A concise asymmetric synthesis of the pheromone 1-methylcyclohex-2-enol *via* a 'merged substitution-elimination reaction'

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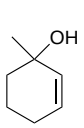
The title compound is prepared (> 94% ee) by a three step synthesis from 1-methylcyclohexene *via* a 'merged substitution-elimination reaction' involving a phenylselenide ion.

One of the constituents of the pheromone system of the beetle *Dendroctonus pseudotsugae Hopkins*, an economically important pest of the Douglas fir tree, is the aggregation pheromone 1-methylcyclohex-2-enol **1**. Previous syntheses of the optically active pheromone **1** have involved the conversion of optically active intermediates, prepared by classical resolution,[1] enzymically,[2,3] from the chiral pool,[4] or by multistep asymmetric syntheses.[5,6]



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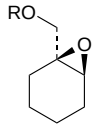

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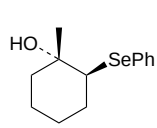

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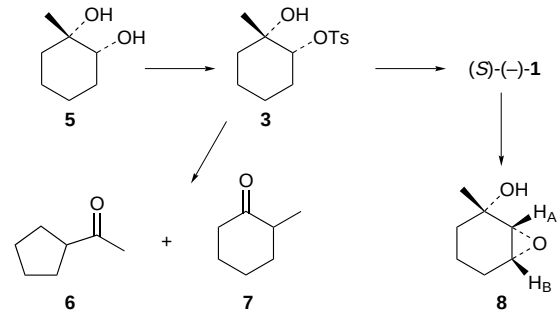
If asymmetric syntheses are to become important for industrial preparations it is necessary to illustrate that they can be made simple and short. However, this is not necessarily a trivial exercise. With this pedagogical principle in mind, we sought to modify our earlier route[5] in the hope that the separate enantiomers might be more readily prepared. Serendipity has played an important role in providing a simple solution to this problem and we disclose a three step asymmetric synthesis of this pheromone which is applicable to the synthesis of either enantiomer, and which gives the constituent in an enantiomeric purity exceeding 94% ee. Ironically the aggregation pheromone found naturally is only 10% ee[7] but the challenge of the asymmetric synthesis has been pedagogically both useful and exciting. A key step in our earlier synthesis[5] of this pheromone involved nucleophilic substitution of the epoxide **2**. Although both the leaving groups in the epoxide **2** and the tosylate **3** are in a *pseudo* neopentyl location, a study of models suggests that tosylate **3** is considerably more hindered to nucleophilic attack than the epoxide **2**. However, it was considered that with the powerful nucleophile NaSePh, tosylate **3** might also, like epoxide **2**, react to give in this case the selenide **4**. Thermal elimination of the selenoxides[5] derived from **4** would give the pheromone **1**. Asymmetric dihydroxylation of 1-methylcyclohexene should give the optically active diol **5** from which the tosylate **3** could be prepared.

After this work had commenced, Sharpless reported,[9] as a footnote, the ee (52%, by chiral HPLC) for the asymmetric dihydroxylation (AD β mix) of 1-methylcyclohexene to the diol **5**, but no experimental details for the preparation were provided. Owing to the water solubility and considerable volatility of the diol **5**, we have found it necessary to modify, somewhat, the standard work-up procedures for this reaction by removal of the KOH wash normally used to remove methanesulfonamide. The product is then isolated, in 85% yield, by fractional distillation of all solvents, chromatography and sublimation (50 °C/0.5 Torr). Conversion of the diol **5** to the mono secondary tosylate **3** (85% yield, 94% yield for the racemate on a larger scale) gives material which, although it is initially only 75% of the major enantiomer,‡ can nevertheless be fractionally recrystallised to high enantiomeric purity (94% ee after four recrystallisations from diethyl ether–hexane, 37% yield, the racemate is less soluble).

Treatment of the tosylate **3** with NaSePh (PhSeSePh, $NaBH_4$, EtOH[10]), in boiling EtOH, did not give the sought after substitution reaction. Rather surprisingly an elimination reaction occurred instead. The initial reaction gave a mixture of the alcohol **1** and the ketones **6** and **7**. It had been assumed from the outset that base treatment of the tosylate **3** would give the ketones **6** and **7**, by a negative-ion pinacol rearrangement,[11] and this was confirmed by treatment of the tosylate with $KOBu^t$ (in THF at room temperature, **6** : **7** = 8 : 1, 90%). Selenide ion is too weak a base to abstract a proton from an alcohol and it was likely that ketones **6** and **7** were artifacts formed from adventitious sources of base. A wash of the glassware with NH_4Cl solution prior to the reaction of tosylate **3** with NaSePh, obviates the formation of these ketones and the volatile alcohol (*S*)-(−)-**1**§ is isolated, in 78% yield, by fractional distillation. The enantiomeric purity of the tertiary allylic alcohol **1** could not be obtained directly by chiral shift NMR experiments and we did not have access to complexation GC.[1] Conversion of the alcohol to the epoxide **8** (with slow addition of MCPBA to alcohol **1**, $NaHCO_3$, Et_2O, 0 °C, 70%, the diastereomer is not formed) and chiral shift NMR experiments‡ on this (94% ee) confirmed that the enantiomeric purity from the tosylate had been maintained.

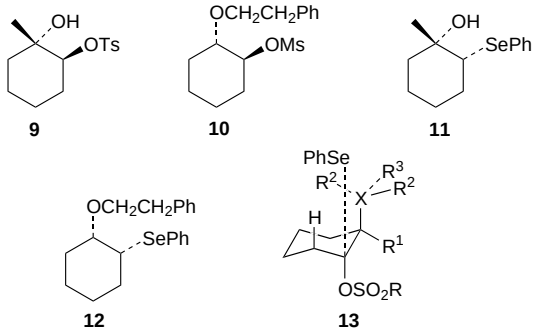
The mechanism for the elimination reaction observed is intriguing. The reaction of the tosylate **3** with NaSePh in EtOH is not an E_1 mechanism since the qualitative observation is that the half-life for the reaction is concentration dependent; because no products from pinacol rearrangement are observed when care is taken to remove adventitious base; and because the tosylate is recovered unchanged after reflux in EtOH. The question arises, therefore, as to why selenide anion, a powerful nucleophile to carbon but non-nucleophilic to hydrogen attached to the oxygen of an alcohol, should suddenly change allegiance and become a nucleophile to hydrogen attached to carbon. Winstein, in a paper published in 1956,[8] first drew attention to the dichotomy of weak bases but good nucleophiles which promote elimination reactions when he wrote about merged substitution-elimination reactions. Since then there has been considerable debate[12,13] as to the veracity of his suggestion but, in our opinion, no clear



Scheme 1

explanation has been given for what is actually occurring in these reactions. Since our example appears to be one of the more extreme examples of this phenomenon, we would like to present our observations in the hope that they will rekindle debate on this subject.

Under the same conditions, with NaSePh, as when the tosylate **3** gives only the elimination product **1**, both the racemic isomeric *trans*-tosylate **9** and the racemic mesylate **10** undergo clean substitution reactions to give the selenide derivatives **11**¶[14] and **12** respectively. It has been shown[15] that for the



4-*tert*-butylcyclohexyl derivatives the axial tosylate reacts faster than the equatorial tosylate in S_N2 reactions. Conformational mobility is clearly demonstrated for the tosylate **3**, even at room temperature, since it is likely that the compounds **6** and **7** come from two different chair conformers. From a study of models it is seen that when the leaving group is axial not only is the rear-side attack less hindered but, the nucleophile, the reaction centre and the leaving group can stay co-linear throughout the reaction.‖ Perhaps herein lies an explanation for our observations. It is likely that the selenide ion follows a trajectory co-incident with the dipole axis of the molecule and that in both the compounds **9** and **10** the propensity for carbon nucleophilicity is not thwarted by steric barriers since only lone pairs (see **13**) would hinder the approach. In the case of the tosylate **3**, however, the methyl group would clearly present an obstacle to rear-side attack and the deflected nucleophile might then encounter the hydrogen atom, held in an antiperiplanar relationship to the leaving group, with sufficient energy to overcome the barrier to elimination and this then becomes the lower energy process.

In conclusion, therefore, we have developed a three step asymmetric synthesis of the pheromone, from achiral starting materials. The route is probably far more efficient than any to date and will be extremely efficient if further developments to the Sharpless procedure allows a more enantioselective preparation of the diol **5**. Furthermore the synthesis has revealed an intriguing elimination reaction which may help to unravel the paradoxes arising in the mechanism of weak-base elimination reactions.

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Footnotes

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‡ All chiral shift NMR experiments were run in 15% C_6D_6 in CCl_4 with Eu(hfc)$_3$. Racemic tosylate **6**. δ_H (200 MHz, $CDCl_3$) 1.14 (s, 3 H, CH_3), 1.2–1.8 (complex, 8 H, methylene envelope), 1.59 (s, 1 H, OH), 2.45 (s, 1 H, Ar-CH_3), 4.36 (dd, 1 H, *J* 4.04, 9.94 Hz, H1), 7.34 (d, 2 H, *J* 8.22 Hz, Ar-H), 7.80 (d, 2 H, *J* 8.22 Hz, Ar-H). The doublet originally at δ 7.80 separates, to baseline, into two doublets with the shift reagent. Racemic epoxide **8**. δ_H (200 MHz, $CDCl_3$) 1.2–2.1 (complex, 6 H, methylene envelope), 1.33 (s, 3 H, CH_3), 2.40 (br s, 1 H, OH), 3.10 (d, 1 H, *J* 4.0 Hz, H2), 3.36 (m, 1 H, H3). The multiplet originally at δ 3.36 separates, to baseline, into two broadened singlets with the shift reagent.

§ Pheromone **1**. δ_H (200 MHz, $CDCl_3$) 1.29 (s, 3 H, CH_3), 1.5–1.8 (complex, 4 H, methylene envelope), 2.0 (m, 2 H, H4), 5.60 (br d, 1 H, *J* 10.0 Hz, H2), 5.75 (td, 1 H, *J* 4.0, 10.0 Hz, H3). δ_C (75.5 MHz, $CDCl_3$) 19.5, 25.0, 29.3, 37.8, 67.9, 128.9, 133.7.

¶ A referee has suggested that this compound might have the structure **4** if it arose through double inversion *via* the epoxide. However, optically active compound **4** is already known[5] and the spectral data are different.

‖ A study of a model (axial leaving group down) shows that the reacting centre can move up smoothly towards the nucleophile as overlap of the orbitals takes place. This would give the product in the boat conformation. No such smooth pathway exists for the equatorial leaving group. We believe that this requirement would also account for the known *trans*-diaxial opening of cyclic epoxides.

References

1 K. Mori, B. G. Hazra, R. J. Pfeiffer and A. K. Gupta, *Tetrahedron*, 1987, **43**, 2249.
2 K. Mori and J. I. J. Ogoche, *Liebigs Ann. Chem.*, 1988, 903.
3 B. D. Johnston, B. Morgan, A. C. Oehlschlager and S. Ramaswamy, *Tetrahedron: Asymmetry*, 1991, **2**, 377.
4 P. Ceccherelli, M. Curini, F. Epifano, M. C. Marcotullio and O. Rosati, *J. Org. Chem.*, 1996, **61**, 2882.
5 D. P. G. Hamon, R. A. Massy-Westropp and J. L. Newton, *Tetrahedron: Asymmetry*, 1990, **1**, 771.
6 A. B. Bueno, M. C. Carreno, J. L. G. Ruano and C. Hamdouchi, *Tetrahedron: Asymmetry*, 1995, **6**, 1237.
7 B. S. Lindgren, G. Gries, H. D. Pierce and K. Mori, *J. Chem. Ecol.*, 1992, **18**, 1201.
8 S. Winstein, D. Darwish and N. J. Holness, *J. Am. Chem. Soc.*, 1956, **78**, 2915.
9 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483 and footnote 53 therein.
10 K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, 1973, **95**, 2697.
11 P. D. Bartlett and R. H. Rosenwald, *J. Am. Chem. Soc.*, 1934, **56**, 1900.
12 D. J. McLennan, *Tetrahedron*, 1975, **31**, 2999.
13 H. Kwart, K. A. Wilk and D. Chatellier, *J. Org. Chem.*, 1983, **48**, 756.
14 D. P. G. Hamon and R. J. Kennedy, unpublished observations.
15 E. L. Eliel, S. H. Wilen and L. N. Mander, in *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, p. 723.

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