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Hydrolytic kinetic resolution of mono- and bisepoxides as a key step in the synthesis of insect pheromones†

Sharon Chow and William Kitching*

Department of Chemistry, The University of Queensland, Brisbane, 4072, Australia.
E-mail: kitching@chemistry.uq.edu.au

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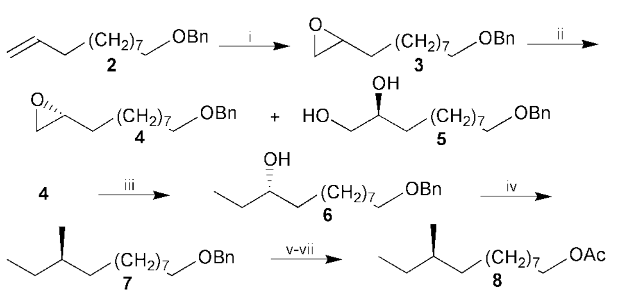
The synthetic utility of the readily separated epoxides, diols, epoxydiols and tetrols of high enantiomeric excesses, obtained by hydrolytic kinetic resolution (HKR) of functionalised mono- and bisepoxides with (salen)Co(OAc) complexes, is demonstrated by their efficient transformations to important insect pheromones.

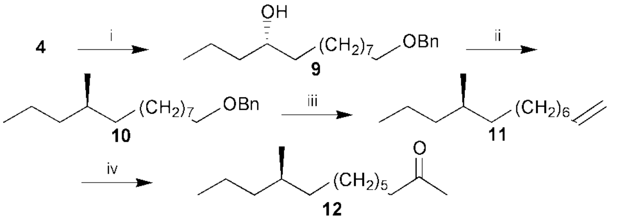
Many insect pheromones incorporate a medium to long alkyl chain with some oxygen functionality, often alkyl branching, with a specific or strongly dominating chirality and double bond configuration.[1] These structural features, and the regio- and stereo-regularities associated with nucleophilic opening of terminal epoxides and displacement of sulfonate ester groups, suggest that ready availability of epoxides and 1,2-diols of high enantiomeric excesses (ee's), would expedite acquisition of such pheromones. Most hydrolytic kinetic resolutions (HKR)[2] of terminal epoxides relate to simple epoxides not bearing other functionality.[3] We now demonstrate that structurally more diverse epoxides respond well to the procedures developed by Jacobsen,[2] which utilise (salen)Co(OAc) complexes, such as, (acetato)(aqua)((*R*,*R*)(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino)cobalt(III) (**1**).[4]

Our exploratory work was directed towards (*R*)-(−)-10-methyldodecyl acetate **8** and (*R*)-(−)-10-methyltridecan-2-one **12**. The acetate is a pheromone from the smaller tea tortrix moth (*Adoxophyes* species), with the (*R*)-enantiomer slightly more bioactive than the (*S*).[4] (*R*)-(−)-10-Methyltridecan-2-one is the sex pheromone of the southern corn rootworm (*Diabrotica undecimpunctata*).[4] The procedure (Scheme 1) commenced with the benzyl ether of undecen-10-ol, **2**, which was epoxidised to furnish the HKR substrate **3**. This was stirred with 0.5 mole% of (*R*,*R*)-**1** and 0.55 mole eq. H_2O at rt (*ca.* 22 °C) for 20–24 h.[2,4] Chromatography on silica yielded (*R*)-epoxide **4** and (*S*)-diol **5**, with excellent recovery (48 and 46% respectively). Manipulation of the epoxide afforded (*R*)-acetate **8** with $[\alpha]_D^{23}$ −5.40° (*c* 0.97, $CHCl_3$). (Reported for **8**, acquired by longer routes: $[\alpha]_D$ −5.84° ($CHCl_3$)[5] and −5.93° ($CHCl_3$).[6]) Reconstitution of diol **5** afforded the (*S*)-epoxide, which was transformed to the (*S*)-(+)-pheromone, with $[\alpha]_D^{23}$ +5.29° (*c* 1.02, $CHCl_3$).



Scheme 1 *Reagents and conditions*: i, *m*-CPBA (78%); ii, 0.5% eq. (*R*,*R*)-**1**, 0.55 eq. H_2O (48% for **4**, 46% for **5**); iii, Me_2CuLi (99%); iv, MsCl, Et_3N then Me_2CuLi (60%); v, O_3, Me_2S (42%); vi, K_2CO_3, MeOH (67%); vii, Ac_2O, Py (100%).

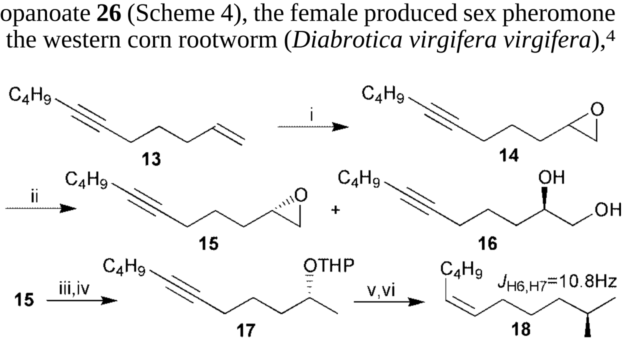
The methyl ketone **12** was obtained by processing epoxide **4** as summarised in Scheme 2. After epoxide opening and mesylate displacement, [2,3]-Wittig rearrangement of **10** afforded terminal alkene **11**, which under Wacker conditions, provided the desired compound **12** ($[\alpha]_D^{23}$ −1.63° (*c* 0.70, $CHCl_3$); reported value, $[\alpha]_D^{24}$ −1.71° ($CHCl_3$)[7]). The less active (*S*)-(+)-ketone could be obtained from the corresponding (*S*)-epoxide, by reconstituting from diol **5**.



Scheme 2 *Reagents and conditions*: i, EtMgBr, CuI (62%); ii, MsCl, Et_3N then Me_2CuLi (40%); iii, ^{n}BuLi, −78 °C (43%); iv, $PdCl_2$, CuCl, DMF–H_2O, O_2 (90%).

An important component from ant-lions (*Euroleon nostras* and *Grocus bore*) is (*R*)-(−)-(*Z*)undec-6-en-2-ol (nostrenol) **18**,[8] and its synthesis (Scheme 3) begins with chemoselective epoxidation of enyne **13**. HKR of epoxide **14** furnished (*S*)-epoxide **15** of 95% ee (Mosher ester analysis of the alcohol resulting from hydride opening). Ti-mediated stereospecific *Z*-reduction[9] of protected alcohol **17** led to (*R*)-(−)-pheromone **18**, $[\alpha]_D^{23}$ −5.48° (*c* 0.70, $CHCl_3$) (reported value, $[\alpha]_D$ −6.08° (neat).[8]) As before, reconstitution of diol **16** to the (*R*)-epoxide could afford (*S*)-(+)-(*Z*)undec-6-en-2-ol.

Whereas asymmetric dihydroxylation of dienes affords tetrols,[10] successful HKR of bisepoxides would afford three easily separable components, with the predominating epoxydiol facilitating bi-directional and selective functionalisation. The conversions of nona-1,8-diene to (1*R*,7*R*)-1,7-dimethylnonyl propanoate **26** (Scheme 4), the female produced sex pheromone of the western corn rootworm (*Diabrotica virgifera virgifera*),[4]



Scheme 3 *Reagents and conditions*: i, *m*-CPBA, CH_2Cl_2; ii, 0.5% eq. (*S*,*S*)-**1**, 0.55 eq. H_2O (43% for **16**); iii, $NaBH_4$, EtOH (73% over 2 steps); iv, DHP, H^+ (84%); v, Ti(O^{i}Pr)$_4$, ^{i}PrMgBr, Et_2O then H_2O; vi, MeOH, H^+ (54% over 2 steps).

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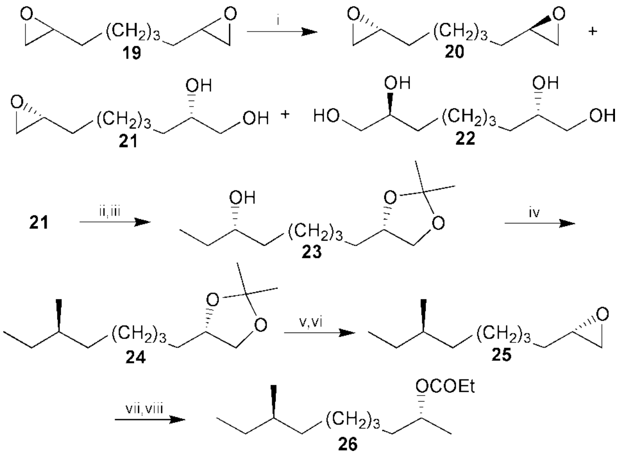
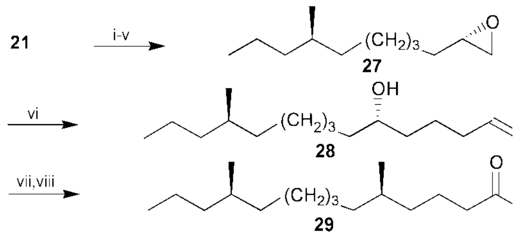
† Electronic supplementary information (ESI) available: references describing previous syntheses of insect pheromones, an illustrative procedure for HKR of a bisepoxide and a comparison between asymmetric dihydroxylation (of an alkene) and HKR (of the corresponding epoxide). See http://www.rsc.org/suppdata/cc/b1/b102181h/



Scheme 4 *Reagents and conditions*: i, 1.0% eq. (*R*,*R*)-**1**, 0.8 eq. H_2O, (24% for **20**, 46% for **21**, 15% for **22**); ii, DMP, H^+ (78%); iii, Me_2CuLi (98%); iv, MsCl, Et_3N then Me_2CuLi (70%); v, MeOH, H^+ (76%); vi, MsCl, Et_3N then K_2CO_3, MeOH (27%); vii, $NaBH_4$, EtOH (92%); viii, $(EtCO)_2O$, Py (79%).

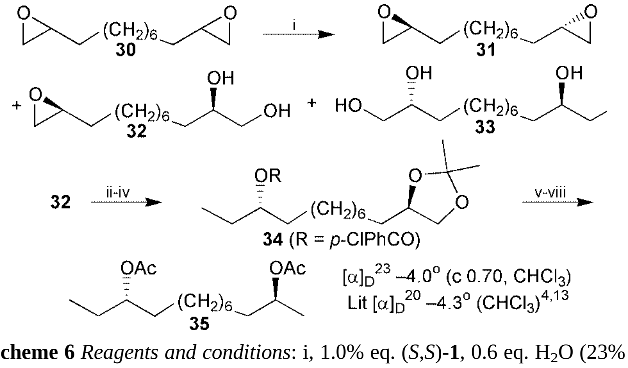


Scheme 5 *Reagents and conditions*: i, DMP, H^+ (82%); ii, EtMgBr, CuI (91%); iii, MsCl, Et_3N then Me_2CuLi (41%); iv, MeOH, H^+ (99%); v, MsCl, Et_3N then K_2CO_3, MeOH (48%); vi, $H_2C{=}CH(CH_2)_2MgBr$, CuI (34%); vii, MsCl, Et_3N then Me_2CuLi (53%); viii, $PdCl_2$, CuCl, DMF–H_2O, O_2 (74%).

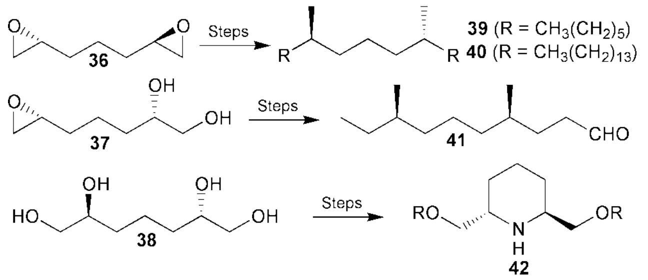
and to (6*R*,12*R*)-6,12-dimethylpentadecan-2-one **29**, the female produced pheromone of the banded cucumber beetle (*Diabrotica balteata*)[4] illustrate this. Thus, racemic bisepoxide **19** was exposed to (*R*,*R*)-**1** and 0.8 eq. H_2O to provide (2*R*,8*R*)-bisepoxide **20** (24%), epoxydiol **21** (46%) and tetrol **22** (15%). Manipulation of epoxydiol **21** afforded (1*R*,7*R*)-pheromone **26**, with $[\alpha]_D^{23}$ −7.17° (*c* 0.70, $CHCl_3$) (reported value, $[\alpha]_D$ −7.57° ($CHCl_3$)[11]).

The same epoxydiol, **21**, provided the bioactive (6*R*,12*R*)-6,12-dimethylpentadecan-2-one,[4] **29**, by the procedure summarised in Scheme 5. (For **29**, $[\alpha]_D^{23}$ −0.43° (*c* 0.40, $CHCl_3$); reported value, $[\alpha]_D^{22}$ −0.5° ($CHCl_3$).[12])

HKR of the bisepoxide of dodeca-1,11-diene, **30**, proceeded satisfactorily to afford epoxydiol **32** that has been processed to (2*S*,11*S*)-2,11-diacetoxytridecane **35**, a sex pheromone component of the female pea midge, *Contarinia pisi*, a serious pest of commercial peas.[4,13] (Scheme 6). Similarly, reductive opening ($NaBH_4$, EtOH, 84%) of the (*R*,*R*)-bisepoxide of tridecan-1,12-diene led to (2*S*,12*S*)-2,12-diacetoxytridecane ($[\alpha]_D^{23}$ +1.77° (*c* 1.21, $CHCl_3$); reported value, $[\alpha]_{578}$ +2.04° ($CHCl_3$)[13]), also from the pea-midge.



Scheme 6 *Reagents and conditions*: i, 1.0% eq. (*S*,*S*)-**1**, 0.6 eq. H_2O (23% for **31**, 26% for **32**, 12% for **33**); ii, DMP, H^+ (65%); iii, CH_3MgBr, CuI (91%); iv, Ph_3P, *p*-chlorobenzoic acid, DEAD, THF (80%); v, MeOH, H^+ (83%); vi, MsCl, Et_3N then K_2CO_3, MeOH (44%); vii, $LiAlH_4$, Et_2O (79%); viii, Ac_2O, Py (68%).



Scheme 7

The bisepoxide of hepta-1,6-diene with 1.4 mole% (*R*,*R*)-**1** and 1.0 mole eq. H_2O (Scheme 7) afforded bisepoxide **36**, free of its *meso* isomer (NMR), and epoxydiol **37** was stereoisomerically pure. Routes to (4*R*,8*R*)-4,8-dimethyldecanal (Tribolure) **41**, an important pheromone component of several *Tribolure* species including the red flour and confused flour beetles,[4] and C_2 symmetric dimethylalkanes, **39** and **40**, pheromone components of female spring hemlock looper (*Lambdina athasaria*) and female stable flies (*Stomoxys calcitrans*) respectively,[4] have been developed. Tetrol **38** has been converted to C_2 symmetric piperidines **42**.[14]

The above examples considerably widen the scope of the HKR approach. High ee's have resulted, and solvent addition with the longer chain bisepoxides may be beneficial.[3] A full discussion of these and related results will be reported at a later date.

We thank Professor Dr W. Francke for a listing of optical rotations of some compounds described in ref. 13.

Notes and references

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