Diastereoselective Synthesis of Polysubstituted Tetrahydropyrans and Thiacyclohexanes via Indium Trichloride Mediated Cyclizations[1]

Xiao-Fan Yang, Joel T. Mague, and Chao-Jun Li*

Department of Chemistry, Tulane University, New Orleans, Louisiana 70118

cjli@tulane.edu

Received July 26, 2000

Polysubstituted tetrahydropyrans and thiacyclohexanes were synthesized in high yields with excellent diastereoselectivities via indium trichloride mediated cyclizations between homoallyl alcohols and mercaptans with aldehydes. In the case of tetrahydropyran products, the stereochemistry of the product was found to be directly correlated with the geometry of the homoallyl alcohols; whereas the cross-cyclization of aldehydes with *trans*-homoallyl alcohols generated (*up-down-up)* 2,3,4-trisubstituted tetrahydropyran products exclusively, the reaction of aldehydes with *cis*-homoallyl alcohols provided mainly (*up-up-up*) 2,3,4-trisubstituted products. When a trisubstituted homoallyl alcohol was used, its cross-cyclization with aldehydes generated (*up-down-up-down-up*) pentasubstituted tetrahydropyran derivatives with simultaneous controlling of *five stereogenic centers*. On the other hand, a cyclization−decyclization equilibrium was observed in the formation of thiacyclohexanes. The reaction of both *cis*- and *trans*-homoallyl mercaptans with aldehydes provided the same major diastereomers.

Introduction

Six-membered saturated oxygen and sulfur heterocycles are structural features of a variety of biologically important natural products such as polyether antibiotics, marine toxins, pheromones, and pharmaceutical agents.[2] Tetrahydropyran is also the structural core of most carbohydrates, as well as their oligomers and polymers, which are the most abundant biological molecules on earth and play several crucial roles in living organisms.[3] Considerable efforts have been made toward the synthesis of tetrahydropyran type compounds.[4] Some examples are via hetero-Diels−Alder reactions,[5] oxiranyl anions,[6] carbonyl ylides,[7] Claisen rearrangements,[8] ring opening of epoxides,[9] iodocyclizations,[10] olefin-metathesis,[11] and many others. Thiacyclohexanes, sometimes called thiotetrahydropyrans, are less frequently encountered in nature. Some thiacyclohexane derivatives are found in petroleum oil.[12] Thiacyclohexane rings also play a key role in the biological activities of a number of pharmaceutical agents such as cephalosporins and dithiathromboxane A_2.[13] Recently, there has been an increasing interest in developing sulfur analogues of oligosaccharides as potential enzyme inhibitors.[14] In addition, thiacyclohexane derivatives can be transformed into a variety of structures through simple reactions such as hydrogenolysis, oxidation, and olefination.[15]

The condensation of olefins with aldehydes under strongly acidic conditions, known as the Prins reaction, was discovered in 1899 to give a mixture of compounds.[16] Major products of classical Prins reactions are normally 1,3-dioxanes, 1,3-glycols, unsaturated alcohols, and alcohols derived from hydration of the olefins, as well as products obtained from acid-catalyzed polymerization of the olefin. In the late 1960s, Stapp briefly examined the direct synthesis of tetrahydropyran derivatives via the Prins reaction.[17] Recently, there has been an increasing

(1) Taken in part from the M.S. thesis of Xiao-Fan Yang, Tulane University, 2000.

(2) Reviews: Wesley, J. W. *Annu. Rep. Med. Chem.* **1975**, *10*, 246. Pressman, B. C. *Annu. Rev. Biochem.* **1976**, *45*, 501. Bhagwat, S. S.; Hamann, P. R.; Still, W. C.; Buntiny, S.; Fitzpatrick, F. A. *Nature* **1985**, *315*, 511. Ohuchida, S.; Hamanaka, N.; Hayashi, M. *Tetrahedron* **1983**, *39*, 4203. Kale, V. N.; Clive, D. L. J. *J. Org. Chem.* **1984**, *49*, 1554.

(3) Horton, H. R.; Moran, L. A.; Ochs, R. S.; Rawn, J. D.; Scrimgeour, K. G. *Principles of Biochemistry*, 2nd ed.; Prentice Hall: Upper Saddle River, NJ, 1996.

(4) For a review, see: Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.

(5) For a review, see; Tietze, L. F.; Kettschau, G.; Gewert, J. A.; Schuffenhauer, A. *Curr. Org. Chem.* **1998**, *2*, 19. Schmidt, R. R. *Acc. Chem. Res.* **1986**, *19*, 250.

(6) Mori, Y. *Chem. Eur. J.* **1997**, *3*, 849.

(7) Padwa, A. *Acc. Chem. Res.* **1991**, *24*, 22.

(8) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227.

(9) For an example, see: Nicolaou, K. C.; Prasad, C. V. C.; Somers, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.

(10) For a review, see; Bartlett. P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, Chapter 6.

(11) For examples of cycloether formations, see: Rutjes, F. P. J. T.; Kooistra, T. M.; Hiemstra, H.; Schoemaker, H. E. *Synlett* **1998**, 192. Clark, J. S.; Hamelin, O.; Hufton, R. *Tetrahedron Lett.* **1998**, *39*, 8321 and refs therein. For a review, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(12) Gal'pern, G. D. *Int. J. Sulfur Chem. B* **1971**, *6*, 115.

(13) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbruggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852. Casy, G.; Lane, S.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1397. Ohuchida, S.; Hamanaka, N.; Hagashi, M. *Tetrahedron Lett.* **1983**, *39*, 4273.

(14) Mehta, S.; Andrews, J. S.; Johnston, B. D.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 9783.

(15) Block, E. *Reactions of Organosulfur Compounds*; Academic Press: New York, 1978. Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au−Yeung, B. W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H. *J. Am. Chem. Soc.* **1981**, *103*, 3210.

(16) Arundale, E.; Mikesaka, L. A. *Chem. Rev.* **1952**, *51*, 505. Kovacs, O.; Kovari, I. *Magy. Kem. Foly.* **1964**, *70*, 223. Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661. Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed., Pergamon Press: Oxford, 1991; Vol. 2, pp 527−561.

10.1021/jo001136i CCC: $20.00
Published on Web 01/12/2001

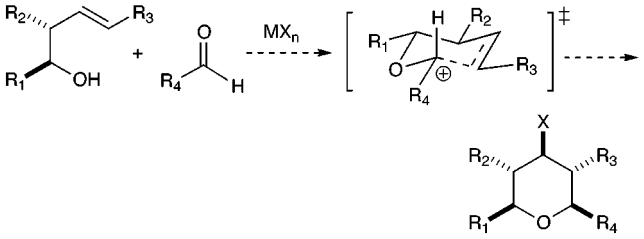


Figure 1.

interest in using Prins-cyclization to generate tetrahydropyran derivatives in a stereocontrolled manner, with potential applications to the synthesis of polyether antibiotics and other complex natural products that contain tetrahydropyran backbones. A large number of papers have been published on this type of cyclization during the past decade.[18] A variety of Lewis acids have been used to mediate such a cyclization. In most cases, the cyclization products are either 2,6-disubstituted dihydropyran or 2,4,6-trisubstituted tetrahydropyran derivatives. Some methodologies start with the formation of a stable acetal compound whereas others involve direct condensation of a homoallylic alcohol with aldehyde through a hemiacetal intermediate. The most striking feature of tetrahydropyran derivatives in natural products is the attachment of multiple substituents with well-defined stereochemistry. We envisioned that an efficient method toward the stereocontrolled formation of poly-substituted tetrahydropyran and thiacyclohexane derivatives is through the Prins-type cyclization of substituted homoallyl alcohols and mercaptans with aldehydes (Figure 1).[19] Herein, we describe our results of investigation on this subject by using indium chloride as a mild mediator.

Results and Discussions

2,3,4-Trisubstituted Tetrahydropyrans. Although 2,4,6-trisubstituted tetrahydropyrans were readily synthesized with high diastereoselectivities through a number of Prins-cyclizations, extension of the method to tetra- or pentasubstituted derivatives has not been reported.[19] With internal olefins the regioselectivity becomes crucial when the double bond attacks the oxonium ion intermediate: tetrahydropyran derivatives will be formed with the attack from the terminal carbon of the olefin moiety whereas attack from the other end of the double bond generates the tetrahydrofuran products (Scheme 1).[20] Unlike most strong Lewis acid catalysts (such as $TiCl_4$, $SnCl_4$) developed for Prins-cyclization, a milder Lewis acid like $InCl_3$ was envisioned to be effective in promoting

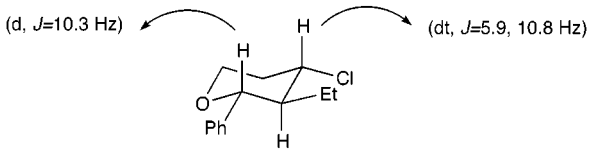
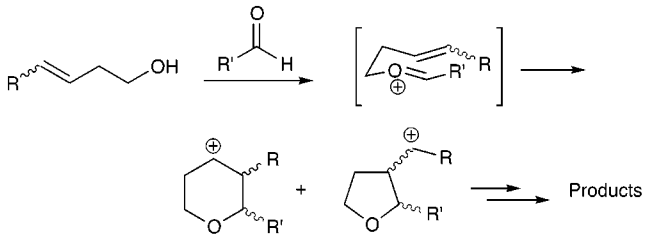


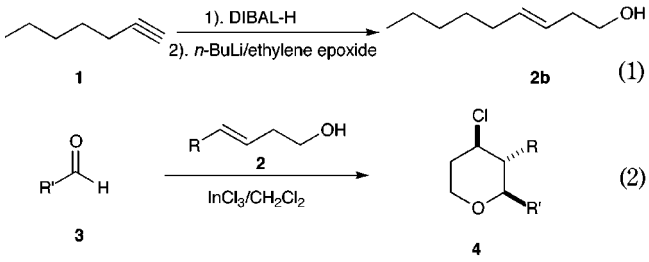
Figure 2.

Scheme 1



the formation of tetrahydropyran derivatives as the major products selectively and tetrahydrofuran derivatives as the minor products due to their stability difference.[21]

Most homoallyl alcohols used in our research are commercially available and *trans*-3-nonen-1-ol **2b** was readily prepared from 1-heptyne (**1**) via hydroalumination followed by reaction with ethylene oxide (eq 1).[22] When *trans*-3-hexen-1-ol (**2a**) was stirred with benzaldehyde (**3a**) and indium trichloride in methylene chloride at ambient temperature, an immediate color change was observed. Disappearance of the starting material was then detected by TLC after 3 h of stirring. After a usual workup, an unsymmetrical 2,3,4-trisubstituted tetrahydropyran **4a** was generated in high yield with an exclusive *up-down-up* (>99:1) diastereoselectivity as estimated by ^{1}H NMR analysis of the crude reaction mixture. After purification, the stereochemistry was further confirmed by DQF−COSY NMR analyses, examination of the coupling constants (Figure 2), and comparison with related compounds reported in the literature. A variety of other aromatic aldehydes (entries 1−5) were also examined, providing high yield and diastereoselectivity in each case (eq 2) (Table 1). Changing the homoallyl alcohol to *trans*-3-nonen-1-ol (**2b**) did



not affect the stereoselectivity but decreased the yield slightly, possibly due to an increase of steric hindrance in the transition state for the ring-closing step. Cyclization of the alcohols with aliphatic aldehydes (entries 6−8)

(17) Stapp, P. R. *J. Org. Chem.* **1969**, *34*, 479.

(18) For some examples with other Lewis acids for Prins-type cyclizations, see: Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958. Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271. Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426. Nishizaw, M.; Shigaraki, T.; Takao, H.; Imagawa, H.; Sugihara, T. *Tetrahedron Lett.* **1999**, *40*, 1153. Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092. Wei, Z. Y.; Li, J. S.; Wang, D.; Chan, T. H. *Tetrahedron Lett.* **1987**, *28*, 3441. Wei, Z. Y.; Wang, D.; Li, J. S.; Chan, T. H. *J. Org. Chem.* **1989**, *54*, 5768. Coppi, L.; Ricci, A.; Taddi, M. *J. Org. Chem.* **1988**, *53*, 911; Marko, I. E.; Dobbs, A. P.; Scheirmann, V.; Chelle, F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, *38*, 2899. Brown, M. J.; Harrison, T.; Herrinton, P. M.; Hopkins, M. H.; Hutchinson, K. D.; Mishra, P.; Suginome, M.; Iwanami, T.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 6096.

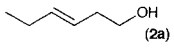
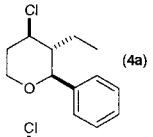
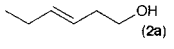
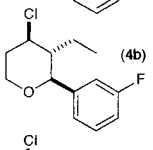
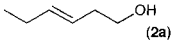
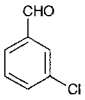
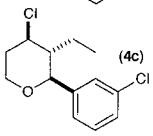
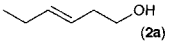
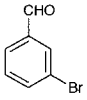
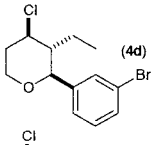
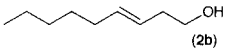
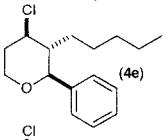
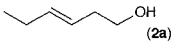
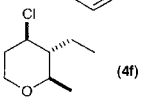
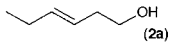
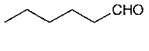
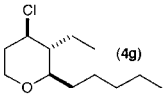
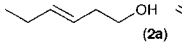
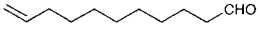
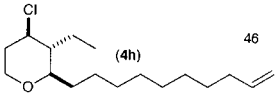
(19) For a preliminary communication on the thiacyclohexane study, see: Yang, X. F.; Li, C. J. *Tetrahedron Lett.* **2000**, *41*, 1321; see also: Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217.

(20) Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5365.

(21) Yang, J.; Viswanathan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627. Viswanathan, G. S.; Yang, J.; Li, C. J. *Org. Lett.* **1999**, *1*, 993. For reviews on synthetic applications of indium and indium reagents, see: Cintas, P. *Synlett* **1995**, 1087. Hashmi, A. S. K. *J. Prakt. Chem., Chem. Zeit.* **1998**, *340*, 84. Paquette, L. A. In *Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes*; Anastas, P. A.; Williamson, T. C., Eds.; Oxford University Press: Cary, NC, 1998. Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. Ranu, B. C. *Eur. J. Org. Chem.* **2000**, 2347.

(22) Negishi, E.; Baba, S.; King, A. O. *J. Chem. Soc. Chem. Commun.* **1976**, 17.

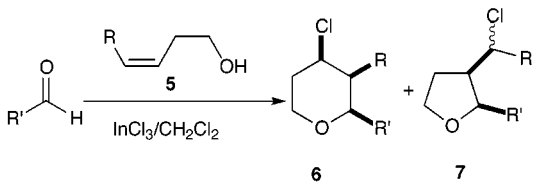
Table 1. Stereoselective Formation of 2,3,4-Trisubstituted Tetrahydropyrans from *trans*-Homoallyl Alcohols[a]

Entry	Alcohol (2)	R'CHO(3)	Product(4)	Yield(%)
1	 (2a)		 (4a)	85
2	 (2a)		 (4b)	90
3	 (2a)		 (4c)	86
4	 (2a)		 (4d)	88
5	 (2b)		 (4e)	80
6	 (2a)	CH_3CHO	 (4f)	71
7	 (2a)		 (4g)	81
8	 (2a)		 (4h)	46

[a] All reaction were carried out with the general procedure. Yields were Isolated ones after column chromatography.

gave the same high diastereoselectivity; however, the yields decreased as the length of aliphatic chain increased, also possibly due to the steric effect.

To study the effect of the olefin geometry on the product formation, *cis*-homoallyl alcohols were also examined. The condensation between *cis*-3-hexen-1-ol (**5a**) and benzaldehyde was carried out under the same reaction conditions as with the *trans* homoallyl alcohols. In this case, no color change was observed and disappearance of the starting material was detected by TLC after 10 h of vigorous stirring at room temperature. Unlike the cyclization of *trans* homoallyl alcohols, the formation of two cyclic ether compounds **6** and **7** were observed, with *(up,up,up)*-2,3,4-trisubstituted tetrahydropyran derivative **6** as the major product and *cis*-2,3-disubstituted tetrahydrofuran derivative **7** as the minor one (eq 3). The combined overall yield was less than the cyclization with the corresponding *trans* homoallyl alcohols. Replacing benzaldehyde with acetaldehyde, the cyclization generated an all *cis* tetrahydropyran product in moderate yield whereas aldehydes with longer aliphatic chains gave rise to a mixture of inseparable products in low overall yields. Changing the alcohol to *cis*-3-nonen-1-ol (**5b**) gave the two products as a 1:1 mixture of the tetrahydropyran and tetrahydrofuran derivatives. However, the overall yield was not significantly affected (Table 2). The relative configurations of the tetrahydropyran derivatives were assigned via careful examinations of coupling constants of the two distinct pair of signals at ca. 4.0 ppm. The structure of the tetrahydrofuran products was determined by DQF−COSY NMR analysis and the *cis* configuration was assigned by comparison with NMR data of similar compounds reported in the literature (Figure 3).[23]

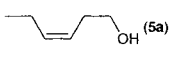
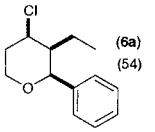
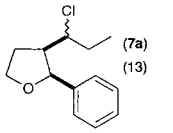
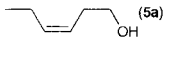
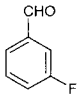
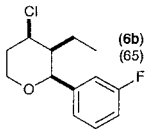
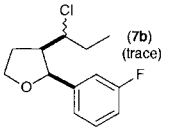
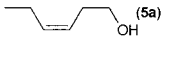
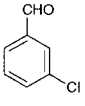
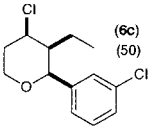
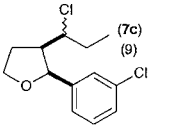
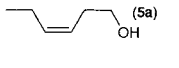
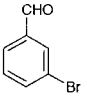
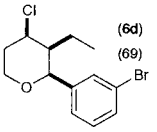
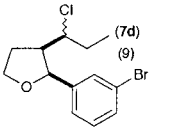
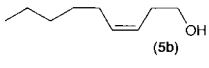
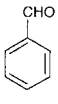
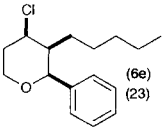
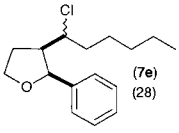
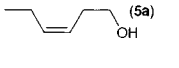
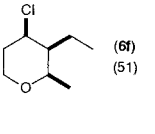
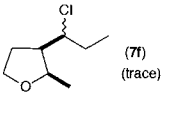
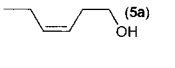
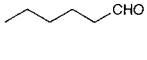
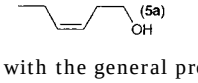
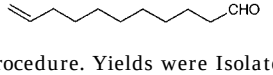


(3)

The formation of tetrahydrofuran derivatives suggested that a different transition-state might be involved in the cyclization of *cis* homoallyl alcohols as compared to the cyclization of *trans* homoallyl alcohols in which no such products were detected. A possible explanation is that in the case of *trans* homoallyl alcohol, the intermediate **8a** undergoes cyclization via the usual chair transition-state **8b** in which all the substituents are equatorial; whereas in the case of *cis* homoallyl alcohols,

(23) Dana, G.; Touboul, E.; Convert, O.; Pascal, Y. L. *Tetrahedron* **1988**, *44*, 429.

Table 2. Stereoselective Formation of 2,3,4-trisubstituted Tetrahydropyrans from *cis* Homoallyl Alcohols[a]

Entry	Alcohol (5)	R'CHO (3)	Product(6/7)/(Yield(%)
1	 (5a)		 (6a) (54)  (7a) (13)
2	 (5a)		 (6b) (65)  (7b) (trace)
3	 (5a)		 (6c) (50)  (7c) (9)
4	 (5a)		 (6d) (69)  (7d) (9)
5	 (5b)		 (6e) (23)  (7e) (28)
6	 (5a)	CH_3CHO	 (6f) (51)  (7f) (trace)
7	 (5a)		inseparable mixture of **2b** and **2c**
8	 (5a)		inseparable mixture of **2b** and **2c**

[a] All reactions were carried out with the general procedure. Yields were Isolated ones after column chromatography.

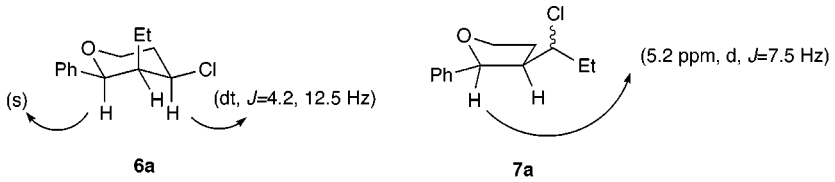
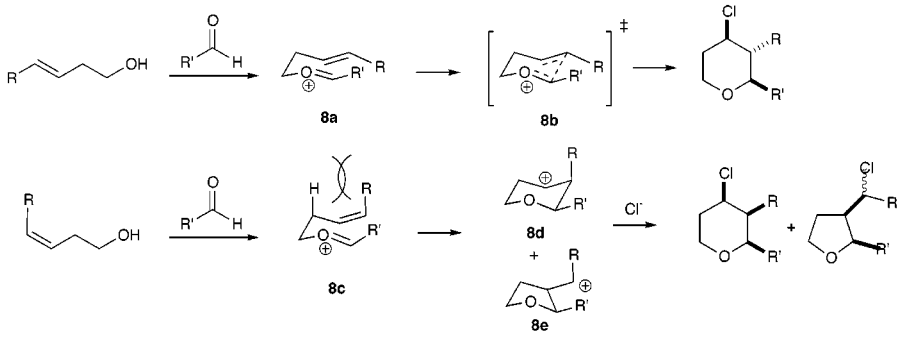


Figure 3.

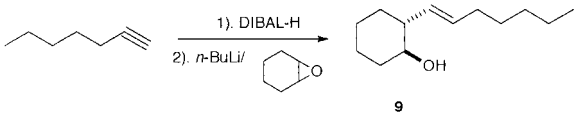
the disfavored pseudo 1,3-diaxial interaction in **8**c leads to a mixture of carbocations **8d** and **8e**. Subsequently, nucleophilic attack of **8d** by the chloride ion gave the more stable tetrahydropyran products whereas attack of **8e** produced tetrahydrofuran derivatives (Scheme 2).

Diastereoselective Synthesis of Pentasubstituted Tetrahydropyrans. To study the formation of pentasubstituted tetrahydropyran derivatives, commercially available cyclohexene oxide was converted into *trans*-2-(1-hepten-1-yl)cyclohexanol (**9**) in high yield by a method

Scheme 2



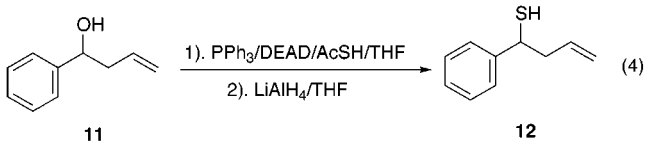
Scheme 3



9

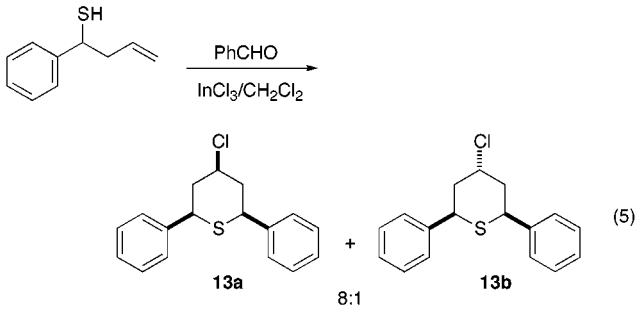
of Alexakis and Jachiet (Scheme 3).[24] Condensations of **9** with both benzaldehyde and hexanal were carried out under the same standard reaction conditions. The reactions generated a pentasubstituted tetrahydropyran derivative **10a** and **10b** (essentially as a single product in both cases) in which five stereogenic centers (*up-down-up-down-up*) were controlled (Scheme 4). X-ray crystal analysis of **10a** confirmed the stereochemistry of this compound, in which all five substituents on the tetrahydropyran ring occupy equatorial positions.[25]

Formation of Trisubstituted Thiacyclohexanes. Indium trichloride mediated cross-coupling between homoallyl mercaptans and aldehydes was also investigated. The homoallyl mercaptans such as **12** were readily synthesized by reacting the corresponding homoallyl alcohols (such as compound **11**) with thioacetic acid via a modification of the Mitsunobu protocol[26] followed by lithium aluminum hydride (LAH) reduction (eq 4). Attempts to synthesize the thiols by using the Lawesson's reagent[27] were not successful. The stirring of phenyl homoallyl mercaptan **12** with benzaldehyde and indium chloride in methylene chloride led to the smooth formation of 2,4,6-trisubstituted thiacyclohexanes **13a** and **13b** (97%) as a 8:1 mixture of diastereomers (eq 5). However, reaction of this thiol with other substituted aromatic aldehydes gave rise to a mixture of at least three cyclization products **13**, **15**, and **16** (as was shown by GC/



(4)

11 **12**

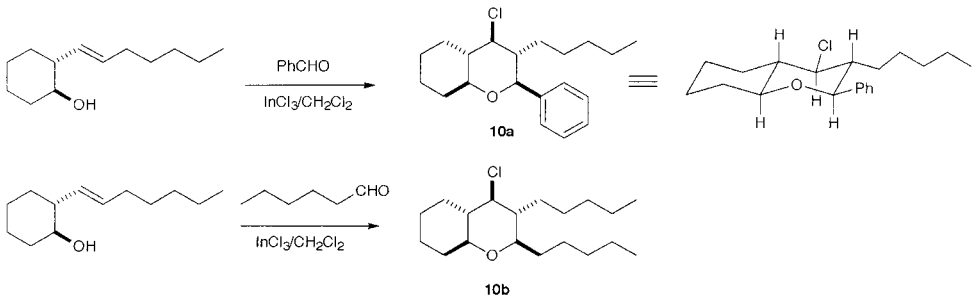


(5)

13a 8:1 **13b**

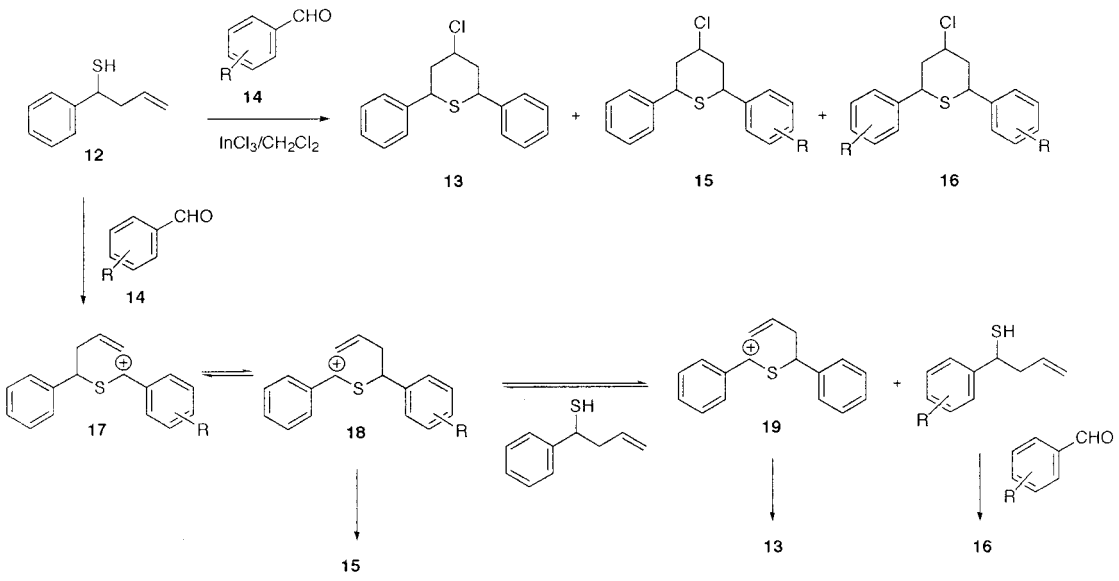
MS analysis of the reaction mixture). A plausible explanation of this scrambling is the existence of equilibrium between different kinds of carbocation intermediates **17**, **18**, and **19** during the course of reaction (Scheme 5). On the other hand, the reaction of an aliphatic homoallyl mercaptan **20** (when a *cis* isomer **20a** was used) with aldehydes generated unsymmetrical 2,3,4-trisubstituted thiacyclohexanes **21** and **22** in high yield with good diastereoselectivity together with a trace amount of thiacyclohexene derivative **23** (eq 6). The diastereoselectivity remains nearly the same in all cases at ca. 7:1

Scheme 4



10a **10b**

Scheme 5



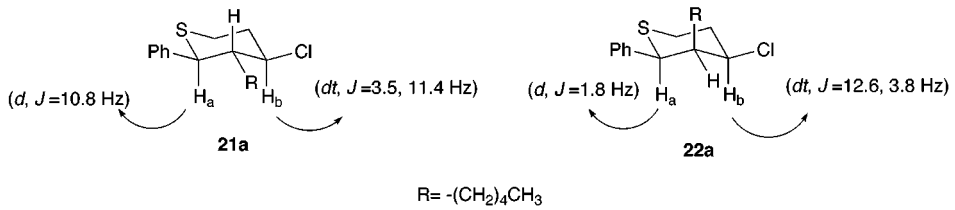
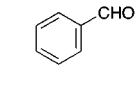
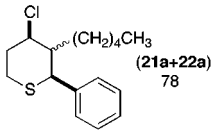
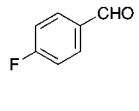
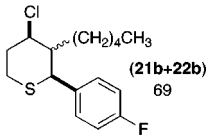
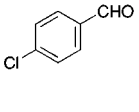
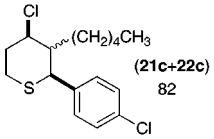
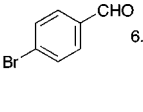
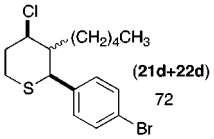
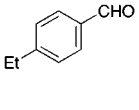
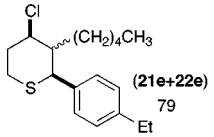


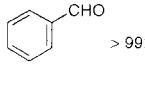
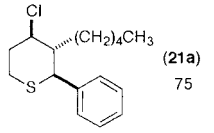
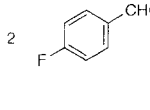
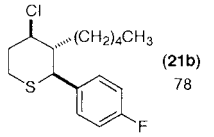
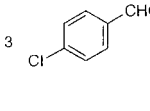
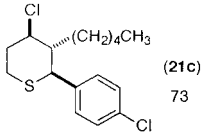
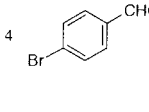
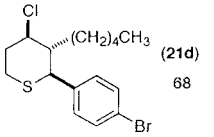
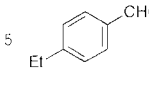
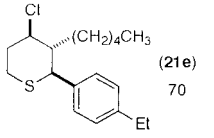
Figure 4.

Table 3. Diastereoselective Synthesis of Thiacyclohexanes via *cis*-3-Nonene-1-thiol (20a)[a]

Entry	RCHO	21/22	Product (21+22) (Yield%)
1		7:1	 (21a+22a) 78
2		8:1	 (21b+22b) 69
3		6:1	 (21c+22c) 82
4		6.5:1	 (21d+22d) 72
5		6:1	 (21e+22e) 79

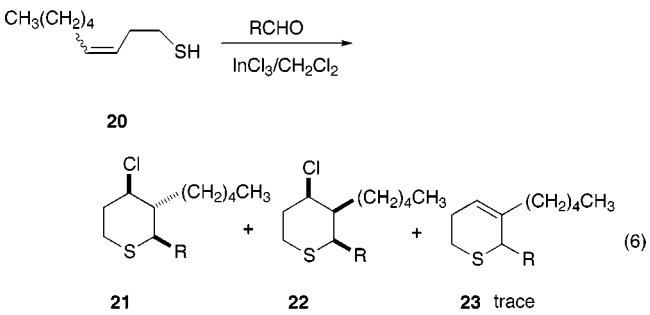
[a] Yields are (total) isolated ones (after column chromatography on silica gel) for both diastereomers. Ratios of diastereomers were measured with GC/MS or ^{1}H NMR on the crude reaction mixtures.

Table 4. Diastereoselective Synthesis of Thiacyclohexanes *via* with *trans*-3-Nonene-1-thiol (20b)[a]

Entry	RCHO	21/22	Product (21+22) (Yield%)
1		> 99:1	 (21a) 75
2		> 99:1	 (21b) 78
3		> 99:1	 (21c) 73
4		> 99:1	 (21d) 68
5		> 99:1	 (21e) 70

[a] Yields are (total) isolated ones (after column chromatography on silica gel) for both diastereomers. Ratios of diastereomers were measured with GC/MS or ^{1}H NMR on the crude reaction mixtures.

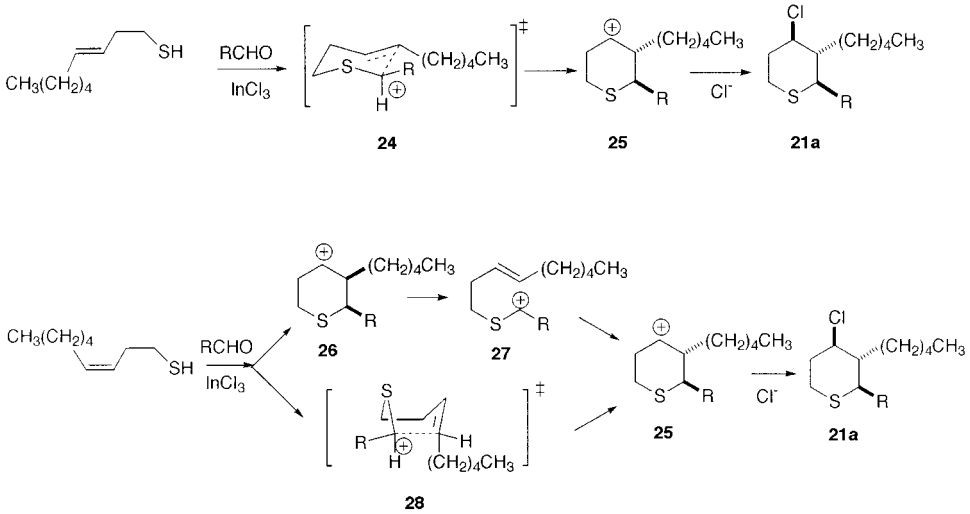
favoring the *up-down-up* isomers (Table 3). The relative configurations of the diastereomers were assigned via the coupling constants of the two distinct pairs of peaks at ca. 4.0 ppm as shown in Figure 4.



To investigate the effect of *cis*−*trans* conformations of the mercaptan on the diastereoselectivity of the cyclization, the corresponding *trans*-isomer mercaptan **20b** was also prepared by the previous method and was reacted with the aldehydes used earlier and indium trichloride under the same reaction conditions. Interestingly, reactions of both *cis* and *trans* mercaptans generated the major cyclized product **21** with the same configuration but different selectivity. Whereas the use of the *cis*-mercaptan gave rise to a mixture of *up-up-up* and *up-down-up* thiacyclohexane derivatives **21** and **22** with the latter as the predominant product, the reaction of the *trans* mercaptan generated a *up-down-up* thiacyclohexane derivative **21** exclusively (Table 4). Therefore, unlike the alcohol cyclization, stereoselective formation of the more stable *up-down-up* isomer took place regardless of the geometry of the starting mercaptan. The results would suggest that, with the use of the *trans*-mercaptan, the stereospecificity associated with the product formation was most likely due to the formation of a chair-transition-state **24** in the ring closure process which generated carbocation **25** and leading to product **21a**; whereas, in the case of the *cis*-mercaptan, an isomerization of the less stable carbocation intermediate **26** to the more stable carbocation **25** might have occurred (possibly via a decyclization to give **27** followed by recyclization)

(24) Alexakis, A.; Jachiet, D. *Tetrahedron* **1989**, *45*, 6179.
(25) See Supporting Information for ORTEP Figure of **4a** and tables of X-ray crystallographic data.
(26) Mitsunobu, O. *Synthesis* **1981**, 1.
(27) Nishio, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1113.

Scheme 6



which also led to the formation of the more stable *up-down-up* product **21a** (Scheme 6). Alternatively, a boat-transition-state **28** might be involved in the cyclization of the *cis*-isomer, generating the same major product as in the case of the *trans*-isomer. The scope and mechanism of the reaction, as well as the biological activities of the thiacyclohexane derivatives are under investigation.

In conclusion, indium chloride mediated Prins-type cyclization provided a convenient method in generating polysubstituted tetrahydropyrans and thiacyclohexanes in high yields with excellent stereochemical control. Further investigation would include a more detailed mechanistic study and possible applications of this methodology to natural product synthesis.

Experimental Section

Commercially available reagents were used without further purification. Methylene chloride was dried with 4 Å molecular sieves overnight, and tetrahydrofuran was distilled over metal sodium and benzophenone prior to use. All other solvents were used as purchased. NMR spectra were recorded on GE Omega 400 MHz FT-NMR Spectrometer. Advanced NMR structural analyses such as DQF−COSY, TOCSY, and ROESY were provided by Tulane University Coordinated Instrumental Facilities (CIF). IR spectra were obtained with Perkin-Elmer RX I FT-IR Spectrometer and GC-MS analysis was performed with Hewlett-Packard 5890 Series II Gas Chromatography and Hewlett-Packard 5989A Mass Spectrometer. Thin-layer chromatography (TLC) was carried out on glass supported plates and compounds were visualized by cerium molybdate, potassium permanganate, or UV light. Elemental analysis was also performed at CIF.

A General Procedure for the Cyclization of Homoallyl Alcohols with Aldehydes. To a slurry of indium trichloride (332 mg, 1.5 mmol) and benzaldehyde (106 mg, 1 mmol) in 15 mL methylene chloride (which was predried with 4 Å molecular sieves overnight) was added *trans*-3-hexen-1-ol (200 mg, 2 mmol) dropwise. After 3 h (10 h for *cis*-homoallyl alcohol) of stirring at room temperature, the reaction mixture was concentrated in vacuo. Flash chromatography of the crude mixture over silica gel (eluting with hexane/ethyl acetate = 350:1) gave 190 mg (85%) of 4-chloro-3-ethyl-2-phenyltetrahydropyran (*up-down-up* isomer).

4-Chloro-3-ethyl-2-phenyltetrahydropyran (*up-down-up*) (4a): IR(neat, cm^{-1}): 2964, 2851, 1457, 1088, 755, 699; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.30−7.41 (m, 5H), 4.07−4.16 (m, 3H), 3.59 (dt, J = 3.3, 11.8 Hz, 1H), 2.17−2.32 (m, 2H), 1.96 (ddt, J = 2.9, 4.8, 10.6 Hz, 1H), 1.60−1.69 (m, 1H), 1.18−1.30 (m, 1H), 0.73 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 140.0, 128.6, 128.4, 127.4, 83.7, 67.3, 60.3, 50.8, 37.8, 20.5, 9.0. Anal. Calcd for $C_{13}H_{17}OCl$: C, 69.48; H, 7.62. Found: C, 69.62; H, 7.66.

4-Chloro-3-ethyl-2-phenyltetrahydropyran (*up-up-up*) (6a): IR (neat, cm^{-1}): 2961, 2848, 1450, 1264, 1151, 1115, 1073, 1001, 764, 743, 702; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.24−7.38 (m, 5H), 4.53 (s, 1H), 4.44 (dt, J = 12.5, 4.2 Hz, 1H), 4.18 (dd, J = 5.1, 11.7 Hz, 1H), 3.59 (dt, 2.6, 12.1 Hz, 1H), 2.01−2.14 (m, 2H), 1.85−1.92 (m, 1H), 1.42−1.60 (m, 2H), 0.38 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 140.4, 128.1, 127.0, 125.2, 81.3, 67.7, 62.3, 49.8, 32.0, 15.7, 15.3. Anal. Calcd for $C_{13}H_{17}OCl$: C, 69.48; H, 7.62. Found: C, 69.53; H, 7.60.

***cis*-3-(1-Chloropropyl)-2-phenyltetrahydrofuran (7a):** IR (neat, cm^{-1}): 2969, 2875, 1454, 1066, 751, 699; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.26−7.40 (m, 5H), 5.23 (d, J = 7.3 Hz, 1H), 4.34 (dt, J = 1.8, 8.4 Hz, 1H), 4.02 (ddd, J = 7.0, 8.8, 10.3 Hz, 1H), 3.22 (dt, J = 2.7, 9.2 Hz, 1H), 2.91 (ddt, J = 9.5, 11.4, 7.1 Hz, 1H), 2.03−2.21 (m, 1H), 1.86−1.98 (m, 1H), 1.71−1.80 (m, 1H), 1.54−1.67 (m, 1H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 140.1, 128.0, 127.5, 127.3, 82.6, 68.5, 64.6, 52.0, 29.5, 28.1, 10.3.Anal. Calcd for $C_{13}H_{17}OCl$: C, 69.48; H, 7.62. Found: C, 69.58; H, 7.58.

4-Chloro-3-ethyl-2-(*m*-fluorophenyl)tetrahydropyran (*up-down-up*) (4b): IR (neat, cm^{-1}): 2969, 2857, 1593, 1450, 1266, 1138, 1092, 790, 698; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.30−7.37 (m, 1H), 6.99−7.17 (m, 3H), 4.04−4.16 (m, 3H), 3.57 (dt, 1H, J = 2.9, 12.1 Hz, 1H), 2.15−2.30 (m, 2H), 1.89 (ddt, J = 2.9, 4.8, 10.6 Hz, 1H), 1.58−1.70 (m, 1H), 1.17−1.29 (m, 1H), 0.74 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 164.1, 161.7, 142.6, 142.5, 130.1, 130.0, 123.1, 123.1, 115.4, 115.1, 114.4, 114.2, 82.9, 82.9, 67.3, 60.0, 50.9, 37.6, 20.4, 9.0. Anal. Calcd for $C_{13}H_{16}OClF$: C, 64.33; H, 6.64. Found: C, 64.56; H, 6.69.

4-Chloro-3-ethyl-2-(*m*-fluorophenyl)tetrahydropyran (*up-up-up*) (6b): IR (neat, cm^{-1}): 2966, 2849, 1592, 1445, 1277, 1251, 1114, 1078, 770, 693; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.25−7.34 (m, 1H), 7.04−7.12 (m, 2H), 6.91−6.98 (m, 1H), 4.51 (s, H), 4.41 (dt, J = 12.5, 4.4 Hz, 1H), 4.17 (ddd, J = 1.5, 5.1, 6.6 Hz, 1H), 3.58 (dt, J = 2.7, 12.5 Hz, 1H), 1.99−2.12 (m, 2H), 1.84−1.92 (m, 1H), 1.38−1.60 (m, 2H), 0.41 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 164.2, 161.7, 143.2, 143.1, 129.6, 129.5, 120.9, 120.9, 113.9, 113.7, 112.6, 112.4, 80.6, 67.6, 61.9, 49.6, 31.8, 15.7, 15.3. Anal. Calcd for $C_{13}H_{16}OClF$: C, 64.33; H, 6.64. Found: C, 64.42; H, 6.56.

4-Chloro-3-ethyl-2-(*m*-chlorophenyl)tetrahydropyran (*up-down-up*) (4c): IR (neat, cm^{-1}): 2964, 2851, 1575, 1437, 1206, 1139, 1088, 775, 699; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.21−7.40 (m, 4H), 4.04−4.13 (m, 3H), 3.56 (dt, J = 2.6, 12.1 Hz, 1H), 2.14−2.30 (m, 2H), 1.90 (ddt, J = 2.9, 4.8, 10.6

Hz, 1H), 1.59−1.70 (m, 1H), 1.16−1.28 (m, 1H), 0.74 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 142.1, 134.5, 129.8, 128.5, 127.5, 125.6, 82.9, 67.3, 59.9, 50.7, 37.6, 20.4, 9.0. Anal. Calcd for $C_{13}H_{16}OCl_2$: C, 60.25; H, 6.22. Found: C, 60.49; H, 6.24.

4-Chloro-3-ethyl-2-(*m*-chlorophenyl)tetrahydropyran (*up-up-up*) (6c): IR (neat, cm^{-1}): 2964, 2849, 1575, 1150, 1113, 1076, 767, 688; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.16−7.38 (m, 4H), 4.48 (s, 1H), 4.40 (dt, J = 12.5, 4.2 Hz, 1H), 4.16 (ddd, J = 1.5, 5.1, 6.6 Hz, 1H), 3.56 (dt, J = 2.6, 12.1 Hz, 1H), 1.99−2.11 (m, 2H), 1.84−1.91 (m, 1H), 1.49−1.61 (m, 1H), 1.37−1.49 (m, 1H), 0.42 (t, J = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 142.6, 134.3, 129.4, 127.2, 125.6, 123.5, 80.6, 67.6, 61.9, 49.5, 31.8, 15.7, 15.4. Anal. Calcd for $C_{13}H_{16}OCl_2$: C, 60.25; H, 6.22. Found: C, 60.14; H, 6.14.

***cis*-3-(1-Chloropropyl)-2-(*m*-chlorophenyl)tetrahydrofuran (7c):** IR (neat, cm^{-1}): 2969, 2878, 1574, 1204, 1071, 787, 683; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.25−7.36 (m, 4H), 5.20 (d, J = 7.3 Hz, 1H), 4.34 (dt, J = 1.8, 8.8 Hz, 1H), 4.01 (ddd, J = 6.2, 8.4, 10.3 Hz, 1H), 3.20 (dt, J = 1.9, 9.2 Hz, 1H), 2.91 (ddt, J = 9.5, 11.4, 7.3 Hz, 1H), 2.03−2.11 (m, 1H), 1.82−1.94 (m, 1H), 1.71−1.82 (m, 1H), 1.55−1.68 (m, 1H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 142.4, 134.0, 129.2, 127.7, 127.4, 125.7, 82.0, 68.7, 64.2, 52.1, 29.6, 28.2, 10.2. Anal. Calcd for $C_{13}H_{16}OCl_2$: C, 60.25; H, 6.22. Found: C, 60.28; H, 6.25.

4-Chloro-3-ethyl-2-(*m*-bromophenyl)tetrahydropyran (*up-down-up*) (4d): IR (neat, cm^{-1}): 2965, 2853, 1571, 1207, 1141, 1090, 777, 695; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.53 (s, 1H), 7.44−7.49 (m, 1H), 7.21−7.30 (m, 2H), 4.04−4.13 (m, 3H), 3.56 (dt, J = 2.6, 12.1 Hz, 1H), 2.14−2.30 (m, 2H), 1.90 (ddt, J = 3.3, 4.8, 10.6 Hz, 1H), 1.59−1.71 (m, 1H), 1.17−1.28 (m, 1H), 0.74 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 142.3, 131.4, 130.4, 130.1, 126.1, 122.7, 82.8, 67.3, 59.8, 50.7, 37.6, 20.4, 9.0. Anal. Calcd for $C_{13}H_{16}OClBr$: C, 51.43; H, 5.31. Found: C, 51.40; H, 5.33.

4-Chloro-3-ethyl-2-(*m*-bromophenyl)tetrahydropyran (*up-up-up*) (6d): IR (neat, cm^{-1}): 2964, 2852, 1568, 1153, 1117, 1071, 769, 703; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.52 (s, 1H), 7.40 (dt, J = 7.0, 2.0 Hz, 1H), 7.18−7.25 (m, 2H), 4.48 (s, 1H), 4.39 (dt, J = 12.1, 4.2 Hz, 1H), 4.16 (ddd, J = 1.5, 5.1, 6.6 Hz, 1H), 3.56 (dt, J = 2.6, 12.1 Hz, 1H), 1.99−2.15 (m, 2H), 1.84−1.91 (m, 1H), 1.49−1.61 (m, 1H), 1.36−1.49 (m, 1H), 0.43 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 142.8, 130.1, 129.7, 128.5, 123.9, 122.5, 80.5, 67.6, 61.8, 49.5, 31.8, 15.7, 15.4. Anal. Calcd for $C_{13}H_{16}OClBr$: C, 51.43; H, 5.31. Found: C, 51.49; H, 5.29.

***cis*-3-(1-Chloropropyl)-2-(*m*-bromophenyl)tetrahydrofuran (7d):** IR (neat, cm^{-1}): 2970, 2876, 1561, 1457, 1068, 783, 664; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.19−7.52 (m, 4H), 5.19 (d, J = 7.3 Hz, 1H), 4.34 (dt, J = 1.8, 8.4 Hz, 1H), 3.81 (ddd, J = 6.6, 8.4, 10.3 Hz, 1H), 3.20 (dt, J = 2.9, 9.2 Hz, 1H), 2.91 (ddt, J = 9.9, 12.7, 7.0 Hz, 1H), 2.03−2.11 (m, 1H), 1.81−1.93 (m, 1H), 1.71−1.81 (m, 1H), 1.55−1.68 (m, 1H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 142.7, 130.7, 130.3, 129.5, 126.2, 122.3, 82.0, 68.7, 64.2, 52.1, 29.6, 28.2, 10.2. Anal. Calcd for $C_{13}H_{16}OClBr$: C, 51.43; H, 5.31. Found: C, 51.37; H, 5.27.

4-Chloro-3-pentyl-2-phenyltetrahydropyran (*up-down-up*) (4e): IR (neat, cm^{-1}): 2954, 2928, 2857, 1455, 1138, 1087, 754, 698; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.30−7.40 (m, 5H), 4.02−4.15 (m, 3H), 3.58 (dt, J = 3.3, 11.7 Hz, 1H), 2.15−2.30 (m, 2H), 1.94 (ddt, J = 2.6, 4.8, 10.6 Hz, 1H), 1.44−1.55 (m, 1H), 0.95−1.25 (m, 7H), 0.79 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 140.1, 128.5, 128.3, 127.4, 84.3, 67.4, 61.3, 50.4, 37.8, 32.0, 28.0, 24.6, 22.3, 13.9; IR (neat, cm^{-1}): 2954, 2928, 2857, 1455, 1138, 1087, 754, 698. Anal. Calcd for $C_{16}H_{23}OCl$: C, 72.03; H, 8.69. Found: C, 72.14; H, 8.77.

4-Chloro-3-pentyl-2-phenyltetrahydropyran (*up-up-up*) (6e): IR (neat, cm^{-1}): 2957, 2931, 2853, 1450, 1151, 1125, 1084, 743, 702; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.22−7.37 (m, 5H), 4.52 (s, 1H), 4.43 (dt, J = 12.5, 4.4 Hz, 1H), 4.18 (ddd, J = 1.5, 5.1, 6.6 Hz, 1H), 3.59 (dt, J = 2.6, 12.5 Hz, 1H), 2.01−2.12 (m, 2H), 1.84−1.92 (m, 1H), 1.40−1.48 (m, 2H), 0.78−1.09 (m, 5H), 0.66 (t, J = 7.0 Hz, 3H), 0.31−0.46 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 140.4, 128.1, 127.0, 125.2, 81.5, 67.7, 62.2, 47.8, 32.0, 31.7, 30.0, 22.4, 22.1, 13.9. Anal. Calcd for $C_{16}H_{23}OCl$: C, 72.03; H, 8.69. Found: C, 72.07; H, 8.73.

***cis*-3-(1-Chlorohexyl)-2-phenyltetrahydrofuran (7e):** IR (neat, cm^{-1}): 2957, 2931, 2869, 1455, 1094, 1058, 753, 702; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.26−7.40 (m, 5H), 5.22 (d, J = 7.3 Hz, 1H), 4.33 (dt, J = 2.2, 8.4 Hz, 1H), 4.02 (ddd, J = 7.0, 8.4, 9.9 Hz, 1H), 3.30 (dt, J = 2.9, 8.8 Hz, 1H), 2.92 (ddt, J = 9.2, 11.0, 8.0 Hz, 1H), 2.04−2.13 (m, 1H), 1.89−2.01 (m, 1H), 1.44−1.70 (m, 3H), 1.07−1.30 (m, 5H), 0.85 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 140.0, 128.0, 127.5, 127.2, 82.6, 68.4, 63.3, 52.2, 36.2, 31.2, 28.1, 25.5, 22.5, 14.0. Anal. Calcd for $C_{16}H_{23}OCl$: C, 72.03; H, 8.69. Found: C, 71.99; H, 8.67.

4-Chloro-3-ethyl-2-methyltetrahydropyran (*up-down-up*) (4f): IR (neat, cm^{-1}): 2964, 2848, 1464, 1379, 1152, 1097, 775;^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 3.19−4.00 (m, 2H), 3.42 (dt, J = 2.2, 12.1 Hz, 1H), 3.30 (dq, J = 9.5, 6.2 Hz, 1H), 2.15−2.18 (m, 1H), 2.03 (dq, J = 4.8, 12.1 Hz, 1H), 1.73−1.85 (m, 1H), 1.44−1.64 (m, 2H), 1.26 (d, J = 6.2 Hz, 3H), 0.88 (t, J = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 76.2, 66.8, 60.3, 51.5, 37.8, 20.6, 19.7, 8.9. Anal. Calcd for C_8H_{15}-OCl: C, 59.07; H, 9.29. Found: C, 59.14; H, 9.23.

4-Chloro-3-ethyl-2-methyltetrahydropyran (*up-up-up*) (6f): IR (neat, cm^{-1}): 2966, 2847, 1465, 1268, 1107, 1081, 765, 557;^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 4.22 (dt, J = 11.4, 4.4 Hz, 1H), 3.95 (ddd, J = 2.6, 4.8, 11.7 Hz, 1H), 3.55 (dq, J = 2.2, 6.6 Hz, 1H), 3.44 (dt, J = 2.9, 11.0 Hz, 1H), 1.93 (ddt, J = 4.8, 13.2, 11.4 Hz, 1H), 1.77−1.84 (m, 1H), 1.52−1.68 (m, 3H), 1.24 (d, J = 6.6 Hz, 3H), 1.01 (t, J = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 76.1, 66.1, 62.0, 48.2, 32.3, 18.7, 16.5, 15.9. Anal. Calcd for $C_8H_{15}OCl$: C, 59.07; H, 9.29. Found: C, 59.25; H, 9.33.

4-Chloro-3-ethyl-2-pentyltetrahydropyran (*up-down-up*) (4g): IR (neat, cm^{-1}): 2959, 2853, 1459, 1379, 1152, 1097, 775; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 3.91−4.00 (m, 1H), 3.37 (dt, J = 2.2, 12.1 Hz, 1H), 3.11−3.18 (m, 1H), 2.10−2.17 (m, 1H), 2.01 (dq, J = 4.8, 12.1 Hz, 1H), 1.72−1.84 (m, 1H), 1.18−1.70 (m, 10H), 0.89 (t, J = 7.0 Hz, 3H), 0.87 (t, J = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 79.7, 66.8, 60.7, 49.4, 37.9, 33.0, 31.9, 24.9, 22.7, 20.5, 14.1, 9.0. Anal. Calcd for $C_{12}H_{23}OCl$: C, 65.88; H, 10.60. Found: C, 65.93; H, 10.65.

4-Chloro-3-ethyl-2-(9-decen-1-yl)tetrahydropyran (*up-down-up*) (4h): IR (neat, cm^{-1}): 2929, 2853, 1640, 1464, 1152, 1097, 991, 911, 775; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.82 (ddt, J = 10.3, 16.9, 6.6 Hz, 1H), 4.96−5.03 (m, 1H), 4.93 (ddt, J = 2.2, 10.3, 1.1 Hz, 1H), 3.92−4.00 (m, 2H), 3.37 (dt, J = 2.2, 12.1 Hz, 1H), 3.11−3.18 (m, 1H), 2.10−2.17 (m, 1H), 1.95−2.08 (m, 3H), 1.20−1.84 (m, 17H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 139.2, 114.1, 79.7, 66.8, 60.7, 49.4, 37.9, 33.8, 33.1, 29.7, 29.6, 29.5, 29.1, 28.9, 25.2, 20.5, 9.0. Anal. Calcd for $C_{17}H_{31}OCl$: C, 71.17; H, 10.89. Found: C, 71.09; H, 10.84.

***Trans-fused* 4-chloro-3-pentyl-2-phenyloctahydrobenzopyran (10a):** IR (film, cm^{-1}): 2935, 2853, 1452, 1095, 756, 697, 532; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.28−7.39 (m, 5H), 4.22 (d, J = 10.3 Hz, 1H), 3.76 (t, J = 10.8 Hz, 1H), 3.17 (dt, J = 4.0, 10.3 Hz, 1H), 2.31−2.39 (m, 1H), 1.96−2.06 (m, 2H), 1.72−1.86 (m, 2H), 1.61−1.72 (m, 1H), 0.90−1.56 (m, 12H), 0.79 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 140.3, 128.5, 128.2, 127.5, 83.7, 80.7, 68.1, 50.7, 50.6, 32.4, 32.1, 28.9, 28.2, 25.3, 24.8, 24.5, 22.3, 14.0. The structure was confirmed by X-ray analysis.

***Trans-fused* 4-chloro-2,3-dipentyloctahydrobenzopyran (10b):** IR (film, cm^{-1}): 2937, 2864, 1457, 1374, 1099, 751, 611; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 3.61 (t, J = 10.6 Hz, 1H), 3.20 (dt, J = 2.4, 9.1 Hz, 1H), 2.93 (dt, J = 4.0, 10.1 Hz, 1H), 2.22−2.30 (m, 1H), 1.91−1.98 (m, 1H), 1.12−1.84 (m, 23H), 0.81−0.95 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 80.2, 79.7, 68.7, 50.7, 49.4, 33.1, 32.5, 32.4, 31.9, 29.0, 28.4, 25.3, 25.1, 24.9, 24.7, 22.7, 22.5, 14.1,

14.1. Anal. Calcd for $C_{19}H_{35}ClO$: C, 72.46; H, 11.20. Found: C, 72.54; H, 11.25.

A General Procedure for Synthesis of Homoallyl Mercaptans.[26] Diethyl azodicarboxylate (8.33 g, 40 mmol) was added to an efficiently stirred solution of triphenyl phosphine (10.50 g, 40 mmol) in 100 mL of tetrahydrofuran at 0 °C. The mixture was stirred at 0 °C for 30 min. A solution of *cis*-3-nonen-1-ol (2.85 g, 20 mmol) and thioacetic acid (3.04 g, 40 mmol) in 50 mL of tetrahydrofuran was added dropwise over 10 min, and the mixture was stirred for 1 h at 0 °C and 1 h at ambient temperature. A clear yellowish solution was formed. The solution was concentrated, and the residue was purified by flash chromatography over silica gel (eluting with hexane/methylene chloride = 5:2) to gave 3.4 g (85%) of the desired thioacetate. The thioacetate (3.02 g, 15 mmol) was then dissolved in 25 mL of anhydrous tetrahydrofuran and added dropwise to a suspension of lithium aluminum hydride (0.57 g, 4 equiv) in 15 mL of anhydrous ether under a nitrogen atmosphere. The reaction mixture was stirred at ambient temperature for 30 min, and the excess lithium aluminum hydride was destroyed by careful addition of 10 mL of 1 N aq HCl. The ether layer was separated and dried over magnesium sulfate. Evaporation of the solvent gave 2.35 g (100%) of *cis*-3-nonene-1-thiol (**20a**) as a colorless oil, which was used directly without further purification.

1-Phenyl-3-butene-1-thiol (12): FTIR (film): 3045, 2903, 2574, 897, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.22−7.38(m, 5H), 5.67−5.79(m, 1H), 5.06−5.17 (m, 2H), 4.08 (ddd, J = 4.8, 6.4, 7.5 Hz, 1H), 2.60−2.80 (m, 2H), 2.06 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 143.9, 135.3, 128.7, 127.3, 127.1, 117.8, 44.1, 43.8. The thiol was used directly upon preparation.

***cis*-3-Nonene-1-thiol (20a):** FTIR (film): 2989, 2940, 2553, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 5.46−5.56 (m, 1H), 5.30−5.40 (m, 1H), 2.55 (q, J = 7.2 Hz, 2H), 2.30 (q, J = 7.1 Hz, 2H), 2.00 (q, J = 7.2 Hz, 2H), 1.20−1.45 (m, 7H), 0.88 (t, J = 6.8 Hz, 3H);^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 133.3, 127.2, 36.9, 32.5, 31.4, 29.2, 24.7, 22.6, 14.1. The thiol was used directly upon preparation.

***trans*-3-Nonene-1-thiol (20b):** FTIR (film): 2995, 2937, 2564, 679 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 5.45−5.55 (m, 1H), 5.30−5.39 (m, 1H), 2.54 (q, J = 7.2 Hz, 2H), 2.30 (q, J = 7.0 Hz, 2H), 1.99 (q, J = 7.0 Hz, 2H), 1.22−1.44 (m, 7H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 133.3, 127.2, 36.9, 32.5, 31.4, 29.1, 24.7, 22.5, 14.1. The thiol was used directly upon preparation.

A General Procedure for the Cyclization of *cis*- and *trans*-3-Nonene-1-thiol and Aldehydes. Indium trichloride (265 mg, 1.2 mmol) was added to a mixture of benzaldehyde (212 mg, 2.0 mmol) and *trans*-3-nonene-1-thiol (158 mg, 1.0 mmol) in 15 mL of methylene chloride which was predried with 4 Å molecular sieves overnight. After being stirred at room temperature for 10 h (same as *cis*- homoallyl thiol), the mixture was concentrated. Flash chromatography of the crude reaction mixture over silica gel (eluting with pure hexane) gave 220 mg (yield, 75%) of 4-chloro-3-pentyl-2-phenylthiacyclohexane as a colorless oil.

2,6-Diphenyl-4-chlorothiacyclohexane (*up-down-up*) (13a): IR (cm^{-1}, neat): 2931, 1490, 1451, 762, 695; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.23−7.41 (m, 10H), 4.89 (p, J = 3.6 Hz, 1H,), 4.65 (dd, J = 3.2, 11.6 Hz, 2H), 2.38−2.54 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 140.6, 128.7, 127.7, 127.7, 59.6, 42.2, 41.0. Anal. Calcd for $C_{17}H_{17}SCl$: C, 70.69; H, 5.93. Found: C, 70.77; H, 5.96.

4-Chloro-3-pentyl-2-phenylthiacyclohexane (*up-down-up*) (21a): IR (neat, cm^{-1}): 2953, 2927, 2861, 1455, 733, 692; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.26−7.37 (m, 5H), 3.93 (dt, J = 3.3, 11.4 Hz, 1H), 3.82 (d, J = 11.0 Hz, 1H), 2.83−2.93 (m, 1H), 2.62−2.70 (m, 2H), 2.24−2.35 (m, 2H), 1.65−1.75 (m, 1H), 0.98−1.35 (m, 7H), 0.79 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 139.9, 128.7, 128.0, 127.8, 63.5, 51.1, 50.7, 39.5, 32.0, 29.9, 29.5, 23.4, 22.3, 14.0. Anal. Calcd for $C_{16}H_{23}SCl$: C, 67.94; H, 8.19. Found: C, 67.90; H, 8.22.

2,6-Diphenyl-4-chlorothiacyclohexane (*up-up-up*) (22a): IR (cm^{-1}, neat): 2931, 1401, 1262, 695; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.24−7.39 (m, 10H), 4.12 (dd, J = 2.4, 12.0 Hz, 2H), 4.05 (tt, J = 4.0, 11.6 Hz, 1H), 2.68−2.76 (m, 2H), 2.30 (q, J = 12.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 140.1, 128.8, 127.9, 127.4, 58.4, 48.3, 44.6. Anal. Calcd for $C_{17}H_{17}SCl$: C, 70.69; H, 5.93. Found: C, 70.62; H, 5.92.

4-Chloro-3-pentyl-2-(*p*-fluorophenyl)thiacyclohexane (*up-down-up*) (21b): IR (neat, cm^{-1}) 2951, 2929, 2858, 1507, 1228, 832, 797, 529; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.27−7.33 (m, 2H), 6.99−7.06 (m, 2H), 3.91 (dt, J = 3.3, 11.4 Hz, 1H), 3.81 (d, J = 11.0 Hz, 1H), 2.81−2.92 (m, 1H), 2.59−2.69 (m, 2H), 2.18−2.33 (m, 2H), 1.63−1.74 (m, 1H), 0.95−1.26 (m, 7H), 0.80 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 163.3, 160.9, 135.7, 135.7, 129.6, 129.5, 115.7, 115.5, 63.3, 51.2, 49.9, 39.4, 32.0, 29.9, 29.5, 23.4, 22.3, 13.9. Anal. Calcd for $C_{16}H_{22}SClF$: C, 63.87; H, 7.37. Found: C, 63.81; H, 7.40.

4-Chloro-3-pentyl-2-(*p*-chlorophenyl)thiacyclohexane (*up-down-up*) (21c): IR (neat, cm^{-1}): 2950, 2926, 2857, 1489, 1093, 1015, 815, 741; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.24−7.32 (m, 4H), 3.90 (dt, J = 3.2, 11.7 Hz, 1H), 3.79 (d, J = 11.0 Hz, 1H), 2.82−2.92 (m, 1H), 2.61−2.68 (m, 2H), 2.18−2.33 (m, 2H), 1.64−1.75 (m, 1H), 0.97−1.24 (m, 7H), 0.80 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 138.4, 133.4, 129.3, 128.9, 63.1, 51.0, 49.9, 39.4, 32.0, 29.9, 29.5, 23.3, 22.3, 13.9. Anal. Calcd for $C_{16}H_{22}SCl_2$: C, 60.56; H, 6.99; Found: C, 60.62; H, 6.96.

4-Chloro-3-pentyl-2-(*p*-bromophenyl)thiacyclohexane (*up-down-up*) (21d): IR (neat cm^{-1}): 2951, 2928, 2859, 1490, 1073, 1010, 816, 736; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.44−7.49 (m, 2H), 7.18−7.23 (m, 2H), 3.90 (dt, J = 3.3, 11.3 Hz, 1H), 3.78 (d, J = 11.0 Hz, 1H), 2.82−2.92 (m, 1H), 2.60−2.68 (m, 2H), 2.18−2.33 (m, 2H), 1.64−1.75 (m, 1H), 0.98−1.25 (m, 7H), 0.80 (t, J = 7.2 Hz, 3H);^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 139.0, 131.9, 129.7, 121.5, 63.1, 50.9, 50.0, 39.4, 32.0, 29.9, 29.5, 23.3, 22.3, 13.9. Anal. Calcd for $C_{16}H_{22}SClBr$: C, 53.12; H, 6.13. Found: C, 53.07; H, 6.11.

4-Chloro-3-pentyl-2-(*p*-ethylphenyl)thiacyclohexane (*up-down-up*) (21e): IR (neat, cm^{-1}): 2956, 2931, 2867, 1511, 1456, 821, 756; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.21−7.26 (m, 2H), 7.13−7.18 (m, 2H), 3.92 (dt, J = 3.3, 11.4 Hz, 1H), 3.80 (d, J = 10.6 Hz, 1H), 2.82−2.92 (m, 1H), 2.60−2.69 (m, 4H), 2.22−2.34 (m, 2H), 1.63−1.73 (m, 1H), 1.24 (t, J = 7.6 Hz, 3H), 1.00−1.28 (m, 7H), 0.79 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 143.7, 137.0, 128.1, 127.9, 63.6, 51.2, 50.4, 39.5, 32.0, 29.9, 29.5, 28.5, 23.4, 22.3, 15.4, 13.9. Anal. Calcd for $C_{18}H_{27}SCl$: C, 69.53; H, 8.75. Found: C, 69.58; H, 8.72.

Registration numbers (supplied by author): *trans*-3-nonen-1-ol [10339-61-4]; *cis*-3-nonen-1-ol [10340-23-5]; *trans*-2-(*E*,1-heptenyl)cyclohexanol [127128-25-0].

Acknowledgment. We are grateful to NSF (Early CAREER Award program) for partial support of this research. X.F.Y. thanks Tulane's Center of Bioenvironmental Research (DoD) for a CBR Research Scholarship. We thank Dr. K. Maskos for help on NOE experiments.

Supporting Information Available: X-ray data for compound **10a** and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001136I