A New Method for Stereocontrolled Synthesis of Substituted Tetrahydrothiophenes

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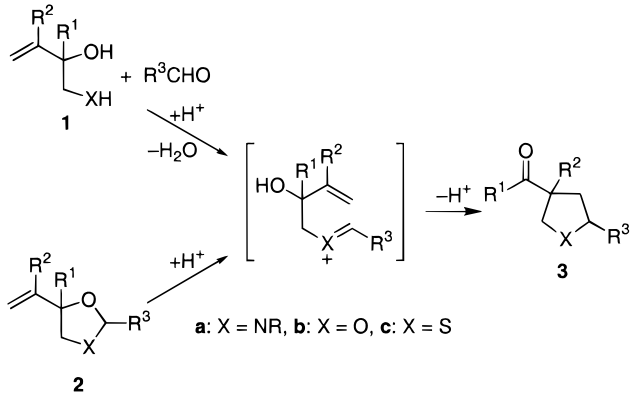
Abstract: A variety of substituted 3-acyltetrahydrothiophenes can be prepared with high stereoselectivity in 50−70% yield by acid-promoted condensation of mercapto allylic alcohols **1** (X = S) with aldehydes and ketones. The mercapto allylic alcohol must be substituted at the internal alkene carbon and the terminal alkene carbon must be unsubstituted. This new synthesis of tetrahydrothiophenes will be most useful for preparing 3-acyltetrahydrothiophenes having cis side chains at C2 and C5. The complete preservation of enantiomeric purity in the conversion of (4*R*)-**9** to tetrahydrothiophene **22** is consistent with a cyclization-pinacol pathway (**24** → **25** → **26** → **27**, Scheme 8).

Introduction

The development of versatile methods for forming carbon−carbon bonds under mild conditions is a central objective of synthetic organic chemistry. Previous investigations in our laboratories have shown that five-membered nitrogen and oxygen heterocycles **3a** and **3b** can be prepared with high stereoselectivity by acid-catalyzed condensations of allylic alcohols **1a** or **1b** with carbonyl compounds, or by rearrangements of 5-alkenyl oxazolidines **2a** or 4-alkenyldioxolanes **2b** (Scheme 1).[1] This pyrrolidine synthesis (X = NR), often termed the aza-Cope-Mannich reaction, constitutes a powerful method for assembling complex nitrogen heterocycles and has served as the cornerstone of total syntheses of a wide variety of alkaloids.[1,2] The related preparation of tetrahydrofurans also has been developed extensively,[1a,b,3] and shown to be effective at solving formidable stereochemical problems in the assembly of complex cyclic ethers.[4]

Substituted tetrahydrothiophenes find a number of uses. Biotin is an essential coenzyme, which is produced on large scale by chemical synthesis.[5] Polysubstituted tetrahydrothiophenes are reported to display various other biological activities, including leukotriene antagonism,[6a] plant growth regulation,[6b] and antioxidant activity.[6c] In addition, many tetrahydrothiophenes, or their sulfoxide or sulfonium analogues, have been prepared as mimics of natural and synthetic ligands for pharmacologically important targets.[7] The tetrahydrothiophene ring system is also found in tetronothiodin, a structurally novel cholecystokinin type-B receptor antagonist isolated from a Streptomyces strain,[8] and also has served as a platform for developing new chiral ligands for asymmetric catalysis.[9] Despite their utility, few stereocontrolled methods for forming substituted tetrahydrothiophenes have been developed.[10,11]

Scheme 1



We report herein that a variety of 3-acyltetrahydrothiophenes **3c** can be prepared by acid-promoted condensations of 1-mercapto-3-alken-2-ols **1c** and carbonyl compounds, or by rearrangement of 5-alkenyl oxathiolanes **2c** (Scheme 1). The defining feature of this new tetrahydrothiophene synthesis is use of a carbon−carbon bond-forming reaction to form the cyclic thioether product and regulate stereochemical outcome. This approach differs from most syntheses of substituted

(1) For short reviews, see: (a) Overman, L. E. *Aldrichim. Acta* **1995**, *28*, 107−120. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352−359. (c) Thebtaranonth, C.; Thebtaranonth, Y. *Cyclization Reactions*; CRC Press: Boca Raton, 1994; pp 29−35.

(2) For one illustration, see: Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776−5788.

(3) Martinet, P.; Mousset, G. *Bull. Soc. Chim. Fr.* **1970**, 1071−1076.

(4) For one illustration, see: MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391−10392.

(5) For a recent commercial synthesis, see: Imwinkelried, R. *Chimia* **1997**, *51*, 300−302.

(6) (a) Chorghade, M. S.; Gurjar, M. K.; Palakodety, R. K.; Lalitha, S. V. S.; Sadalapure, K.; Adhikari, S. S.; Murugaiah, A. M. S.; Rao, B. V.; Talukdar, A.; Talukdar, A.; Islam, A.; Hariprasad, C.; Rao, A. V. R. Patent Application WO 99-US15050, CAN 132:93203 (b) Tsygankova, V. A.; Blume, Ya. B. *Biopolim. Kletka* **1997**, *13*, 484−492. (c) Kato, T.; Tsuzuki, K. Patent Application JP 92-147881, CAN 120:106750.

(7) (a) Kim, B. M.; Bae, S. J.; Seomoon, G. *Tetrahedron Lett.* **1998**, *39*, 6921−6922. (b) Yamada, K.; Sakata, S.; Yoshimura, Y. *J. Org. Chem.* **1998**, *63*, 6891−6899. (c) Jones, M. F.; Noble, S. A.; Robertson, C. A.; Storer, R. *Tetrahedron Lett.* **1991**, *32*, 247−250. (d) Morimoto, Y.; Achiwa, K. *Chem. Pharm. Bull.* **1987**, *35*, 3845−3849. (e) Harrold, M. W.; Wallace, R. A.; Farooqui, T.; Wallace, L. J.; Uretsky, N.; Miller, D. D. *J. Med. Chem.* **1989**, *32*, 874−888. (f) Popsavin, V.; Beric, O.; Velimirovic, S.; Miljkovic, D. *J. Serb. Chem. Soc.* **1993**, *58*, 717−719. (g) Aloup, J. C.; Bouchaudon, J.; Farge, D.; James, C.; Deregnaucourt, J.; Hardy-Houis, M. *J. Med. Chem.* **1987**, *30*, 24−29.

(8) Ohtsuka, T.; Kotaki, H.; Nakayama, N.; Itezono, Y.; Shimma, N.; Kudoh, T.; Kuwahara, T.; Arisawa, M.; Yokose, K.; Seto, H. *J. Antibiot.* **1993**, *46*, 11−17.

(9) Hauptman, E.; Shapiro, R.; Marshall, W. *Organometallics* **1998**, *17*, 4976−4982.

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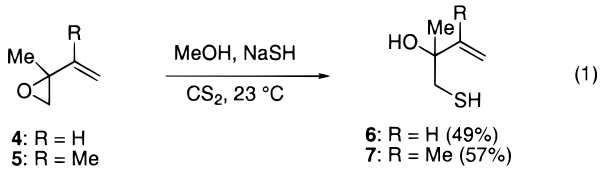
tetrahydrothiophenes that typically involve carbon−sulfur bond formation.[10,11]

Results

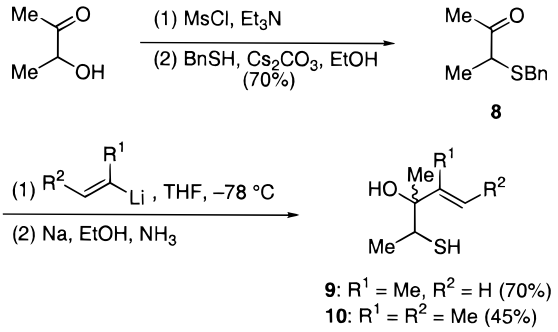
Preparation of Unsaturated Mercapto Alcohols. 1-Mercapto-3-alkene-2-ols **6** and **7** were prepared from allylic epoxides **4**[12] and **5**[13] by reaction with a slight excess of freshly prepared anhydrous sodium hydrosulfide[14] at room temperature (eq 1).



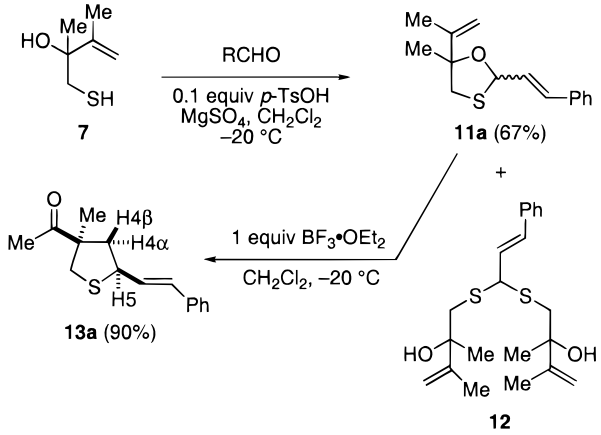
Purification of the crude product by vacuum distillation provided analytically pure **6** and **7** in ∼50% yield. The yield of **6** was somewhat reduced when commercial sodium hydrosulfide hydrate was employed. 2-Mercapto-4-alkene-3-ols **9** and **10** were synthesized from 3-hydroxy-2-butanone by activation with methanesulfonyl chloride followed by displacement of the crude mesylate with cesium benzylsulfide at room temperature (Scheme 2).[15] Addition of alkenyllithium reagents derived from 2-bromopropene or (*E*)-2-bromo-2-butene to α-mercapto ketone **8** provided the corresponding allylic alcohols. The benzyl protecting group was removed from these crude intermediates by reaction with sodium and ethanol in ammonia, and the mercapto alcohol products were purified by vacuum distillation to provide **9** and **10** in 30−50% overall yield from 3-hydroxy-2-butanone. Mercapto alkenols **9** and **10** were 2:3 mixtures of allylic alcohol epimers, which were not separated.

Formation of 3-Acyltetrahydrothiophenes by Rearrangement of 5-Alkenyl Oxathiolanes. A two-step sequence for preparing 3-acyltetrahydrothiophenes was examined initially. In early scouting experiments, mercapto allylic alcohol **7** was condensed with cinnamaldehyde to generate 5-alkenyl oxathiolane **11a** (Scheme 3). When this condensation was conducted in the presence of 0.1 equiv of *p*-toluenesulfonic acid at 0 °C in CH_2Cl_2, a ∼2:1 mixture of **11a** and dithioacetal **12** was produced. Alkenyl oxathiolane **11a**, a 2:1 mixture of C2 epimers, showed diagnostic doublets at δ 5.78 (J = 7.6 Hz) and δ 5.62 (J = 7.9 Hz) for the C2 methine hydrogens, whereas dithioacetal

Scheme 2



Scheme 3



12 exhibited a doublet (J = 7 Hz) at δ 4.4 for its methine hydrogen. In an attempt to minimize formation of **12**, the condensation was conducted at various temperatures and in the presence of several alternative acid catalysts (BF_3•OEt_2, pyridine *p*-toluenesulfonate, and oxalic acid).[16] *p*-Toluenesulfonic acid proved to be optimal, and conducting the reaction at −20 °C somewhat minimized competing formation of **12**.[17] Under these conditions,[18] **11a** was isolated in 67% yield after purification on silica gel.

Initial survey experiments showed that the rearrangement of styrenyl oxathiolane **11a** to the corresponding 3-acyltetrahydrothiophene was promoted in CH_2Cl_2 at temperatures ranging from −50 to 0 °C by addition of 1 equiv of various Lewis acids: BF_3•OEt_2, $SnCl_4$, $TiCl_4$, $MnCl_2$, $AlCl_3$, and $EtAlCl_2$. Yields were highest with BF_3•OEt_2; in the presence of this Lewis acid, **11a** was cleanly converted to crystalline 3-acyl-3-methyl-5-styrenyltetrahydrothiophene **13a** within 1 h at −20 °C. After purification on silica gel, **13a** was isolated in 90% yield. Examination of the crude product by ^{1}H NMR failed to reveal the presence of other products showing an acetyl methyl singlet in the vicinity of δ 2.0−2.4. The stereochemistry of **13a** followed unambiguously from large reciprocal ^{1}H NMR nOe enhancements observed between the C3-Me, H4α and H5. When Lewis acids other than BF_3•OEt_2 were employed, the yield of **13a** was compromised by competing fragmentation of oxathiolane **11a** to regenerate *trans*-cinnamaldehyde. For example, when **11a** was exposed to 1 equiv of $TiCl_4$ in CH_2Cl_2 at −20 °C, acyltetrahydrothiophene **13a** and *trans*-cinnamaldehyde were isolated in yields of 65% and 18%, respectively.

(10) (a) For an early review, see: Wolf, E.; Folkers, K. *Org. React.* **1951**, *6*, 410−468. For representative recent syntheses, see: (b) Linderman, R. J.; Cutshall, N. S.; Becicka, B. T. *Tetrahedron Lett.* **1994**, *35*, 6639−6642. (c) Eames, J.; Kuhnert, N.; Jones, R. V. H.; Warren, S. *Tetrahedron Lett.* **1998**, *39*, 1247−1250. (d) Vlattas, I.; Dellureficio, J.; Cohen, D. S.; Lee, W.; Clarke, F.; Dotson, R.; Mathis, J.; Zoganas, H. *Bioorg., Med. Chem. Lett.* **1994**, *4*, 2067−2072. (e) Brånalt, J.; Kvarnström, I.; Svensson, C. T.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1994**, *59*, 4430−4432. (f) Uenishi, J.; Motoyama, M.; Takahashi, K. *Tetrahedron: Asymmetry* **1994**, *5*, 101−110. (g) Jones, M. F.; Noble, S. A.; Robertson, C. A.; Store, R. *Tetrahedron Lett.* **1991**, *32*, 247−250. (h) Dyson, M. R.; Coe, P. L.; Walker, R. T. *J. Chem. Soc., Chem. Commun.* **1991**, 741−742. (i) Bredenkamp, M. W.; Holzapfel, C. W.; Swanepoel, A. D. *Tetrahedron Lett.* **1990**, *31*, 2759−2762.

(11) Tetrahydrothiophenes have been made by C−C bond-forming 1,3-dipolar cycloadditions of thiocarbonyl ylides. For representative examples, see: (a) Karlsson, S.; Hogberg, H.-E. *Org. Lett.* **1999**, *1*, 1667−1669. (b) Terao, Y.; Aono, M.; Achiwa, K. *Heterocycles* **1986**, *24*, 1571−1574. (c) Hojo, M.; Ohkuma, M.; Hosomi, A. *Chem. Lett.* **1992**, *6*, 1073−1076. (d) Aono, M.; Terao, Y.; Achiwa, K. *Heterocycles* **1995**, *40*, 249−260. (e) Aono, M.; Terao, Y.; Achiwa, K. *Heterocycles* **1986**, *24*, 313−315.

(12) (a) Johnston, B. D.; Oehlschlager, A. C. *Can. J. Chem.* **1984**, *62*, 2148−2154. (b) Overman, L. E.; Kakimoto, M.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622−6629.

(13) Annis, G. D.; Ley, S. V.; Self, C. R.; Sivaramakrishnan, R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 270−277.

(14) Eibeck, R. E. *Inorg. Synth.* **1963**, *7*, 128−131.

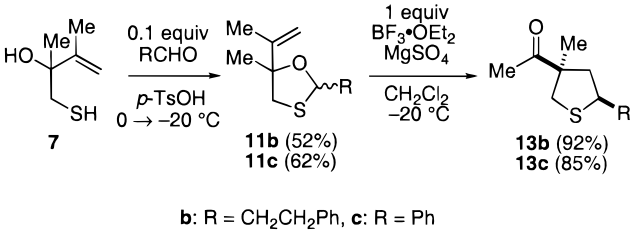
(15) Stritjtveen, B.; Kellogg, R. M. *J. Org. Chem.* **1986**, *51*, 3664−3671.

(16) Facile rearrangement of **11a** to acyltetrahydrothiophene **13a** limited possible condensation conditions.

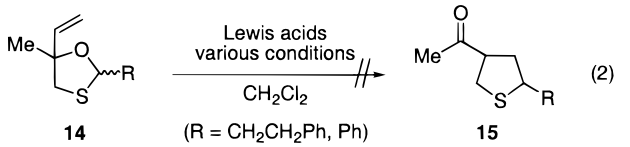
(17) Under no conditions examined was competing formation of **12** minimized significantly.

(18) Small amounts (∼5%) of acyltetrahydrothiophenes were formed under these conditions.

Scheme 4



Qualitatively similar results were observed with alkenyl oxathiolanes **11b** and **11c**, which were derived from representative aliphatic and aromatic aldehydes (Scheme 4). Rearrangement of these intermediates with 1 equiv of $BF_3{\cdot}OEt_2$ and 2 equiv of $MgSO_4$ at −20 °C in CH_2Cl_2 provided acetyltetrahydrothiophenes **13b** and **13c** in high yields. In marked contrast, no acyltetrahydrothiophene products were observed when 5-vinyloxathiolanes **14** were exposed to various Lewis acids under a variety of reaction conditions (eq 2).[19] This latter result shows

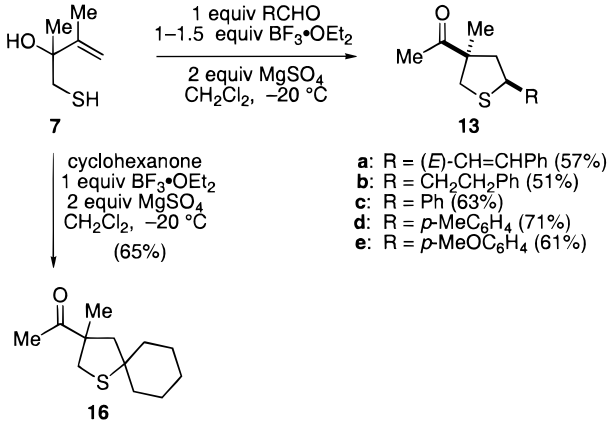


that this tetrahydrothiophene synthesis is limited to precursors having an alkene more nucleophilic than a terminal vinyl group.

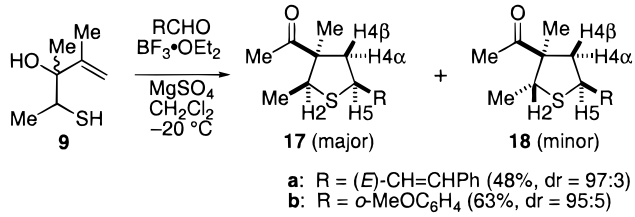
Direct Formation of 3-Acyltetrahydrothiophenes by Condensation of Aldehydes and Unsaturated Mercapto Alcohols. We soon discovered that 3-acyltetrahydrothiophenes could be prepared more conveniently by direct condensation of mercapto alkenols with aldehydes and ketones. As summarized in Scheme 5, condensation of **7** with 1 equiv of a representative set of aliphatic, α,*β*-unsaturated and aromatic aldehydes in the presence of 1 equiv of $BF_3{\cdot}OEt_2$ and 2 equiv of $MgSO_4$ at −20 °C in CH_2Cl_2 provided the 3-acetyl-3-methyl-5-substituted tetrahydrothiophenes **13a**−**e** in 51−71% yields. When these reactions were monitored by TLC, the oxathiolane was detected as an intermediate. As in the earlier rearrangements of related oxathiolanes, only a single stereoisomer of **13**, that having the 5-substituent and the acetyl groups cis, was isolated. The yield of **13b**, formed from the saturated aliphatic aldehyde hydrocinnamaldehyde, was improved by employing 1.5 equiv of $BF_3{\cdot}OEt_2$. That this tetrahydrothiophene synthesis is not limited to aldehydes was shown by formation of 1-thiaspiro[4.5]decane **16** in 65% yield from similar condensation of **7** and cyclohexanone. When the reaction of **7** and *trans*-cinnamaldehyde was attempted in the presence of 1 equiv of the proton-selective base 2,6-di-*tert*-butyl-4-methylpyridine,[20] **13a** was not detected after 12 h. This experiment suggests that a complex protic acid formed by the reaction of $BF_3{\cdot}OEt_2$ with water, which is a byproduct of the reaction, is the acid promoter for the reaction.

To pursue preparation of more highly substituted tetrahydrothiophenes, unsaturated mercapto alcohol **9** (a 3:2 mixture of epimers) was condensed with two representative aldehydes (Scheme 6). Reaction of **9** with *trans*-cinnamaldehyde under

Scheme 5

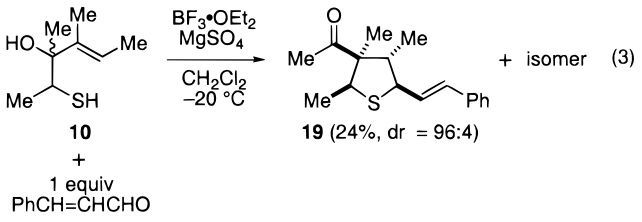


Scheme 6



standard conditions ($BF_3{\cdot}OEt_2$ and 2 equiv of $MgSO_4$ at −20 °C) provided trisubstituted tetrahydrothiophenes **17a** and **18a** in a 97:3 ratio and 48% combined yield. The stereochemistry of the major stereoisomer **17a** was secured by ^{1}H NMR nOe experiments. Particularly diagnostic were large enhancements observed for H2, H4α, and H5 upon irradiation of the C3 methyl singlet at δ 1.45, and for H4*β* upon irradiation of the C2 methyl doublet at δ 1.24. The minor diastereoisomer **18a**, which we assign as the C2 epimer of **17a**, showed diagnostic large nOe enhancements between the C2 and C3 methyl groups and no detectable nOe between H2 and the C3 methyl group. In similar fashion, acid-promoted condensation of mercapto alcohol **9** with anisaldehyde delivered **17b** and **18b** in a 95:5 ratio and 63% combined yield.

Our attempts to extend this synthesis to preparation of tetrahydrothiophenes containing substituents at each ring carbon met with limited success. Thus, reaction of mercapto alkenol **10** (a 3:2 mixture of epimers) with *trans*-cinnamaldehyde under standard conditions proceeded in low yield to give two acyltetrahydrothiophene stereoisomers in a 96:4 ratio (eq 3).



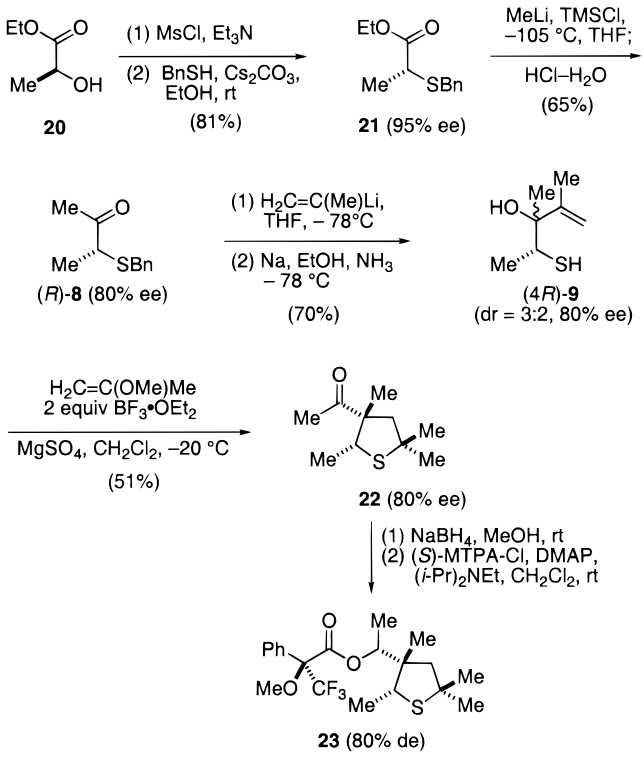
^{1}H-nOe studies were consistent with the major stereoisomer **19** being the product that would arise from incorporating the trisubstituted alkene in a suprafacial sense.

Preparation of Enantioenriched 3-Acyltetrahydrothiophenes. To pursue application of this chemistry to enantioselective synthesis of tetrahydrothiophenes, as well as probe the mechanism of the condensation rearrangement, (4*R*)-**9** was prepared as summarized in Scheme 7. Conversion of (*S*)-(−)-

(19) The following Lewis acids and reaction temperatures were surveyed in CH_2Cl_2 for rearrangement of **14** (R = CH_2CH_2Ph): $BF_3{\cdot}OEt_2$ (−50, −20 and 23 °C), $SnCl_4$ (−95, −50 and −20 °C), Me_2AlCl (−20 and 23 °C), Et_2AlCl (−25 °C), $EtAlCl_2$ (−25 °C), and *p*-toluenesulfonic acid (23 °C). No reaction was observed with Me_2AlCl at −20 °C or Et_2AlCl at −25 °C. Under the other conditions, hydrocinnamaldehyde was the major product produced. No singlets in the ^{1}H NMR spectra of the crude reaction product attributable to an acetyl methyl group were seen.

(20) Brown, H. C.; Kanner, B. *J. Am. Chem. Soc.* **1966**, *88*, 986−987.

Scheme 7



ethyl lactate (**20**) to its mesylate derivative and displacement of this intermediate with cesium benzylsulfide gave α-thioester **21** in high enantiopurity.[15,21] Reaction of **21** with an excess of methyllithium in the presence of trimethylsilyl chloride at −105 °C, following a procedure developed by us earlier for a related lactate-derived silyl ether,[22] provided (*R*)-**8** in 65% yield. Due to the acidity of the methine hydrogen α to sulfur, racemization of **8** under these conditions was a serious complication. Attempts to prevent racemization by changing the order of addition of reagents, reaction temperature, and workup conditions met with limited success. Under the best conditions found, (*R*)-**8** could be generated in 80% ee.[21] Condensation of (*R*)-**8** of this enantiopurity with 2-propenyllithium at −78 °C and cleavage of the benzyl group with sodium and ethanol in liquid ammonia yielded (4*R*)-**9** as a 3:2 mixture of C3 epimers. The enantiomeric purity of this intermediate was accurately determined to be 80 ± 2% ee by conversion to the di-*p*-bromobenzoyl derivative followed by HPLC analysis using a Diacel OD-H column.

Reaction of (4*R*)-**9** with 2-methoxypropene in the presence of 2 equiv of BF_3•OEt_2 and excess $MgSO_4$ at −20 °C in CH_2Cl_2 provided one predominant acyltetrahydrothiophene product (+)-**22**, $[\alpha]_D$ +149 (*c* 1, CH_2Cl_2), in 55% yield. Reduction of (+)-**22** with $NaBH_4$ and ^1H NMR analysis of the Mosher ester **23** of the resulting major alcohol diastereomer established that there was no detectable loss of enantiomeric purity during the conversion of (4*R*)-**9** to **22**.[23] Although the absolute configuration of **22** was not established, it likely has the 2*R*,3*S* configuration as depicted in Scheme 7.

Discussion

A variety of substituted 3-acyltetrahydrothiophenes can be prepared in 50−70% yield by simple acid-promoted condensation of mercapto allylic alcohols and aldehydes and ketones. Alternatively, this tetrahydrothiophene synthesis can be accomplished by first condensing the mercapto allylic alcohol and carbonyl compound to form the corresponding 5-alkenyl oxathiolane, followed by acid-promoted rearrangement of this intermediate to the 3-acyltetrahydrothiophene. Even though the rearrangement step of this latter sequence takes place in superb yield (>85%), the overall efficiency of the two-step procedure is no higher than that realized by more convenient direct condensation of the mercapto allylic alcohol and carbonyl compound in the presence of BF_3•OEt_2. Although this synthesis of substituted tetrahydrothiophene is highly stereoselective, its scope is more limited than that of the related preparations of 3-acylpyrrolidines or 3-acyltetrahydrofurans.[1] The alkene component must be substituted at the internal alkene carbon, and tetrahydrothiophene formation takes place in good yield only when the terminal alkene carbon is unsubstituted. As a result, the tetrahydrothiophene synthesis reported here will be most useful for preparing 3-acyltetrahydrothiophenes having cis side chains at C2 and C5. Since the stereochemistry of the side chains evolves from a single stereocenter of the mercapto allylic alcohol precursor, this reaction should be of particular utility for enantioselective construction of substituted tetrahydrothiophenes.

5-Alkenyl oxathiolanes are undoubtedly intermediates in the direct condensation of mercapto allylic alcohols and carbonyl compounds to form 3-acyltetrahydrothiophenes. Two plausible mechanisms for evolution of a 5-alkenyl oxathiolanes to a 3-acyltetrahydrothiophene are thionium ion-alkene cyclization[24] followed by pinacol rearrangement, or 2-thionia[3,3]-sigmatropic rearrangement[25−27] followed by aldol-type condensation (Scheme 8). As we have discussed previously in our analysis of related transformations in the nitrogen and oxygen series,[28] a cyclization-pinacol sequence would proceed with retention of the configuration at the homoallylic stereogenic center.[29] In contrast, a [3,3] sigmatropic rearrangement-aldol process would yield racemic products, if α-thiocarbenium ion **28** contained no stereogenic centers and the barrier for aldol cyclization were higher than that of C−C single bond rotation.[30] The complete preservation of enantiomeric purity in the conversion of (4*R*)-**9** to **22** (Scheme 7) is consistent with a cyclization-pinacol pathway. As we saw in the related synthesis of 3-acyltetrahydrofurans, the rate of the cyclization step appears to be critical in the success of this tetrahydrothiophene synthesis.[31] When the

(21) The enantiomeric excess of this intermediate was determined by ^1H NMR analysis in the presence of Eu(hfc)$_3$.

(22) Overman, L. E.; Rishton, G. M. *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. IX; pp 139−142.

(23) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

(24) For a review of carbon−carbon bond forming reactions of α-thio carbocations, see: Ishibashi, H.; Ikeda, M. *Rev. Heteroatom. Chem.* **1992**, *7*, 191−213.

(25) To the best of our knowledge, this hetero-3,3-sigmatropic rearrangement has not been described. The related variant in the nitrogen series (2-azonia-[3,3]-sigmatropic rearrangement) is well-established,[26] and the analogous rearrangement in the oxygen series has been proposed.[27]

(26) For reviews, see: (a) Heimgartner, H.; Hansen, H.-J.; Schmid, H. In *Iminium Salts in Organic Chemistry*; Böhme, H., Viehe, H. G., Eds.; Wiley: New York, 1979; Part 2, pp 655−732. (b) Blechert, S. *Synthesis* **1989**, *2*, 71−82.

(27) Lolkema, L. D. M.; Semeyn, C.; Ashek, L.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7129−7140.

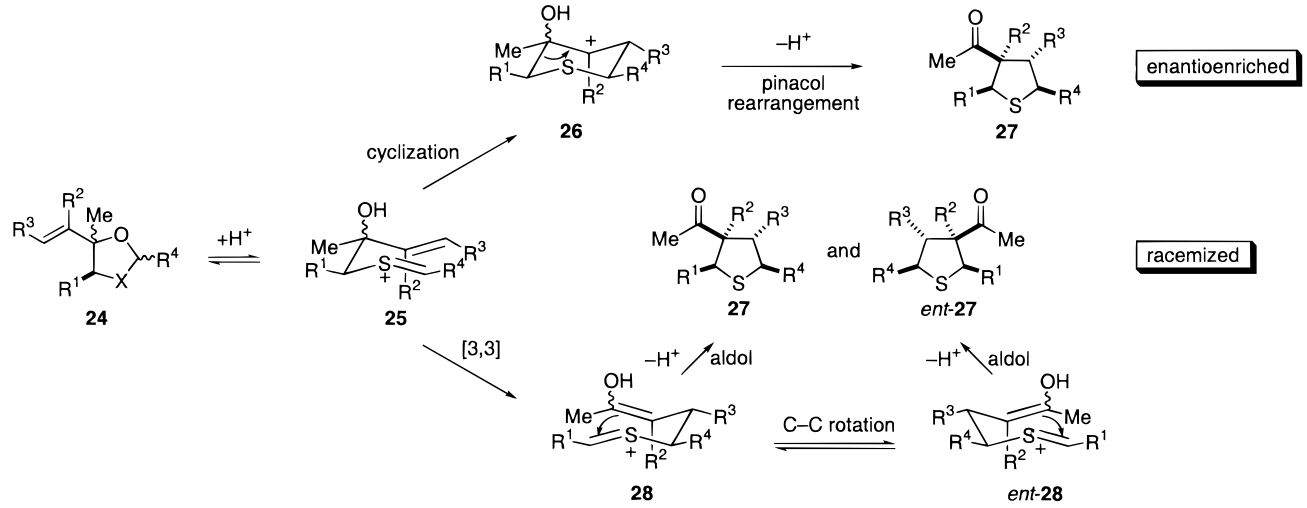
(28) Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4329−4335. (b) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354−5365.

(29) For reviews of pinacol rearrangements, see: (a) Bartok, M.; Molnar, A. In *Chemistry of Ethers, Crown Ethers, Hydroxyl Compounds and Their Sulfur Analogues*; Patai, S., Ed.; New York, 1980; Part 2, pp 722−732. (b) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 721−732.

(30) This is a reasonable assumption considering the low barriers of C−C single bond rotations: Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; American Chemical Society; Washington, DC, 1965; Chapters 2 and 3.

(31) For kinetic studies of the addition of stabilized carbenium ions to alkenes, see: Mayr, H. *Angew. Chem.* **1990**, *29*, 1371−1384.

Scheme 8



internal alkene carbon is unsubstituted, thionium ion-alkene cyclization would lead to a relatively unstable secondary carbenium ion intermediate **26** (R^2 = H). Apparently in this case, **24** or its precursor mercapto allylic alcohol decomposes more rapidly than **25** cyclizes to **26**, most likely by ionization of the tertiary allylic C−O bond.

The high stereoselectivity observed in this tetrahydrothiophene synthesis can be rationalized as follows.The lowest energy chair cyclization conformer derived by ring opening of **24** should be **25** having the thionium ion in a more stable *E* configuration[32] and the R^1 substituent quasiequatorial. This preference could manifest irrespective of the relative stereochemistry of the alcohol stereocenter. Pinacol rearrangement of **26** would then yield acyltetrahydrothiophene **27**. When R^1 and R^4 are both nonhydrogen, the relative rates of pinacol rearrangement and conformational dynamics of **26** would be expected not to affect stereoselection, because chair tetrahydrothiopyranyl carbenium ion conformer **26** would be considerably more stable than the alternative chair conformer. More interesting is the high stereoselectivity observed in the reactions reported in Schemes 3−5 where R^1 and R^3 are both hydrogen. In these cases, the two chair conformers of a 4-thiatetrahydropyranyl cation intermediate would be more similar in energy. The high stereoselectivity observed in these transformations is consistent with pinacol rearrangement of **26** occurring more rapidly than conformational interconversion of this intermediate.[33]

Experimental Section[34,35,36]

General Procedure for Preparing 3-Acyltetrahydrothiophenes by Direct Condensation of Mercapto Allylic Alcohols and Aldehydes or Ketones. **Preparation of (±)-1-(3-Methyl-1-thiaspiro[4.5]dec-3-yl)ethanone (16).** Boron trifluoride etherate (190 μL, 1.5 mmol) was added dropwise to a stirring mixture of **7** (99 mg, 0.75 mmol), cyclohexanone (74 mg, 0.75 mmol), $MgSO_4$ (200 mg), and CH_2Cl_2 (15 mL) at −20 °C. The resulting mixture was maintained at −20 °C for 28 h and then poured into saturated aqueous NH_4Cl (30 mL). This mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL) and stirred overnight with aqueous $NaHSO_3$ (20 mL). The organic phase was separated, dried ($MgSO_4$), and concentrated, and the residue was purified by flash chromatography (95:5 hexanes−EtOAc) to give 102 mg (64%) of **16** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.31 (d, J = 11.7 Hz, 1H), 2.69 (d, J = 11.7 Hz, 1H), 2.51 (d, J = 13.3 Hz, 1H), 2.24 (s, 3H), 1.79−1.20 (m, 10H), 1.61 (d, J = 13.3 Hz, 1H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.8, 60.3, 59.1, 52.4, 42.1, 41.1, 39.3, 25.2, 25.1, 25.0, 24.5, 24.4; IR (KBr) 1708 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 212.1234 (212.1234 calcd for $C_{12}H_{20}OS$, M). Anal. Calcd for $C_{12}H_{20}OS$: C, 67.87; H, 9.49; S, 15.10. Found: C, 68.15; H, 9.55; S, 14.83.

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Supporting Information Available: Experimental details and characterization data for new compounds not reported in the Experimental Section (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) For examples of other reactions where the *E* stereoisomer of α-thio carbenium ions are suggested to react preferentially, see: (a) Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 7199−7200. (b) Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 5966−5977.

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(34) Boron trifluoride etherate was distilled from CaH_2 at atmospheric pressure. Molarities indicated for organolithium reagents were established by double titration using the Gilman procedure.[35] ^{1}H NMR and ^{13}C NMR were measured at 500 MHz with Bruker Omega 500 and Bruker GN-500 spectrometers. Other general experimental details were recently described.[36]

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