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TETRAHEDRON: *ASYMMETRY*

A facile synthetic method for chiral 1,2-epoxides and the total synthesis of chiral pheromone epoxides

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Abstract

Chiral 1,2-epoxy-3-alkanol tosylates were successfully synthesized from alkynols in three steps using the Sharpless AD reaction as a key step in good yields. Two chiral insect pheromone epoxides were smoothly obtained from the corresponding key intermediate.

Synthetic chemists always face a major challenge in the preparation of chiral compounds with high enantiomeric excess. The need for pure enantiomers is particularly apparent in the field of insect pheromone chemistry, since insect chemoreception can be highly stereoselective.[1–3] Optically active epoxides are an important class of natural products encountered as sex attractants of lepidopteran pests,[4] and self-defensive substances against rice blast disease.[5] The optically active 1,2-epoxy-3-alkanols are key intermediates in the synthesis of these insect pheromones because they can be easily converted into the corresponding optically active 2,3-epoxy-1-alkanols through the Payne rearrangement[6] or into optically active internal epoxides via an alkylative rearrangement of the corresponding *p*-toluenesulfonate esters.[7] In order to obtain chiral epoxides via these synthetic approaches, the most frequently used key reaction until now has been the Sharpless AE reaction on the *Z*-allylic alcohols.[7–9] Herein we wish to report an alternative synthetic method for chiral 1,2-epoxy-3-alkanol tosylates using the Sharpless AD reaction[10] as the key reaction and the total synthesis of the insect sex pheromones, (6*Z*,9*S*,10*R*)-9,10-epoxy-6-henicosene and (3*Z*,6*Z*,9*S*,10*R*)-9,10-epoxy-3,6-henicosadiene.

The Sharpless AD reaction on starting material **2**, which has different long alkyl chains (prepared by reduction of the corresponding alkynol **1**[11] using $LiAlH_4$ in THF), installed the two stereogenic centers, with 96% ee.[12] The resulting triol **3** was subsequently treated with NaH and Tos–Im[13] in THF to produce the key intermediate **4** in good yield (Scheme 1). To the best of our knowledge, this new synthetic approach is the shortest and the most efficient among those reported in previous literature.[7–9] Thus 1,2-epoxy-3-tosylates **4a**–**h** with different length alkyl chains were obtained as colorless solids or oils. Their total yields in three steps, specific rotations and melting points are summarized in Table 1. The

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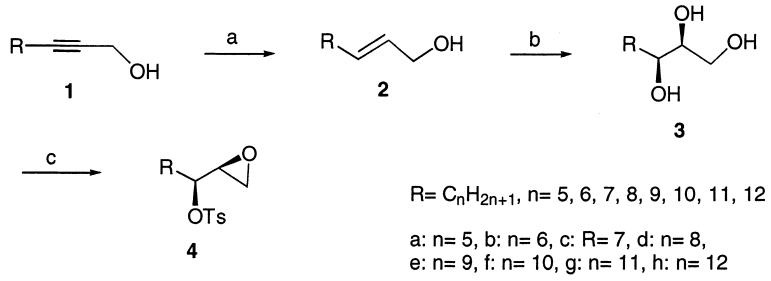
chemical yields of **4a**–**h** slightly increased with the increase in alkyl chain length. The specific rotation of the key intermediate **4g** was very close to that reported in the literature {lit.[8] $[\alpha]_D^{20}$ +8.3 (c 1, $CHCl_3$)}.



Reagents and Conditions: a) $LiAlH_4$, THF, reflux; 95-98% b) $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, $MeSO_2NH_2$, $(DHQ)_2PHAL$, $K_2OsO_2(OH)_4$, ^tBuOH:H_2O (1:1), 0 °C; 84-88%. c) NaH, Tos-Im, THF; 53-66%.

Scheme 1.

Table 1
Yields and physical properties of the obtained 1,2-epoxy-3-tosylates (**4a**–**h**)

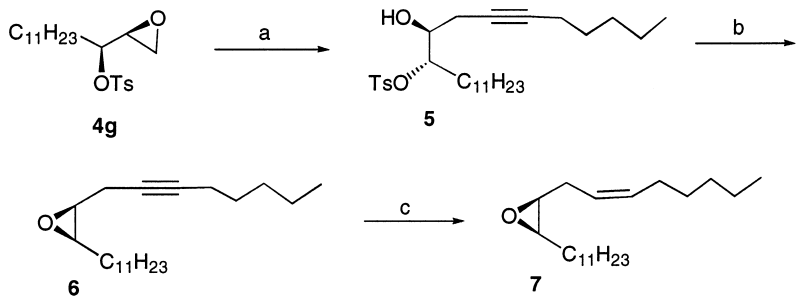
No.	R	m.p.[°C]	$[\alpha]^{20}_D$ (c 1, $CHCl_3$)	Yield/%[a)]
4a	C_5H_{11}	oil	+8.5	42
4b	C_6H_{13}	oil	+8.2	45
4c	C_7H_{15}	54 - 55	+8.5	47
4d	C_8H_{17}	57 - 58	+8.0	48
4e	C_9H_{19}	59 - 60	+8.7	48
4f	$C_{10}H_{21}$	72 - 74	+8.3	50
4g	$C_{11}H_{23}$	71 - 72	+8.6	54
4h	$C_{12}H_{25}$	85 - 86	+8.0	57

[a)] Total yields in three steps.

The synthesis of a sex pheromone of *Phragmatobia fuliginosa* is depicted in Scheme 2. The epoxide **4g** was opened by 1-lithio-heptyne in the presence of $BF_3 \cdot Et_2O$ to afford compound **5**. Treatment of compound **5** with K_2CO_3 in methanol gave another epoxide **6** in good yield. Catalytic hydrogenation of compound **6** over the Lindlar catalyst easily gave the target compound (6*Z*,9*S*,10*R*)-9,10-epoxy-6-henicosene **7** in moderate yield. By the same synthetic procedures, another sex pheromone (3*Z*,6*Z*,9*S*,10*R*)-9,10-epoxy-3,6-henicosadiene could be also obtained using 1-lithio-1,4-heptadiyne as the epoxide opening reagent (Scheme 3).

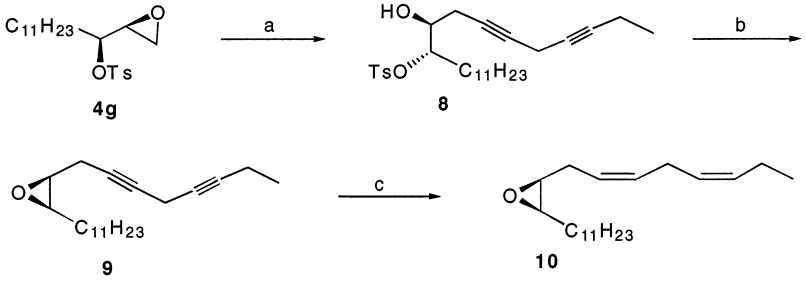
The specific rotations of our synthetic compounds **7** and **10** were very close to those reported in literature {**7**: $[\alpha]_D^{20}$ +8.7 (c 0.97, $CHCl_3$), lit.[14] $[\alpha]_D^{20}$ +9.4 (c 0.55, $CHCl_3$). **10**: $[\alpha]_D^{20}$ +5.7 (c 0.97, CCl_4), lit.[15] $[\alpha]_D^{23}$ +5.9 (c 1.61, CCl_4)}. Their spectral data were completely consistent with those reported in the literature.[14,15]

In conclusion, we have developed an efficient and convenient procedure for the stereocontrolled synthesis of the chiral 1,2-epoxy-3-tosylates (**4a**–**h**) from which two important chiral pheromone epoxides have been successfully synthesized. This new synthetic approach using the Sharpless AD reaction will certainly open a new and effective synthetic route to prepare highly stereoselective chemoreception insect



Reagents and Conditions: a) 1-Heptyne, n-BuLi, $BF_3 \cdot OEt_2$, THF, -78 °C; 87%. b) K_2CO_3, CH_3OH, r.t.; 60%. c) Pd-$CaCO_3$, H_2; 80%.

Scheme 2.



Reagents and Conditions: a) 1,4-Heptadiyne, n-BuLi, $BF_3 \cdot OEt_2$, THF, -78 °C; 30%. b) K_2CO_3, CH_3OH, r.t.; 35%. c) Pd-$BaSO_4$, H_2; 80%.

Scheme 3.

pheromones. In order to disclose the relationship between structure and biological activity, syntheses of their pheromone analogs are in progress.

Acknowledgements

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