synthesis²⁶ of **51** was the application of Sharpless asymmetric epoxidation of allylic alcohol (**51**) to give compound **52**. The epoxy alcohol **52** on reduction with lithium aluminium hydride produced **53** which on exposure to PTS acid afforded (-) frontalin (**50**) (scheme 10).

The synthesis of exo-Brevicomin²⁷ (**54**), a principal component of the sex attractant of the western pine beetle *Dendroctonus brevicomis* the pest of the ponderosa pine tree has been achieved²⁸ in an elegant manner starting from D-xylose (scheme 11). Thus, D-xylose was converted to dibenzylidene derivative (**55**) which on treatment with *n*-butyl lithium followed by reduction with LAH afforded the key synthon **56**. The hydroxy compound (**56**) was further transformed to dibenzyl aldehyde (**57**) which was subsequently elaborated to **58**. Com-

pound **58** on exposure to PTS acid afforded exobrevicomin (**54**).

In another alternative approach^{9b}, the utility of TosMIC for the preparation⁹ of hydrocarbons has been exploited starting from (R,R) tartaric acid. Thus (scheme 12), diethyl tartrate (**59**) was converted to the iodide (**60**) using standard sequence of reaction. Compound **60**, on alkylation with TosMIC and further reduction with lithium in liquid ammonia afforded the hydroxy compound (**61**). Compound **61** on oxidation and Grignard reaction gave compound **62**. The hydroxy functionality in **62** was removed using Barton's reaction to give compound **63** which on further treatment with PTS acid afforded (-) exo-brevicomin (**54**).

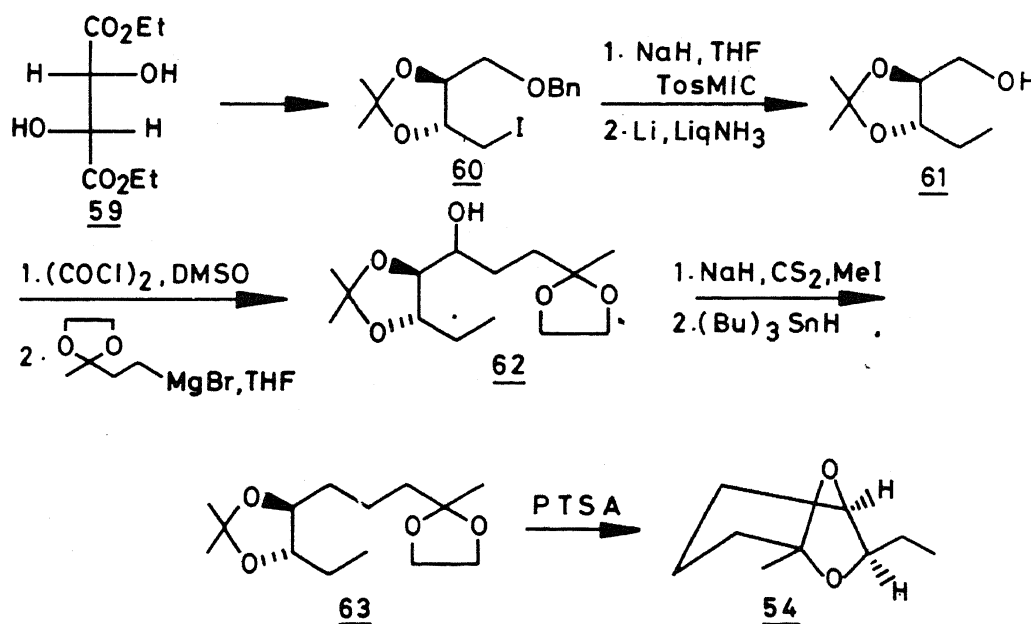
Pheromones with spiro ketal moieties

The cyclic acetal moiety is present in several natural products such as pheromones^{3,4,29} insect antifeedants, polyether antibiotics, etc. A general method has been developed for the preparation of pheromones with spiro ketal linkage in which the utility of TosMIC as a conjugative reagent was successfully exploited³⁰ (scheme 13).

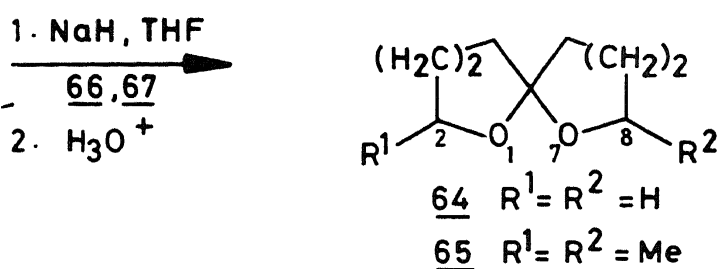
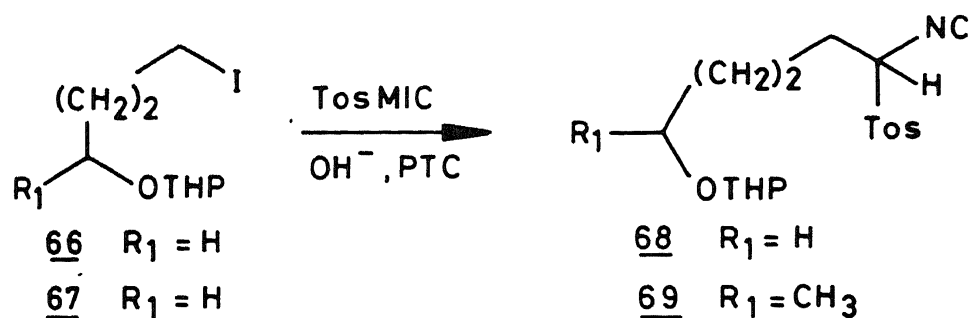
Synthesis of heterocyclic pheromones

Several heterocyclic compounds have been isolated from the glands of several species of ants.

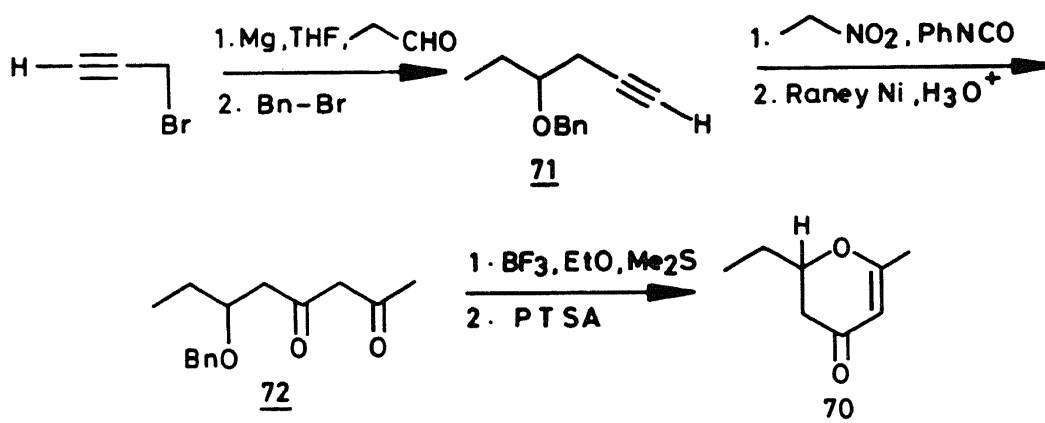
Scheme - 12



Scheme - 13



Scheme - 14



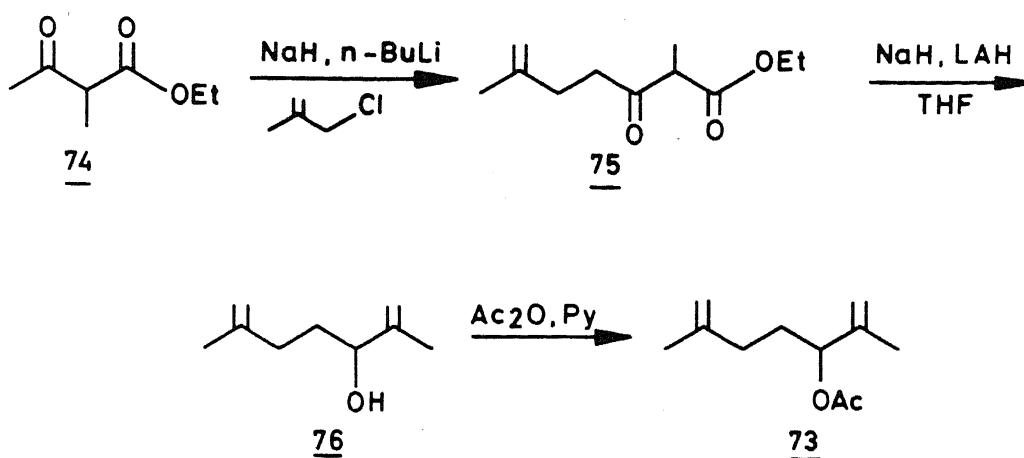
Synthesis of hepialone³¹ (70), a principle component from male sex scales of *Hepialus californicus* has been successfully achieved³² (scheme 14). Thus, the benzyl acetylenic compound (71) on reaction with nitroethane and further elaboration afforded the diketo compound (72) which on debenzoylation and treatment with PTS acid afforded (\pm) hepialone (70).

Terpenoid pheromones

Several mono, sesqui and diterpenoids have been found in the pheromonal components or in the

defensive secretion of different species⁴. These compounds are found to have bizarre skeletal structures. The synthesis of the monoterpene 2,6-dimethyl-1,6-heptadien-3-yl acetate³³ (73), a pheromone component of comstock mealy bug *Pseudococcus comstocki* has been achieved³⁴ (scheme 15). Thus, 2,6-dimethyl-3-oxo-het-6-enoate (75) obtained from 74 was treated with sodium hydride in THF and the resulting enolate on reduction with LAH afforded the alcohol 2,6-dimethyl-1,6-hyptadien-3-ol (76) which on acetylation furnished pheromone 73.

Scheme - 15



CONCLUSION

In the preceding account, we have described the work on the synthesis of insect sex pheromones, carried out during the last five years. Most of the approaches developed for the synthesis of pheromones are novel, innovative and easy to handle in large scale preparations. There is no doubt that the research on pheromones has reached a stage that the pheromone technology can directly be transferred to the farmers for controlling the insect populations.

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1. Henrick, C. A., *Tetrahedron*, 1977, **33**, 1845.
2. Rossi, R., *Synthesis*, 1977, 817.
3. Mori, K., In: *Synthesis of natural products*, (ed.) J. ApSimon, John Wiley, New York, 1981, Vol. 4.
4. Baker, R. and Herbert, R., *Nat. Prod. Rep.*, 1984, **1**, 299.
5. Reddy, P. S., Sahasrabudhe, A. B. and Yadav, J. S., *Synth. Commun.*, 1983, **13**, 379.
6. Smith, R. G., Daterman, G. E. and Daves Jr. G. D., *Science*, 1968, **188**, 63.
7. Tamaki, Y., Honma, K. and Kawasaki, K., *Appl. Entmol. Zool.*, 1977, **12**, 60.
8. Yadagiri, P. and Yadav, J. S., *Synth. Commun.*, 1983, **13**, 1067.
9. (a) Yadav, J. S. and Reddy, P. S., *Tetrahedron Lett.*, 1984, **25**, 4025; (b) Yadav, J. S., Reddy, P. S. and Joshi, B. V., *Tetrahedron*, 1988, **43**.
10. Carlson, D. A., Mayer, M. S., Silhacek, D. L., James, J. D., Beroza, M. and Bierl, B. A., *Science*, 1971, **174**, 76.
11. Reddy, P. S. and Yadav, J. S., *Synth. Commun.*, 1984, **14**, 327.
12. Dehm, K. M. and Mayo, D., *Naturwissenschaften*, 1971, **58**, 215.
13. Cork, A., Chamberlain, D. J., Beevor, P. S., Hall, D. R., Nesbitt, B. F., Cambion, P. G. and Attique, M. R., *J. Chem. Ecol.*, 1988, **14**, 929 and references cited therein.
14. Yadav, J. S., Balkrishnan, K. and Sivadasan, L., *Indian J. Chem.*, 1988 (in press).
15. Klun, J. A. et al., *J. Chem. Ecol.*, 1980, **6**, 165, 177.
16. Yadav, J. S., Chandrasekar, S., Ravishankar, R. and Reddy, E. R., unpublished results.
17. Nesbitt, B. F., Beevor, P. S., Cole, R. A., Lester, R. and Poppi, R. G., *Nature (London)*, 1973, **244**, 208.
18. Hall, D. R., Beevor, P. S., Lester, R. and Nesbitt, B. F., *Experientia*, 1980, **36**, 1523.
19. Yadav, J. S., Deshpande, P. K. and Reddy, E. R., *Synth. Commun.*, 1988, **18**.
20. Roelofs, W. L., Kochansky, J. P., Cadre, R. T., Kennedy, G. G., Henrick, C. A., Labovitz, J. and Corbin, V. L., *Life Sci.*, 1975, **17**, 699.

21. Yadav, J. S. and Reddy, P. S., *Synth. Commun.*, 1986, **16**, 1119.
22. Yadav, J. S., Kulkarni, A. D. and Reddy, P. S., *Indian J. Chem.*, 1986, **B25**, 1220.
23. Hummel, H. E., Gaston, L. K., Shorey, H. H., Kaae, R. S., Byrne, K. J. and Silverstein, R. M., *Science*, 1973, **181**, 873.
24. Yadav, J. S., Upender, V., Shekharam, T. and Reddy, E. R., *Indian J. Chem.*, 1988 (in press).
25. Kinzer, G. W., Fentiman, A. F. Jr., Page, T. F., Filtz, R. L., Vite, J. P. and Pitman, G. B., *Nature (London)*, 1969, **221**, 477.
26. Yadav, J. S., Joshi, B. V. and Sahasrabudhe, A. B., *Synth. Commun.*, 1985, **15**, 797.
27. Silverstein, R. M., Bellas, T. E., Wood, D. L. and Browne, L. F., *Science*, 1968, **159**, 889.
28. Yadav, J. S., Vidyasagar, V. and Reddy, P. S., *Carbohydr. Res.*, 1986, **154**, 236.
29. Franke, W., Reith, W., Bergstrom, G. and Tengo, J., *Naturwissenschaften*, 1980, **67**, 149; Baker, R., Herbert, R., Howse, P. E. and Jones, O. T., *J. Chem. Soc. Chem. Commun.*, 1980, 52.
30. Yadav, J. S. and Gadgil, V. R., unpublished results.
31. Kubo, I., Matsmoto, T. and Wagner, L., *Tetrahedron Lett.*, 1985, **26**, 563.
32. Yadav, J. S. and Rao, E. S., *Synth. Commun.*, 1988, **18**.
33. Uchida, M., Nakagawa, K., Negishi, T., Asano, S. and Mori, K., *Agric. Biol. Chem.*, 1981, **45**, 369.
34. Rao, E. S. and Yadav, J. S., *Indian J. Chem.*, 1986, **B25**, 1174.