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Synthesis of chiral insect pheromones

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Abstract

Syntheses of chiral insect pheromones have been reviewed The pheromones are categorised into three classes based on the root of their chiralities. These were pheromones with chirality due to: (i) methyl branching (Type A), (ii) possession of oxygenated functionality (Type B), and (iii) a combination of both (Type C). Rational synthetic design for the above pheromone types have been discussed highlighting the contributions from our own laboratory.

Key words : Synthesis, chiral pheromones, chiron approach, asymmetric reactions, biochemical catalysts

1. Introduction

Pheromone chemistry was not discussed in three dimensions till the early 1970s. With the discovery[1] of (S)-4-methyl-3-heptanone (3) as the first chiral pheromone, research in this area has gained unprecedented momentum. This has resulted in the isolation and identification of several hundreds of insect pheromones, a sizeable portion of these being optically active. Like other biological phenomena, pheromone perception is expectedly governed by the chirality, if any, in the molecules. However, rationalization of the exact role seems impossible in view of the complex and intriguing nature of the problem. A recent review[2] has comprehensively listed the chiral pheromones isolated so far from the insect kingdom and categorized them in terms of their activity—stereochemistry relationship.

Utility of pheromones as modern-day pest-controlling devices provides a great fillip in their synthesis especially because of the low natural abundance of these semiochemicals. In the case of chiral pheromones, availability of optically pure compounds with predetermined stereochemistry not only helps in the determination of their configuration but is also mandatory for unerroneous bioassay.

In view of the above, this branch of organic synthesis is currently one of the active areas of bioorganic research. Several excellent reviews and monographs[2–5] highlighting the importance of chiral pheromones and their syntheses have been published from time to time.

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Although informative, most of these deal with the synthesis of individual candidates rather than focussing on the crux of the problem associated in this area. The most recent report of Mori[2] has elaborated the types of useful chirons and asymmetric methodologies exploited in this pursuit. In view of the above, and overall enormity of the job, the present paper is restricted to identifying the root of chirality in pheromones and rationalizing the synthetic design with respect to this. Primarily, our own synthetic approaches have been exemplified and relevant works from other laboratories incorporated for the sake of comparison.

2. Genesis of chirality in insect pheromones

Insect pheromones are mostly acyclic in nature although cyclic pheromones, *viz.*, spiroketals, γ- and δ-lactones, macrolides, etc., exist. Understandably, the pheromone chirality owes its genesis to the presence of asymmetric carbon atoms. The only examples of molecular chirality playing a role in the pheromone kingdom can be found in methyl (E)-2,4,5-tetradecatrienoate, the pheromone of dried bean beetle[6] and the spiroketal pheromone [olean (**16**)] of the olive fruit fly[7]. However, the most distinctive feature of pheromone chirality can be envisaged as the presence of methyl branching (Type A) or oxygenated functionality (Type B) in the asymmetric centre or a combination of both (Type C). Consequently, synthesis of chiral pheromones amounts to creation of the above structural features in high optical purity. The following section deals with the synthesis of chiral pheromones as perceived in the above classification. The different approaches of chiral synthesis, *viz.*, chiron route and asymmetric reactions are presented separately while the routine resolution-based syntheses are omitted.

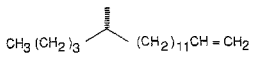
2.1. Insect pheromones of Type A

Compounds with methyl branching are ubiquitous among naturally occurring secondary metabolites. Insect pheromones are no exception and several pheromones so far isolated from the insect kingdom belong to this group. Many of these constitute pheromones of economic significance and possess the $R_1CH(CH_3)$-skeleton where R_1=ethyl, propyl, *n*-butyl, etc. Some of the illustrative examples of this type of pheromones are provided in Fig. 1. Various groups have reported their synthesis *via* chiron approach or asymmetric reaction with chemical/biochemical catalysts.

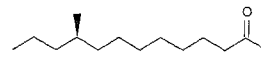
2.1.1. Chiron approach

The most logical chiral pool material for the synthesis of Type A pheromones seems to be (R)-citronellal (**30**) or its different derivatives (**31** and **33**). However, although easily available, the optical purity of natural **30** is variable and rather modest[8]. Consequently, it is desirable to use **33** which can be easily prepared[9] from the optically pure (R)-pulegone. The presence of methyl branching and the bifunctionality in **30–32** is attractive for their exploitation in the syntheses of Type A pheromones. Especially for pheromones with R_1 > *n*-propyl, the (R)-enantiomers of **30**/**31**/**32** alone can furnish both the antipodes of the target compounds as depicted in Schemes 1[10] and 2[11].

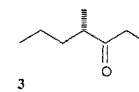
However, for pheromones with R_1=Et, the citronellol-based synthesis of their (R)-antipodes warrants generation of the ethyl group from the alkene side chains of the above



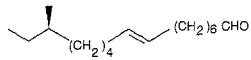
1
Sex pheromone of peach leafminer moth



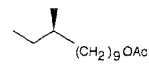
2
Pheromone of southern corn rootworm



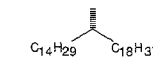
3
Alarm pheromone of leaf-cutting ant



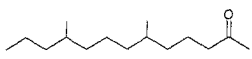
4
Sex pheromone of khapra beetle



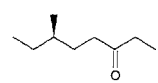
5
Sex pheromone of smaller tea tortrix moth



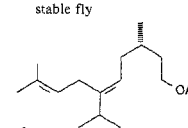
6
Sex pheromone of stable fly



7
Sex pheromone of cucumber beetle

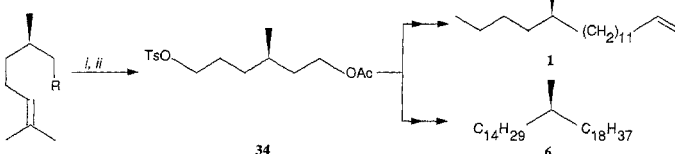


8
Alarm pheromone of *Crematogaster* ants



9
Sex pheromone of yellow scale

FIG. 1. Type A Pheromones.

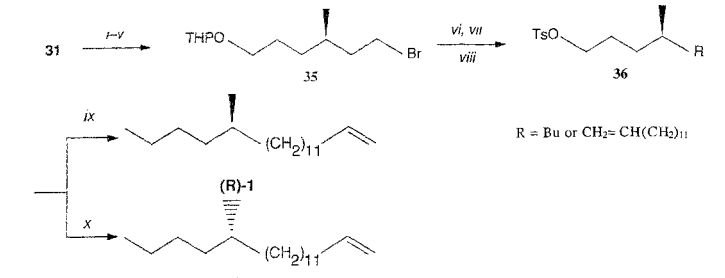


30 R=CHO
31 R=CH_2OH
32 R=CO_2H
33 R=CH_2OAc
(i) O_3, $NaBH_4$; *(ii)* *p*-TsCl/Py.

SCHEME 1.

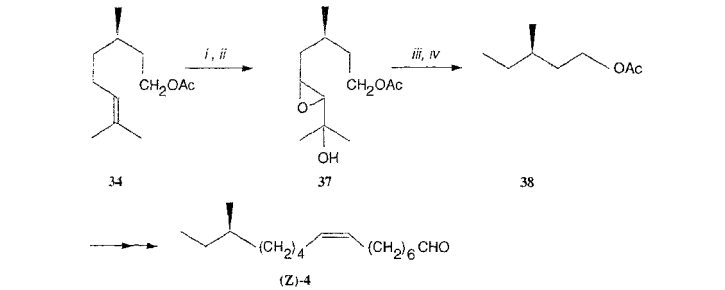
terpenoids. For this, Mori *et al*[12] have developed a route involving one carbon migration of the double bond followed by its cleavage and subsequent functionalisation (Scheme 3). This strategy has been exploited in the synthesis of several pheromones[12].

In view of the requirement of costly and toxic Ph_2Se_2, in the above protocol, alternative strategy for this conversion was desirable. Consequently, we have formulated (Scheme 4) a novel inexpensive method using easily accessible reagents under operationally simple conditions. Essentially this involved oxidative cleavage of the olefinic bond of the chiron (after suitable derivatization) to generate the acid (**40**) which was reductively decarboxylated by refluxing with $K_2S_2O_8$ in the presence of $AgNO_3$ (cat.) in aqueous acetonitrile. This strategy has been exploited for preparing several pheromones[13–15] (Scheme 5).



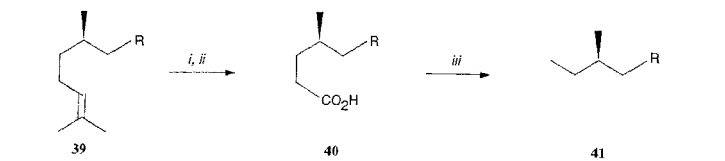
(i) $Ph_3P.Br_2/CH_2Cl_2$; *(ii)* *m*-CPBA/CH_2Cl_2; *(iii)* HIO_4/THF; *(iv)* $NaBH_4$/MeOH; *(v)* DHP/H^+; *(vi)* EtMgBr or $CH_2{=}CH(CH_2)_8MgBr/Li_2CuCl_4$/THF; *(viii)* H^+; *(viii)* TsCl/Py; *(ix)* Me_2CuLi; *(x)* $CH_2{=}CH(CH_2)_8MgBr/Li_2CuCl_4$.

SCHEME 2.



(i) Ph_2Se_2/H_2O_2; *(ii)* *m*-CPBA; *(iii)* HIO_4; *(iv)* $N_2H_4/KOH/\Delta$.

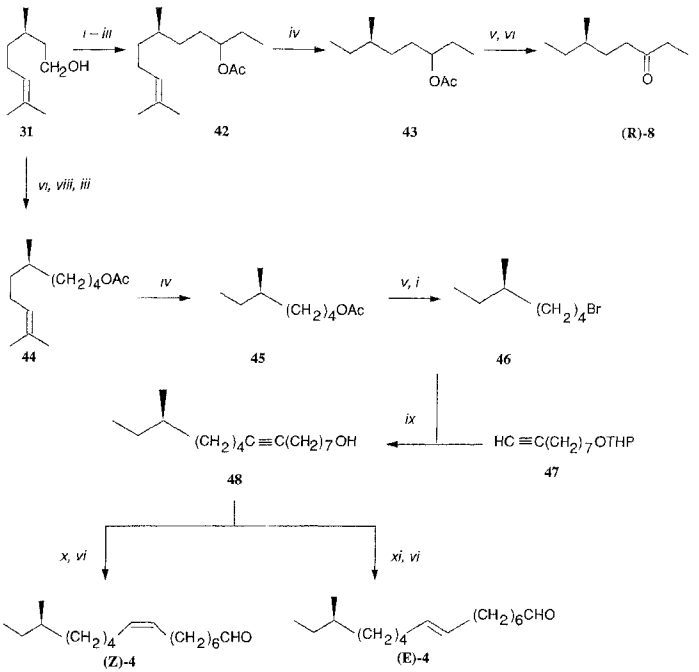
SCHEME 3.



R = any acid compatible group

(i) O_3; *(ii)* Jones' reagent; *(iii)* $K_2S_2O_8/AgNO_3$/aq CH_3CN/Δ.

SCHEME 4.

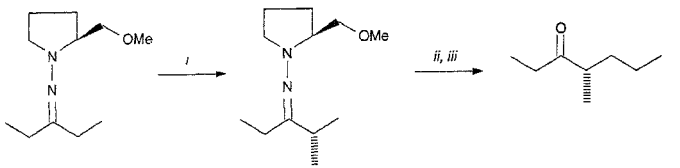


(i) $Ph_3P.Br_2$; *(ii)* Mg/*n*-propanal; *(iii)* Ac_2O/Py; *(iv)* as in Scheme 4; *(v)* KOH; *(vi)* PCC; *(vii)* NaH/$(EtO)_2P(O)CH_2CO_2Et$; *(viii)* Li/NH_3/EtOH; *(ix)* BuLi/46/THF/HMPA, H^+; *(x)* H_2/P-2 Ni; *(xi)* Na/NH_3.

SCHEME 5.

2.1.2. Chemical asymmetric synthesis

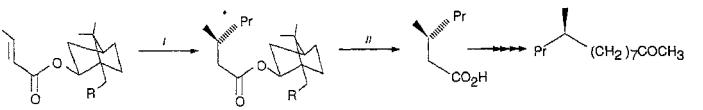
In principle, asymmetric α-alkylation of active methylene group, Michael addition, aldol reaction, etc., can be used for the syntheses of Type A pheromones. Several chiral esters, amides and oxazolines have been explored[16,17] in the alkylation methods. However, in terms of versatility and efficacy for aliphatic systems, alkylation of Ender's chiral hydrazones (RAMP or SAMP) and Michael addition of organo cuprates to Oppolozer's camphor-based sultum needs special mention. As representative examples, the synthesis of (S)-4-methyl-3-heptanone **(3),** the pheromone[1] of leaf-cutting ants, *Atta texana via* hydrazone method[18] (Scheme 6) and (R)-10-methyl-2-tridecanone **(2),** pheromone[19] of southern corn rootworm with sultum[20] (Scheme 7) is presented.



49 **50** **3**

(i) LDA/Et_2O, *n*-C_7H_7I/-100°; *(ii)* MeI; *(iii)* dil. HCl/pentane.

SCHEME 6.

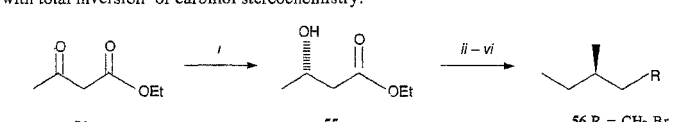


51 **52** **53** **2**

R = (Cyclohex)$_2NO_2S$
(i) PrCu.BF_3.Bu_3P; *(ii)* NaOH.

SCHEME 7.

In view of the amenability of optically pure carbinols both from nature and by other asymmetric routes, invertive alkylation of their suitable derivatives also seems promising for this purpose. Based on this, we have prepared[21] (S)-6-methyl-3-octanone (**8**), the ant pheromone antipode[22] from ethyl (S)-3-hydroxybutyrate (**55**) *via* coupling its tosylate derivative with Me_2CuLi (Scheme 8). To this end, the triflates also work exceptionally well with total inversion of carbinol stereochemistry.



54 **55** **56** R = CH_2 Br
8 R = CH_2CoEt

(i) Baker's yeast; *(ii)* *p*-TsCl/Py; *(iii)* Et_2CuLi; *(iv)* LAH; *(v)* $Ph_3P.Br_2$; *(vi)* Mg/THF/EtCOCl/-78°C.

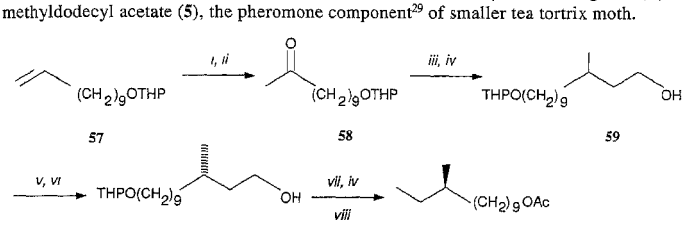
SCHEME 8.

2.1.3. Biochemical route

β-Hydroxyisobutyric acid (HIBA), easily accessible by microbial β-oxidation of isobutyric acid, serves as a useful chiron for this class of pheromones. One example of its application can be found[23] in the synthesis of (–)-invictolide (**27**), the pheromone[24] (Type C) antipode of red imported fireant from the above chiron. Asymmetric hydrolysis of 3-methylglutarates with pig liver esterase furnish the bifunctional methyl branched synthon which has been

employed[25] for the synthesis of yellow-scale pheromone (**9**)[26]. Likewise, baker's yeast-mediated hydrogenation of 2-methyl-2-alkenols or the corresponding aldehydes is known to produce chiral methyl branched intermediates, some of which have provided access to several important insect pheromones[27].

Recently, we have developed (Scheme 9) a practical route for the enantiomers of 3-methyldodecanediol derivative (**60**) *via* lipase-catalyzed acetylation of the β-methylalkanol (**59**). The substituent groups of this were so chosen as to provide several insect pheromones from the same precursor. Its utility has been demonstrated[28] by derivatizing it to (R)-10-methyldodecyl acetate (**5**), the pheromone component[29] of smaller tea tortrix moth.



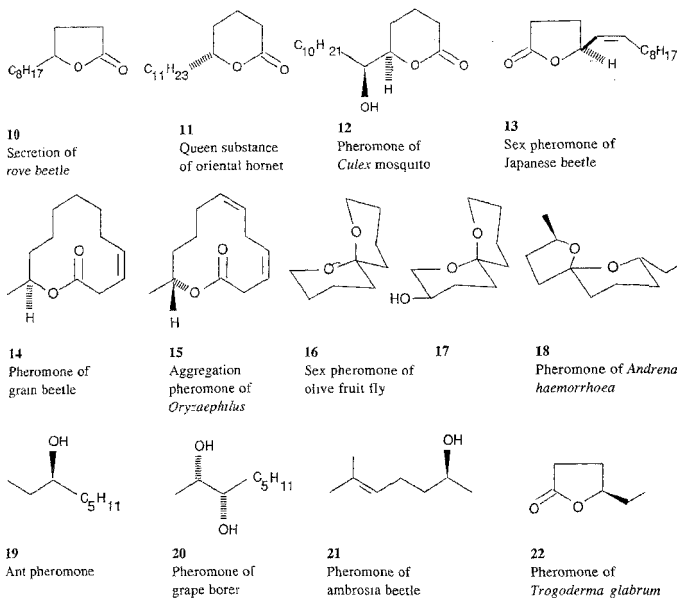
(i) $Hg(OAc)_2$/THF–H_2O, $NaBH_4$; *(ii)* PDC, *(iii)* NaH/$(EtO)_2P(O)CH_2CO_2Et$/THF; *(iv)* LAH/THF; *(v)* CRL/CH_2=CHOAc; *(vi)* KOH; *(vii)* MsCl/TEA; *(viii)* AcCl/AcOH.

SCHEME 9.

2.2. Pheromones of Type B

Majority of the optically active pheromones fall in this class as their chirality is governed by oxygenated functionalities. Several alcohols and their esters, epoxides, γ-, δ- and macrocyclic lactones and spiroketals of various ring sizes constitute Type B pheromones (Fig. 2). Syntheses of all these primarily require generation of chiral carbinol moiety in high optical yields. The correlation of epoxy and various lactonic pheromone structures with hydroxy compounds as their progenitor is apparent and needs no emphasis. For macrolidic pheromones, additional challenge arises in the macrolactonization step. This can be accomplished by *(i)* preparation of required chiral hydroxy esters/acids (*via* chiron or asymmetric routes) and subsequent chemical lactonization by known method or *(ii)* enantioselective lipase-catalyzed intramolecular esterification. For sensitive compounds like 1,4-dienic macrolides (*viz.*, **15**), milder biochemical routes appear to be the method of choice. But for ring size $<C_{12}$, very little success has so far been achieved[30] by this approach.

In the case of spiroketal pheromones, the presence of carbinol is essential not only for ketal formation but also for necessary chirality in all but one (the spiroketal juncture) centres of it. So far, no method for asymmetric spiroketalization is known and its stereochemistry is governed by the preëxisting chirality of the precursor hydroxy ketone along with the anomeric effect being operative during cyclization. From the foregoing it is quite evident that preparation of chiral carbinol is of prime requirement for the syntheses of this class of



10 Secretion of *rove beetle*

11 Queen substance of oriental hornet

12 Pheromone of *Culex* mosquito

13 Sex pheromone of Japanese beetle

14 Pheromone of grain beetle

15 Aggregation pheromone of *Oryzaephilus*

16 Sex pheromone of olive fruit fly

17

18 Pheromone of *Andrena haemorrhoea*

19 Ant pheromone

20 Pheromone of grape borer

21 Pheromone of ambrosia beetle

22 Pheromone of *Trogoderma glabrum*

FIG. 2 Type B pheromones.

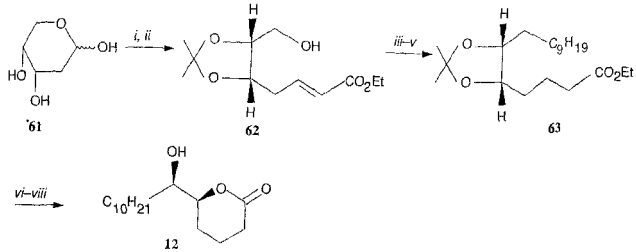
pheromones. Consequently, the relevant methodologies and their applications are dealt with in the following section.

2.2.1. Chiron approach

Nature's repertoire for hydroxyl-bearing chiral pool materials is enormous. Starting with the ubiquitous carbohydrates and their anhydro analogues, the range encompasses the hydroxy acids, *viz.*, (S)-lactic acid, (L)-tartaric acid (S)-malic acid, terpenoids, *viz.*, linalool, etc. In addition, natural amino acids can also be deaminated to the hydroxy compounds with retention of chirality owing to the anchimeric assistance of the neighbouring carboxylic functionality. This aspect has been exemplified (Scheme 17) in our synthesis of the Type C pheromone.

In terms of easy availability and presence of multiple chiral centres and functionalities, the versatility of the carbohydrate chirons is unquestionable. Moreover, the strong stereochemical

bias encountered in subsequent synthetic transformations especially with their cyclic forms is gratifying for the synthesis of complex compounds. However, their use for the preparation of simple compounds like pheromones with one or two chiral centres does not seem attractive. Consequently, only the synthesis[31] of (5R,6R)-6-hydroxyhexadecan-5-olide (**12**), the oviposition attractant[32] for the *Culex* mosquito from (D)-ribose is presented in this paper (Scheme 10).



(i) $CH_3C(OMe)=CH_2$/PPTS; *(ii)* $Ph_3P=CHCO_2Et$/$PhCO_2H$/DME/Δ; *(iii)* PDC; *(iv)* $C_9H_{19}PPh_3Br$/BuLi/THF/HMPA; *(v)* H_2/Pd-C; *(vi)* LiOH/aq. THF; *(vii)* AcOH/PTS/Δ; *(viii)* Ac_2O/Py.

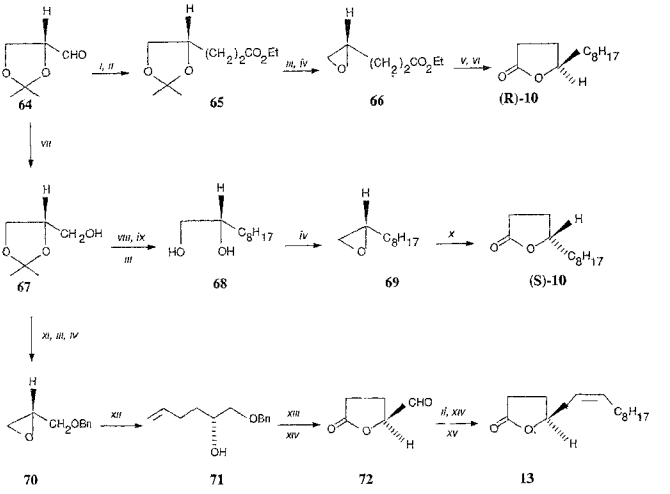
SCHEME 10.

Several hydroxyacids have also been extensively used for the syntheses of this class of pheromones and are nicely depicted in some of the earlier reviews.

(R)-2,3-Isopropylidene glyceraldehyde (**64**), easily accessible[33] from inexpensive (D)-mannitol has also found wide application in the syntheses of different classes of natural products including pheromones. Besides, its chirality, the high functional density and small three-carbon skeleton offers wide latitude for synthetic maneuveur from both the ends thereby shortening the synthetic routes. This also helps in preparing both the enantiomers of the target compounds from (R)-**64** alone, although its antipode can also be prepared from Vitamin C[34] or tartaric acid[35]. We have used[36–38] this for the syntheses of some lactonic pheromones, *viz.*, > *(i)* (4R)- and (4S)-dodecan-4-olide (**10**), the pheromone[39] of rove beetle, *(ii)* > japonilure (**13**)[40] (Scheme 11) and *(iii)* (5R)- and (5S)-hexadecan-5-olide (**11**) (Scheme 12), the queen substance[41] of oriental hornet. In these, for the γ-lactones the introduction of acetate unit at both the terminals of **64** was effected *via* malonate and allylmagnesium bromide/double bond cleavage protocol for the γ-lactones. The δ-lactonic pheromone enantiomers were prepared by coupling of the required alkyl part from the aldehyde site and introducing the propionate unit from the other side as such or after chirality inversion of the intermediate diol [(S)-**73**].

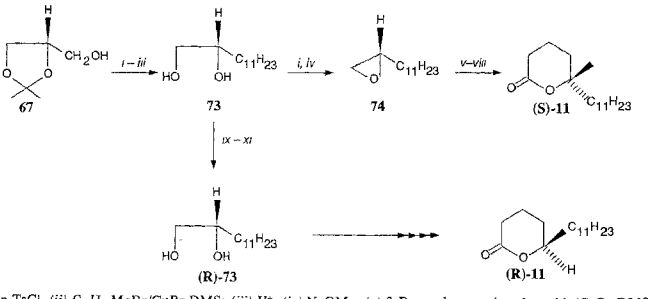
2.2.2. Chemical asymmetric synthesis

Several asymmetric reducing agents are known in literature. Tai's modified Ni catalyst for the hydrogenation of β-ketoesters has been used[42] in the synthesis of several Type B pheromones. Likewise, several derivatized LAH preparations[43–45] as well as pinene-based chiral borane[46],



(i) $NaHCO_3/(EtO)_2P(O)CH_2CO_2Et$; *(ii)* H_2/Pd-C; *(iii)* H^+; *(iv)* *p*-TsCl, NaOEt; *(v)* $(C_7H_{15})_2CuLi$; *(vi)* KOH,H^+; *(vii)* $NaBH_4$; *(viii)*TsCl/Py; *(ix)*$C_7H_{15}MgBr$; *(x)*$NaCH(CO_2Et)_2$/DMF/Δ; *(xi)*NaH/BnCl *(xii)* Allyl magnesium bromide; *(xiii)* O_3/Me_2S; *(xiv)* PCC; *(xv)* $C_6H_{19}PPh_3Br$/dimsyl.

SCHEME 11.

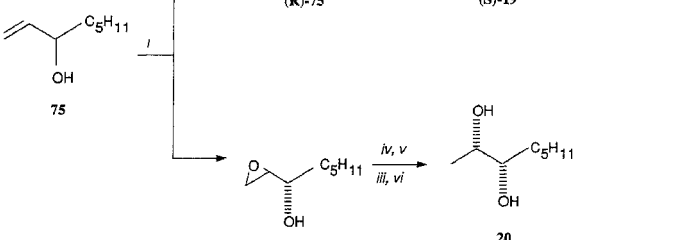


(i) *p*-TsCl, *(ii)* $C_{10}H_{21}MgBr$/CuBr.DMS; *(iii)* H^+; *(iv)* NaOMe; *(v)* 3-Butenylmagnesium bromide/CuBr.DMS; *(vi)* Ac_2O/Py; *(vii)* $RuCl_3$; *(viii)* KOH, H^+; *(ix)* MsCl/Py/DMF/Δ; *(x)* KOAc/Ac_2O/Δ; *(xi)* K_2CO_3/MeOH.

SCHEME 12.

capable of reducing α, β-acetylenic ketones have been instrumental in the syntheses of some lactonic pheromones. Reductions[47,48] of ketonic substrates bearing chiral auxiliaries have also been explored for pheromone syntheses. In addition, aldol condensation *via* chiral amide[17], sulphoxide[49], etc., led to asymmetric syntheses of many pheromones of Type B.

However, Sharpless method[50] for epoxidation of allylic alcohols finds widest application in the syntheses of different types of natural products. Wide substrate acceptability, excellent optical induction, predictable stereochemical outcome and operational simplicity offered by this method make it the most attractive. Based on this, syntheses of several epoxy[51] and spiroketal pheromones[52] have been developed. Another interesting feature of this reaction is the cumulative involvement of both substrate and reagent control which enforces *erythro*-selective epoxidation of prochiral allylic alcohols. This in turn leads to their kinetic resolution also and the chiral products obtained, *viz.*, the epoxy compound and the resolved alcohol can then both be employed to reach different target compounds. This is exemplified in our synthesis[53] for the pheromones of *Myrmecine* ants and the grape borers (Scheme 13). In this, the epoxide (**76**), the precursor of pheromone **20**, did not possess the required stereochemistry at C-2. Consequently, a novel method of carbinol inversion was employed to reach the correct isomer of the target pheromone.

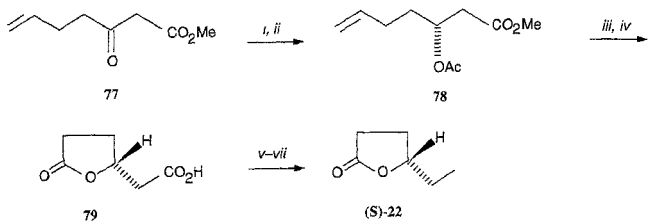


(i) (L)-Diethyl tartarate/$Ti(OPr^i)_4$/TBHP/CH_2Cl_2; *(ii)* H_2/Pd-C; *(iii)* DCC/CuCl/AcOH, NaOMe; *(iv)* DHP/H^+; *(v)* LAH; *(vi)* MeOH/PPTS.

SCHEME 13.

2.2.3. Biochemical synthesis

Several microbial redox systems have been explored to furnish hydroxyl chirons. Two of these, *viz.*, ethyl (S)- and (R)-3-hydroxybutyrate (55) [obtained[54] by baker's yeast reduction of ethyl acetoacetate and depolymerisation of microorganism-generated poly-3-hydroxybutyrate, respectively] and (R)-3-hydroxypentanoic acid [derived by oxidation of pentanoic acid with *Candida rugosa*] have been extensively used[55-56] in pheromone syntheses. We have prepared[57]

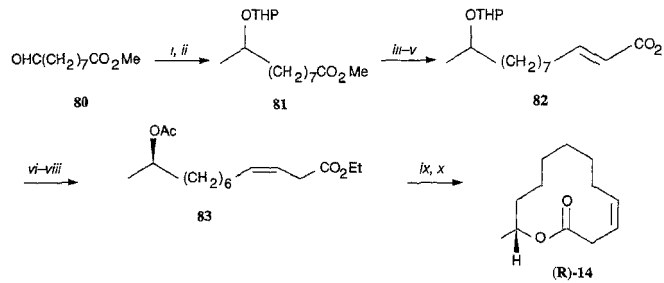


(i) KOH, baker's yeast, CH_2N_2; *(ii)* Ac_2O/Py; *(iii)* $RuCl_3$; *(iv)* KOH, H^+; *(v)* BH_3.THF; *(vi)* $Ph_3P.Br_2$; *(vii)* Bu_3SnH/AIBN.

SCHEME 14.

(Scheme 14) (S)-hexanolide (**22**), the pheromone antipode[58] of *Trogoderma glabrum via* baker's yeast reduction of suitable β-ketocarboxylic compound. In this, it was essential to carry out the microbial reduction on the potassium salt of **77** rather than on the ester to ensure high % ee.

Lipase- or protease-catalyzed asymmetric esterification[59] also shows great promise for the syntheses of Type B pheromones. Some of the examples in this class can be found in Mori[2]. Recently, we have formulated efficient strategies for the syntheses[60] of *(i)* ferrulactone II (**14**) (Scheme 15), the aggregation pheromone[61] of stored grain pests and *(ii)* (R)-9-hydroxydec-2(E)-enoic acid (**87**) (Scheme 16), the queen substance[62] of *Apis mellifera*.

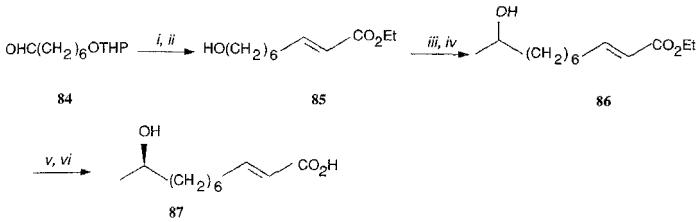


(i) MeMgBr/Et_2O; *(ii)* DHP/H^+; *(iii)* LAH; *(iv)* PCC; *(v)* NaH/$(EtO)_2P(O)CH_2CO_2Et$ *(vi)* Pot. silazide; *(vii)* H^+; *(viii)* PPL/CH_2=CHOAc; *(ix)* KOH; *(x)* Yamaguchi's method.

SCHEME 15.

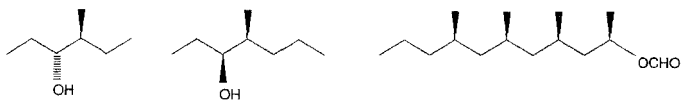
2.3. Pheromones of Type C

Essentially, this class of pheromones possesses the Type B structures with some additional methyl branchings and hence are available in both acyclic and cyclic forms (Fig. 3). From



(i) $NaH/(EtO)_2P(O)CH_2CO_2Et$; *(ii)* H^+; *(iii)* PCC; *(iv)* MeLi/Et_2O; *(v)* PPL/trifluoroethyl butyrate; *(vi)* KOH.

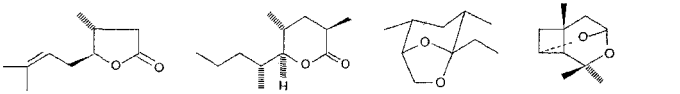
SCHEME 16.



23
Pheromone of
Tetramorium ant

24
Pheromone of
elm bark beetle

25
Pheromone of acarid mite



26
Pheromone of African
sugarcane borer

27
Pheromone of red
imported fire ant

28
Pheromone of
elm bark beetle

23
Pheromone of
Trypodendron lineatum

FIG. 3. Type C pheromones.

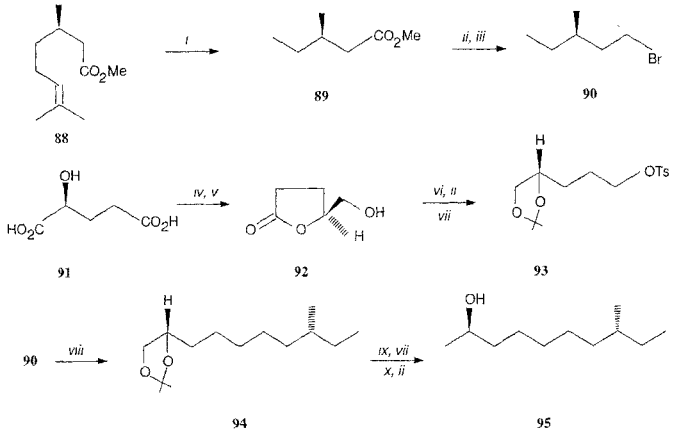
the synthetic point of view, these can further be classified into two distinct categories, *viz.*, *(i)* pheromones with methyl branching and oxygenated chiral centre separated by >2 carbon atoms (Type C1) and *(ii)* those where these functionalities are present either 1,2 or 1,3 with respect to each other (Type C2). Synthesis of the former can be accomplished by preparing the desired chiral building blocks individually followed by their coupling. But the above connective approach merely cannot lead to Type C2 pheromones.

2.3.1. Chiron approach

For the Type C1 pheromones, the chirons discussed earlier can be utilized to produce the target compounds. For example, (2R, 8R)-8-methyl-2-decanol (**95**), the parent alcohols of *Diabrotica* pests were prepared[63] wherein the hydrocarbon and the carbinol parts were

derived from **88** and glutamic acid, respectively (Scheme 17). For this also, inversion of secondary carbinol chirality gave the corresponding 2S-epimer (not shown in scheme).

For the Type C2 pheromones, however, most of the chirons are inadequate. The most suitable chirons are provided by the versatile carbohydrates which can be derivatized to any structural types possessing multiple chiral centres[64-65].

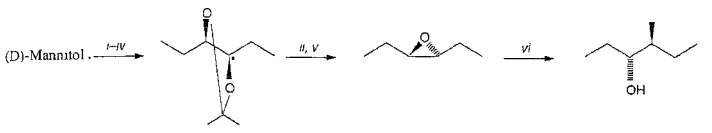


(i) as in Scheme 4, *(ii)* LAH; *(iii)* $Ph_3P.Br_2$; *(iv)* $NaNO_2$/HCl; *(v)* BH_3 DMS; *(vi)* DMAP/MeOH/H$^+$; *(vii)* TsCl/Py; *(viii)* Mg/CuBr.DMS/90; *(ix)* H$^+$; *(x)* NaOMe.

SCHEME 17.

2.3.2. Chemical asymmetric synthesis

The asymmetric reactions mentioned previously have been innovatively explored[2] for the preparation of many Type C1 pheromones. However, these methodologies are most suitable for the difficultly preparable Type C2 pheromones. For example, alkylation of chiral oxazoline[66] and amide[17], Michael addition[67] *via* sultums, etc., were used for the synthesis of many pheromones of this class. In addition, chelation-controlled Grignard addition to chiral aldehydes[68] and borane-based syntheses *via* boron enolate[69] or boronic ester[70] were extremely useful in this pursuit. Diastereocontrolled 2,3-Wittig rearrangement of allylic ether seems tailor made for Type C2 pheromone synthesis[71]. Furthermore, enantioselective opening of chiral epoxides[72] (prepared from chirons, viz., tartaric acid or Sharpless route) or halolactonization[73] were also used for the synthesis of several pheromones of this type. We have synthesized[74] the ant pheromone, (3S,4R)-4-methylhexan-3-ol (**23**) by diastereoselective opening of the chiral epoxide (**97**), prepared from (D)-mannitol (Scheme 18).



(i) Acetone/H$^+$; *(ii)* 70% aq. HAc, *(iii)* MsCl/Py; *(iv)* LAH/Et_2O/Δ; *(v)* HBr–HAc, NaOMe; *(vi)* $Me_2CuLi/Et_2O/-78^0C$.

SCHEME 18.

2.3.3. Biochemical route

The potential of this methodology has not been tested fully. Some of the illustrative examples are: *(i)* baker's yeast-mediated reduction[27] of α-methyl β-ketoesters, *(ii)* diastereoselective alkylation[75] of biochemically produced 3-hydroxy esters, and *(iii)* use of HIBA for the synthesis of lardolure[55].

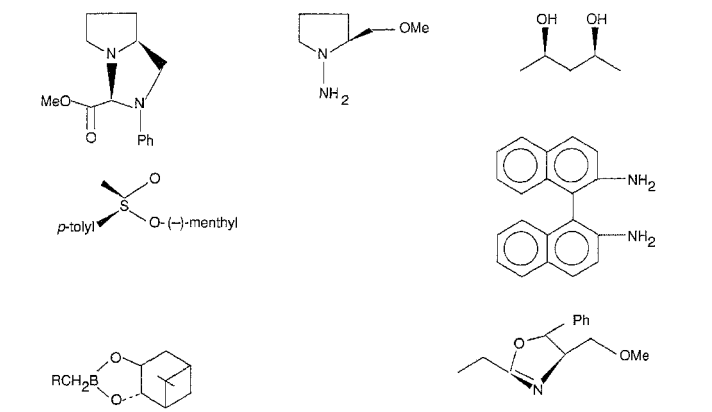


FIG. 4. Some chiral auxiliaries.

3. Conclusion

Majority of the chiral insect pheromones can be classified into three broad categories as mentioned earlier. However, some pheromones with small rings (*e.g.*, grandisol), complex ring patterns (*e.g.*, lineatin, periplanone B), unusual branching (*e.g*, anastrephin, epianastrephin) and the two atropisomeric pheromones mentioned earlier are some of the few exceptions to the above generalization. Syntheses of these from terpenoids (chiron approach), photocyclization

(asymmetric reaction) and HLADH-catalyzed oxidation (biochemical route) have been discussed in some of the earlier reviews. It is worth mentioning that synthesis of the allenic and spiroketal pheromones requires chiral carbinols as their precursors.

Acknowledgement

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