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A General Method for the Synthesis of Nonracemic *trans*-Epoxides: Concise Syntheses of *trans*-Epoxide-Containing Insect Sex Pheromones

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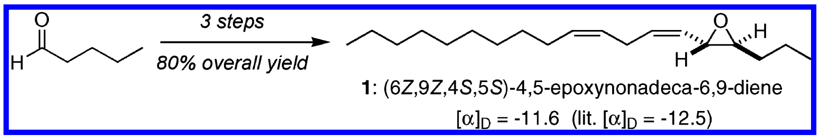
ABSTRACT



A general method for the synthesis of chiral nonracemic *trans*-epoxides has been developed that provides rapid access to alkyl-, alkenyl-, alkynyl-, and phenyl-substituted *trans*-epoxides from aldehydes. This methodology has also been applied in concise and high-yielding syntheses of both *trans*-epoxide containing insect sex pheromones.

Over the last half century the structure elucidation of insect sex pheromones has provided a growing arsenal of chemicals for crop protection. Whereas many methods for insect control often involve the indiscriminate eradication of pestiferous and beneficial insects alike, small quantities of insect sex pheromones can selectively disrupt the reproduction of harmful insects or lure these pests to traps, providing opportunities for ecologically sensible crop management.[1] However, insect chemoreception can be highly enantiodiscriminatory,[2] and oftentimes the development of an economically feasible asymmetric pheromone synthesis represents a significant challenge. In this regard, a number of developments in asymmetric catalysis have had a profound impact.[3] In particular, robust procedures for the asymmetric epoxidation[4] and dihydroxylation[5] of olefins has provided access to a variety of epoxy pheromones with high levels of optical purity.[6] The asymmetric synthesis of vinyl epoxide-containing pheromones, however, remains a significant challenge. Thus, while the asymmetric epoxidation of dienones,[7] α,β,γ,δ-unsaturated amides,[8] esters,[9] and carbinols[10] have been reported, the epoxidation of unfunctionalized dienes[9] often suffer from

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(6) For examples see: (a) Keinan, E.; Sinha, S. C.; Sinha-Bagchi, A.; Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 6411. (b) Mori, K.; Sano, S.; Yokoyama, Y.; Bando, M.; Kido, M. *Eur. J. Org. Chem.* **1998**, 1135. (c) Zhang, Z.-B.; Wang, Z.-M.; Wang, Y.-X.; Liu, H.-Q.; Lei, G.-X.; Shi, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 53.
(7) For examples see: (a) Allen, J. V.; Bergeron, S.; Griffiths, M. J.; Mukherjee, S.; Roberts, S. M.; Williamson, N. M.; Wu, L. E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3171. (b) Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2725.
(8) For examples see: (a) Kakei, H.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 317. (b) Kinoshita, T.; Okada, S.; Park, S.-R.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4680.
(9) For examples see: (a) Chang, S.; Lee, N. H.; Jacobsen, E. N. *J. Org. Chem.* **1993**, *58*, 6939. (b) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948. (c) Burke, C. P.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4475.
(10) Katsuki, T.; Martin, V. S. *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons, Inc.: New York, 1996; Vol. 48, pp 1−285.

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poor regio- and enantiocontrol.[11] Alternative routes to optically active vinyl epoxides include dihydroxylation of dienes and subsequent transformation of the vicinol diol to a *cis*- or *trans*-epoxide,[12] chloroallylboration of aldehydes to afford vinyl chlorohydrins followed by base-induced cyclization,[13] and reaction of chiral sulfur ylides with α,*β*-unsaturated aldehydes.[14] As a complement to these procedures, we report here a general method for the asymmetric synthesis of *trans*-vinyl epoxides and the application of this methodology to the synthesis of both *trans*-epoxide-containing insect sex pheromones.

Recently, the first examples of *trans*-epoxide-containing insect sex pheromones were reported from the pine looper moth *Bupalus piniarius*[15] and the tussock moth *Orgyia postica*.[16] Throughout Europe, the pine looper moth has become a serious threat to the Scots pine (*Pinus sylvestris*), while in Japan the tussock moth is a major concern for litchi and mango producers.[16] Interestingly, the females of these moths rely on unusual *trans*-epoxide containing sex pheromones to attract males. As detailed in Figure 1, the sex

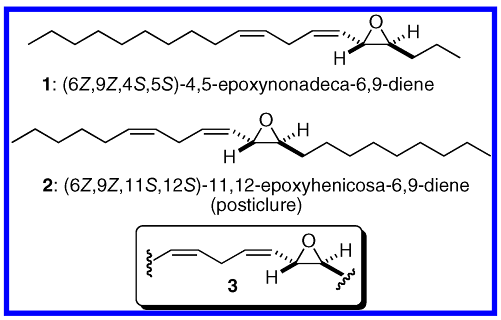
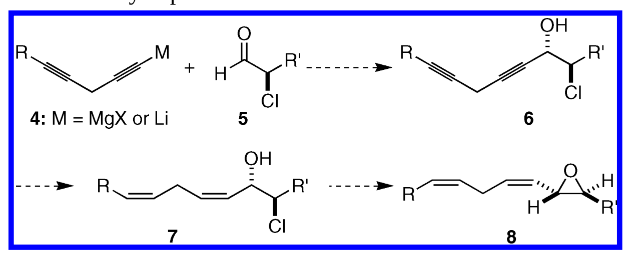


Figure 1. Insect sex pheromones isolated from female *Bupalus piniarius* (**1**) and *Orgyia postica* (**2**) moths and their common (3*Z*,6*Z*,1*S*,2*S*)-1,2-epoxyhepta-3,6-diene subunit **3**.

pheromones isolated from *B. piniarius* and *O. postica* share remarkable structural similarities in that both **1** and **2** contain the (3*Z*,6*Z*,1*S*,2*S*)-1,2-epoxyhepta-3,6-diene subunit **3**. Based on the potential importance of these pheromones for crop protection, syntheses of **1**[15] and **2**[16a,17] have been reported. While these efforts have confirmed the absolute stereochemistry of both of these compounds, the total number of synthetic transformations required (9 and 10−13, respectively) may well limit their practical application. In order to support the field-testing of compound **1**, we sought to develop a concise and general method for the synthesis of *trans*-vinyl epoxides that would also afford access to posticlure (**2**). With this in mind, it was anticipated that both **1** and **2** could be constructed following a straightforward sequence of events that involves the diastereoselective addition of a diynyl anion (e.g., **4**) to an α-chloro aldehyde (e.g., **5**) followed by Lindlar reduction and epoxide formation (Scheme 1). Surprisingly, while the enantioselective synthesis

Scheme 1. General Synthetic Strategy for Construction of the Dienyl Epoxide Subunit Found in Both **1** and **2**



of α-chloro aldehydes was reported independently by Jørgensen[18] and MacMillan[19] close to 3 years ago, to the best of our knowledge, the results presented here represent the first application of this straightforward and seemingly general strategy to the enantioselective synthesis of *trans*-epoxides.

The asymmetric α-chlorination of pentanal and undecanal is summarized in Table 1. In our hands, the α-chlorination of pentanal with the perchlorinated quinone **13** and imidazolidinone catalyst **14**[20] afforded the α-chloro aldehyde **10** in good yield but only moderate enantiomeric excess. In fact, entry 2 represents our most favorable result following this protocol, and typically the enantiomeric excess of **10** varied from 10 to 40%, indicating that racemization occurred during the reaction or subsequent purification. Fortunately, by employing *N*-chlorosuccinimide (NCS) and the diphenylpyrrolidine catalyst **17**,[21] **10** was obtained in good yield and optical purity (entry 3). The enantioselectivity of this process was further improved through the use of commercially available (L)-prolinamide (**16**), affording (2*R*)-2-chloropentanal in 85% enantiomeric excess (entry 4). Following this procedure, the asymmetric α-chlorination of undecanal provided **12** in good yield and enantiomeric excess (entry 5).

(11) Olofsson, B.; Somfai, P. *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH Verlag GmbH & Co.: Weinheim, 2006; Chapter 9, pp 315.

(12) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.

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(17) (a) Fernandes, R. A.; Kumar, P. *Tetrahedron* **2002**, *58*, 6685. (b) Muto, S.; Mori, K. *Eur. J. Org. Chem.* **2001**, 4635.

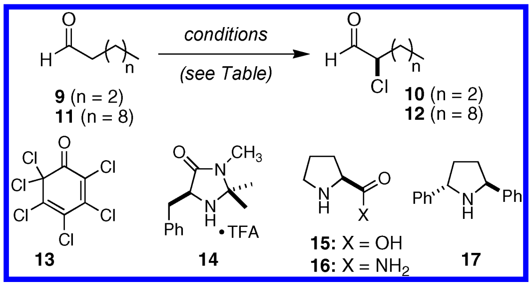
(18) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.

(19) Brochu, M. P.; Brown, S. P.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108.

(20) The imidazolidinone catalyst **14** ($[\alpha]_D = -63.0$ (*c* 2.0, $CHCl_3$)) was prepared as described in: Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. The observed specific rotation of our synthetic material was consistent with the reported value ($[\alpha]_D = -63.2$ (*c* 2.0, $CHCl_3$)).

(21) The (2*S*,5*S*)-Diphenylpyrrolidine catalyst **17** ($[\alpha]_D = -103.8$ (*c* 1.0, $CHCl_3$)) was prepared as described in: Chong, J. M.; Clarke, I. S.; Koch, I.; Olbach, P. C.; Taylor, N. J. *Tetrahedron: Asymmetry* **1995**, *6*, 409. The observed specific rotation of our synthetic material is consistent with that reported for *ent*-**17** ($[\alpha]_D = 104.5$ (*c* 1.0, $CHCl_3$)).

Table 1. Asymmetric α-Chlorination of Pentanal and Undecanal

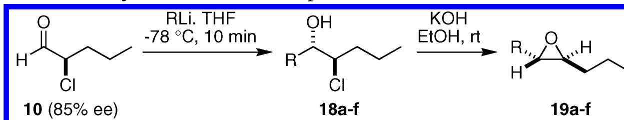


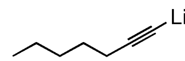
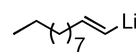
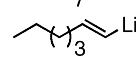
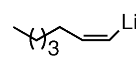
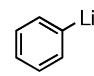
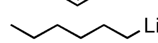
entry	aldehyde	cat. (mol %)	chlorinating reagent	conditions[a]	product (% yield)	% ee
1	**9**	**15** (10)	NCS	A	**10** (>97)	2[b]
2	**9**	**14** (5)	**13**	B	**10** (80)	58[b]
3	**9**	**17** (10)	NCS	A	**10** (>97)	77[b]
4	**9**	**16** (10)	NCS	A	**10** (>97)	85[b]
5	**11**	**16** (10)	NCS	A	**12** (91)	89[c]

[a] A: CH_2Cl_2, 0 °C (1 h) to rt (3 h); B: acetone, −30 °C, (6 h). [b] ee determined by chiral GC analysis (see SI) of the corresponding chlorohydrin generated by $NaBH_4$ reduction. [c] ee determined by conversion to posticlure (**2**) and comparison of the specific rotation of **2** with literature values.

With the optically active α-chloro aldehyde **10** in hand, we next turned our attention to the diastereoselective addition of organometallic reagents to this substance.[22,23] Not suprisingly,[22] the addition of Grignard reagents derived from 1-heptyne to **10** in Et_2O afforded the chlorohydrin **18a** in good yield but moderate diastereomeric excess (dr = 4:1). While a brief survey of solvents (THF, hexane) failed to significantly improve upon this result, we were pleased to find that the alkynyl lithium[24] reagent, derived from the addition of *n*-BuLi to 1-heptyne in Et_2O, reacted with compound **10** to afford the chlorohydrin **18a** as a 9:1 mixture of *anti:syn* diastereomers. This ratio was further improved to 20:1 when the reaction was carried out in THF. Conversion of the crude chlorohydrin **18a** into the corresponding *trans*-epoxide **19a** (KOH, EtOH) proceeded in good overall yield. Following this general procedure, it was demonstrated that a variety of *trans*-epoxides could be synthesized from (2*R*)-2-chloropentanal. Thus, this route provides rapid access to alkynyl-, *trans*-alkenyl-, *cis*-alkenyl-,[25] phenyl-, and alkyl-substituted *trans*-epoxides.[26] While in certain instances the stereochemical outcome of the 1,2-addition reaction (**10** → **18a−f**) could be confirmed by application of Murata's method for *J*-based analysis,[27] the *trans*-configuration of the epoxides **19a−e** was confidently assigned by analysis of NOE spectra and/or scalar coupling constants.[28]

Table 2. Synthesis of *trans*-Epoxides



entry	organolithium reagent	chlorohydrin (1,2-*anti*:1,2-*syn*)[a]		epoxide (% yield)[b]	
1		**18a**	(20:1)	**19a**	(86)
2		**18b**	(17:1)	**19b**	(75)[c]
3		**18c**	(13:1)	**19c**	(87)
4		**18d**	(14:1)	**19d**	(77)
5		**18e**	(13:1)	**19e**	(84)[d]
6		**18f**	(8:1)	**19f**	(79)[e]

[a] Ratio of diastereomers determined by analysis of ^1H NMR spectra obtained on the crude chlorohydrins **18a−f**. [b] Isolated yield from **10**. [c] Isolated as a 17:1 mixture of *trans:cis* epoxide isomers. [d] Isolated as a 14:1 mixture of *trans:cis* epoxide isomers. [e] Isolated as a 8:1 mixture of *trans:cis* epoxide isomers.

The application of this methodology to the synthesis of the two *trans*-epoxide-containing insect sex pheromones is detailed in Scheme 2. The diynes **23** and **24** are readily available from 1-undecyne (**21**) and 1-heptyne (**22**), respectively, following deprotonation and alkylation with propargyl mesylate.[29] As both compounds **23** and **24** proved to be unstable even when stored in solution in the freezer (−22 °C), both were prepared fresh and/or purified immediately prior to their subsequent use. Unfortunately, following our standard procedure (see Table 2), addition of the lithium anion derived from **23** to a THF solution of the α-chloro aldehyde **10** provided a complex mixture of products, from which the desired chlorohydrin **25** was isolated by flash chromatography in very low yield (<10%). However, after considerable experimentation it was found that treatment of

(22) For examples of the diastereoselective addition of organometallic reagents to α-chloro aldehydes see: (a) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112. (b) Bernard, D.; Doutheau, A.; Gore, J.; Moulinoux, J.; Quemener, V.; Chantepie, J.; Quash, G. *Tetrahedron* **1989**, *45*, 1429. (c) Brinkmann, H.; Hoffmann, R. W. *Chem. Ber.* **1990**, *123*, 2395. (d) Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron* **1991**, *47*, 9005. (e) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191. (f) Concellón, J. M.; Rodríguez-Solla, H.; Simal, C.; Gómez, C. *Synlett* **2007**, 75.

(23) For a theoretical investigation of nucleophilic addition to an α-chloro aldehyde see: Cee, V. J.; Cramer, C. J.; Evans, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 2920 and references therein.

(24) For the diastereoselective addition of optically pure lithio-vinyl sulfoxides to a racemic α-chloro aldehyde see: Marino, J. P.; Anna, L. J.; Fernández de la Pradilla, R.; Martinez, M. V.; Montero, C.; Viso, A. *J. Org. Chem.* **2000**, *65*, 6462.

(25) As a prelude to the synthesis of **1** it was also demonstrated that the alkynyl epoxide **19a** could be converted to the *cis*-alkenyl epoxide **19d** (Lindlar's catalyst, quinoline, H_2, EtOH) in excellent yield (94%).

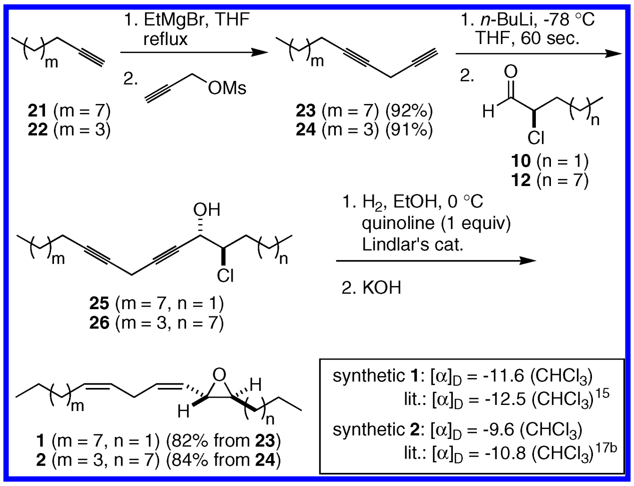
(26) The ee of the epoxides **19a** and **19c−e** was determined to be 85% by chiral GC analysis and/or conversion to known compounds and comparison of $[\alpha]_D$ values with those in the literature (see Supporting Information), indicating that there is no erosion of optical purity during the 1,2-addition reactions (**10** → **18a−f**).

(27) Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866.

(28) The overlapping H4/H5 resonances at δ 2.66 ppm in the ^1H NMR spectrum of **19f** precluded nOe analysis; however, their chemical shift is consistent with those reported for the H4/H5 resonances in *trans*-(4*S*,5*S*)-4,5-epoxynonane (δ 2.61−2.70 ppm) and differ significantly from those reported for *cis*-(4*S*,5*R*)-4,5-epoxynonane (δ 2.87−2.96 ppm) in: Besse, P.; Sokoltchik, T.; Veschambre, H. *Tetrahedron: Asymmetry* **1998**, *9*, 4441.

(29) Gries, G.; Slessor, K. N.; Gries, G.; Khaskin, G.; Wimalaratne, P. D. C.; Gray, T. G.; Grant, G. G.; Tracey, A. S.; Hulme, M. *J. Chem. Ecol.* **1997**, *23*, 19.

Scheme 2. Total Synthesis of *trans*-Epoxide-Containing Insect Sex Pheromones (−)-**1** and (−)-**2**



the diyne **23** with *n*-BuLi at −78 °C in THF followed *after 60 s* by the addition of **10** and, *after a further 5 min at −78 °C*, aqueous workup afforded the desired chlorohydrin **25** in reproducibly excellent yield (>80%). The optimization of this reaction was critical, as all synthetic intermediates involved in the syntheses of **1** or **2** decompose on storage in the freezer (<12 h), and consequently the subsequent Lindlar reduction and epoxidation reactions were necessarily carried out in direct succession. Deviation from this optimized reaction protocol led to the production of numerous byproducts that both compromised the overall yield of the processes and complicated the final purification of the pheromones. With this in mind, the crude chlorohydrins **25** or **26** were treated directly with Lindlar's catalyst and a stoichiometric amount of quinoline and hydrogenated at 0 °C.[30] The progress of these reactions were monitored by ^{1}H NMR spectroscopy, and upon complete reduction of both alkyne functions KOH was directly added to effect the epoxidation reaction, providing the sex pheromones from *B. piniarius* and *O. postica* in excellent overall yields. The spectral data (^{1}H NMR, ^{13}C NMR, MS, IR, $[\alpha]_D$) derived from these substances were in complete agreement with that reported in the literature,[15,16] and the synthetic *B. piniarius* sex pheromone displayed identical chromatographic properties (chiral GC) to an authentic sample of this substance.[31]

In summary, exploiting recent advances in the asymmetric α-chlorination of aldehydes,[18,19] we have developed an efficient and general method for the construction of alkynyl, phenyl, alkyl, and alkenyl *trans*-epoxides that complements existing methodologies for their syntheses. In addition, we have applied this methodology to the synthesis of the *trans*-epoxide-containing insect sex pheromones **(−)-1** and **(−)-2**. Notably, the overall yields for (−)-**1** (80%) and (−)-**2** (76%) from pentanal and undecanal, respectively, and the total number of synthetic steps required compare well with the existing literature syntheses of these substances.[15,16a,17] Moreover, the entire sequence of reactions required to access compounds (−)-**1** or (−)-**2** is often carried out in less than 1 day, further highlighting the efficiency of this process, which has now provided sufficient amounts of (−)-**1** to initiate a population monitoring study of *B. piniarius*.[32] We are currently exploring the utility of variously substituted chlorohydrins as chiral builiding blocks for complex molecule synthesis, and the results of these efforts will be reported in due course.

Acknowledgment. We thank NSERC and Merck Frosst Canada for support. B.K. was supported in part by a SFU Graduate Fellowship. We thank Regine Gries (SFU) for carrying out chiral GC analysis, Dr. Andrew Lewis (SFU) for assistance with NMR spectroscopy, and Tristen Gilchrest for carrying out some preliminary experiments.

Supporting Information Available: Detailed experimental procedures and characterization data for each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) Use of less than one equivalent of quinoline led to partial hydrogenation of the $\Delta^{9,10}$ alkene function in **25** or the $\Delta^{6,7}$ alkene function in **26**. Lindlar reduction of **25** or **26** at room temperature led to the production of unidentified byproducts.

(31) We thank Professor Gerhard Gries for kindly providing an authentic sample of (−)-**1** and Regine Gries for carrying out the comparative GC analysis with our synthetic material.

(32) Field-studies will be carried out by the Forest Research Institute in Eberswalde, Germany. The results of these studies will be published in due course.