102734-03-2; **4a**-3-methyl-1,3-pentadiene reaction product (*o*, *endo*-isomer), 102648-99-7; **4a**-3-methyl-1,3-pentadiene reaction product (*o*, *exo*-isomer), 102734-04-3; **4a**-3-methyl-1,3-pentaidene reaction product (*m*-isomer), 102649-00-3; cyclopentadiene, 542-92-7; isoprene, 78-79-5; *trans*-piperylene, 2004-70-8; 3-methyl-1,3-pentadiene, 4549-74-0.

Supplementary Material Available: Spectroscopic data for compounds in Table I (13 pages). Ordering information is given on any current masthead page.

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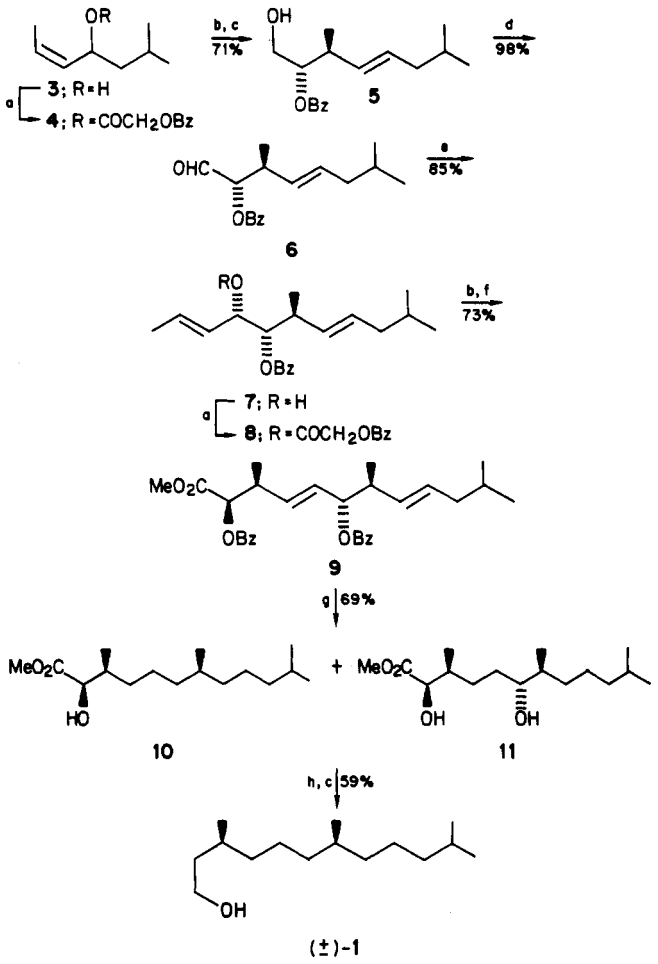
An Effective Strategy for Acyclic Synthesis via Iterative Rearrangement of Allylic Glycolates. Synthesis of a Pine Sawfly Pheromone

Summary: The stereocontrolled preparation of extended acyclic systems using the iterative enolate Claisen rearrangement of allylic glycolates is described. This strategy has been demonstrated in the stereospecific synthesis of a pine sawfly pheromone.

Sir: The development of stereoselective techniques for use in the linear elaboration of complex acyclic targets has been a focus of considerable attention in recent years.[1-4] While linear construction of extended acyclic systems offers unique synthetic advantages, this strategy places rigorous demands on the complement of reactions employed in the homologation of a nascent acyclic intermediate. Since stereochemical heterogeneity at any stage of a linear sequence will be propagated in subsequent transformations, the degree of stereocontrol required of each reaction in the sequence is high.

The Claisen and related [3,3] and [2,3] sigmatropic rearrangements occupy a prominent position among the procedures which can effectively homologate an existing acyclic intermediate with stereochemical induction at newly formed, remote chiral centers.[1,3] A powerful and potentially general strategy for acyclic synthesis is one in which the acyclic framework is developed by an iterative series consisting of sigmatropic rearrangement followed by nucleophilic homologation of the rearrangement product

Scheme I[a]



[a] Reagents: (a) $BzOCH_2COCl$, pyridine; (b) LDA, Me_3SiCl, THF, 78–0 °C; (c) $LiAlH_4$; (d) $(COCl)_2$, Me_2SO, NEt_3; (e) $((E)$-1-propenyl$)_2CuLi$, Et_2O, −78 °C, $MgBr_2{\cdot}Et_2O$; (f) aqueous NH_4Cl, CH_2N_2, Et_2O; (g) Pd–C, H_2, MeOH; (h) MsCl, pyridine.

to give a new substrate for rearrangement.[4] Practical realization of this approach has been complicated by loss of stereochemical fidelity during either the rearrangement or homologation[5] step. Recently, we and others have investigated the enolate Claisen rearrangement of allylic glycolates and demonstrated the potential of this system as an entry to functionalized acyclic intermediates.[6] The high diastereoselectivity exhibited in the rearrangement of allylic glycolates and the potential of the resulting α-alkoxy esters for further stereoselective homologation, via chelation-controlled addition of vinyl nucleophiles, suggested to us that these substrates are uniquely suited for incorporation into an iterative sigmatropic sequence.

The effectiveness of the glycolate Claisen sequence as an iterative vehicle for acyclic homologation is demon-

(1) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.
(2) (a) Lipshutz, B. H.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 1147. (b) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *Ibid.* **1982**, *47*, 1373. (c) Adams, C. E. Walker, F. J.; Sharpless, K. B. *Ibid.* **1985**, *50*, 420. (d) Nicolaou, K. C.; Uenishi, J. *J. Chem. Soc., Chem. Commun.* **1982**, 1292. (e) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.
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(5) An alternative solution to the problem of stereoselective homologation in an iterative sigmatropic sequence is represented by new procedures for asymmetric reduction of acetylenic ketones. See: (a) Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1985**, *26*, 5021. (b) Chan, K.-K.; Saucy, G. *J. Org. Chem.* **1977**, *42*, 3828. (c) Cohen, N.; Lopresti, R. J.; Neukom, C.; Saucy, G. *Ibid.* **1980**, *45*, 582. (d) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J.-S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371.
(6) (a) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3941. (b) Sato, T.; Tajima, K.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 729. (c) Kallmerten, J.; Gould, T. J. *Tetrahedron Lett.* **1983**, *24*, 5177. (d) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221. (e) Fujisawa, T.; Kohama, H.; Tajima, K.; Sato, T. *Ibid.* **1984**, *49*, 5155. (f) Kallmerten, J.; Gould, T. J. *Ibid.* **1985**, *50*, 1128. (g) Kallmerten, J.; Gould, T. J. *Ibid.* **1986**, *51*, 1152.

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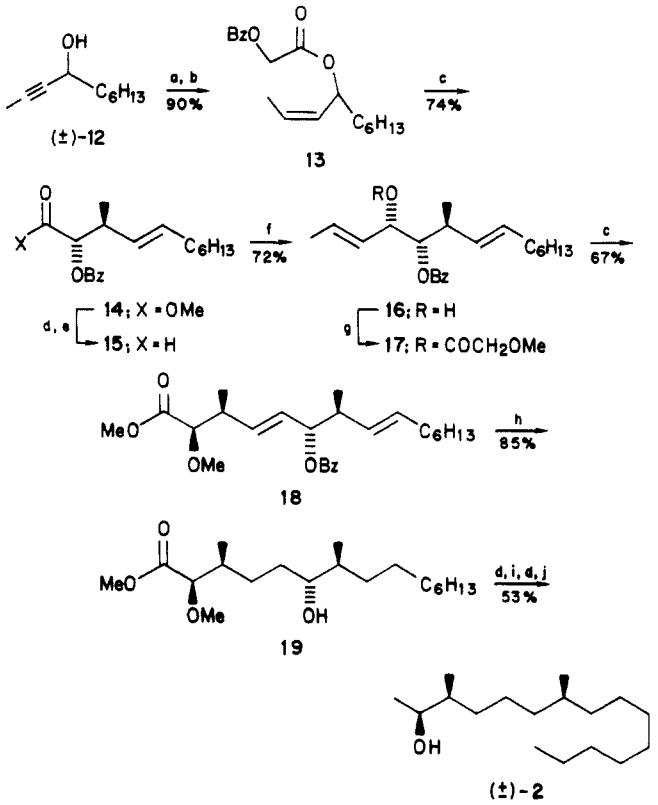
Scheme II[a]



[a] Reagents: (a) Lindlar catalyst, EtOAc, H_2; (b) $BzCH_2COCl$, pyridine; (c) LDA, Me_3SiCl, THF, −78–0 °C, aqueous NH_4Cl, then CH_2N_2, Et_2O; (d) $LiAlH_4$, Et_2O, 0 °C; (e) $(COCl)_2$, Me_2SO, NEt_3; (f) $MgBr_2$–Et_2O, ((*E*)-1-propenyl)Li; (g) $MeOCH_2COCl$, pyridine; (h) Pd–C, H_2, EtOH; (i) TsCl, pyridine, DMAP; (j) Me_3SiI.

strated by a stereoselective synthesis of the tocopherol side chain 1.[7] Acylation of racemic **3**,[4b] previously employed by the Roche group in their classic iterative route to 1,[4a–c] followed by enolate Claisen rearrangement and in situ reduction of the resulting silyl ester afforded alcohol **5** as a single product.[8,9] Completion of the first iterative cycle was accomplished by Swern oxidation of **5** to α-alkoxy aldehyde **6** and chelation-directed addition[3g,10] of (*E*)-propenyl cuprate reagent to give alcohol **7** (>50:1 with minor diastereomer). Trace amounts of the minor diastereomer were conveniently removed by flash chromatography (Scheme I).

Acylation of **7** provided the required substrate for a second sigmatropic event. Enolate Claisen rearrangement of **8** gave ester **9**; we were unable to detect significant amounts of any stereoisomer of **9** by HPLC and ^{13}C NMR analysis of the reaction mixture. The relative stereochemistry introduced by this second rearrangement event was unequivocally established by the conversion of **9** to the tocopherol side chain. Thus, hydrogenation[11] of **9** afforded a 1.4:1 mixture of diol **11** and the hydrogenolysis product **10**. While this mixture could be separated and the individual alcohols carried on to **1**, it proved convenient to mesylate the crude mixture of **10** and **11** and subject the resulting mesylates to reduction by $LiAlH_4$, affording (±)-**1** in 41% yield from ester **9**.[12]

Application of the serial glycolate protocol to the synthesis of complex acyclic targets of polyketide origin required that we demonstrate our ability to retain differentiated oxygen substituents following completion of the iterative cycle. Toward this end we have completed a synthesis of alcohol **2**, a pheromone of the pine sawfly.[13,14] Enolate Claisen rearrangement of racemic **13** as described above yielded (Scheme II) a single product, ester **14**.[8,9] Reduction and oxidation gave aldehyde **15**; upon treatment with (*E*)-propenyl-Grignard reagent[10] a 14:1 mixture of alcohol **16** and its epimer was obtained and separated by flash chromatography. Acylation of **16** and enolate Claisen rearrangement afforded ester **18** which was hydrogenated to give alcohol **19**, accompanied by traces (<2%) of the corresponding hydrogenolysis product. Alcohol **19** was converted to the desired **2** by a four-step sequence consisting of (1) $LiAlH_4$ reduction, (2) tosylation, (3) reduction of the resulting bis-tosylate with $LiAlH_4$, (4) cleavage of the methyl ether using Me_3SiI. The resulting **2** was stereochemically homogeneous to our limits of detection by capillary GC and 126-MHz ^{13}C NMR and consistent in all respects with literature data for this compound.[13,14]

The close resemblance of intermediates **9** and **18** to structural units of the ansa macrolides and other natural products of polyketide and isoprenyl origin suggests that the serial rearrangement of allylic glycolates will provide an expeditious and highly stereoselective entry to these systems. We note that four of the eight diastereomeric arrays possible from two iterative cycles are accessible by variation of allylic olefin geometry. The remaining diastereomers could be addressed by a minor modification of the iterative sequence (i.e., oxidation of allylic alcohols **7** and **16** and chelation-controlled reduction[6e,15]), making this strategy a versatile entry to extended acyclic systems. We anticipate that established procedures for hydroxyl[16] and

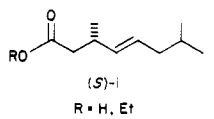
(7) For previous syntheses, see: (a) Takabe, K.; Uchiyama, Y.; Okisaka, K.; Yamada, T.; Katagiri, T.; Okazaki, T.; Oketa, Y.; Kumobayashi, H.; Akutagawa, S. *Tetrahedron Lett.* **1985**, *26*, 5153. (b) Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1984**, *106*, 5004. (c) Berube, G.; Deslongchamps, P. *Can. J. Chem.* **1984**, *62*, 1558. (d) Helmchen, G.; Schmierer, R. *Tetrahedron Lett.* **1983**, *24*, 1235. (e) Fujisawa, T.; Sato, T.; Kawara, T.; Ohashi, K. *Ibid.* **1981**, *22*, 4823. (f) Koreeda, M.; Brown, L. *J. Org. Chem.* **1983**, *48*, 2122 and references therein. See also ref 3c, 4a–c, and 5.

(8) Diastereomeric purity was determined by HPLC. Limits of detection for similar systems is 100:1.

(9) New compounds were characterized by IR, ^1H (500 MHz), and ^{13}C (126 MHz) NMR, GC, or HPLC and elemental analysis.

(10) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031. In our hands, use of vinyl cuprates is significantly more selective than the corresponding Grignard reagents.

(11) In their original synthesis of the tocopherol side chain,[4b] the Roche workers observed some epimerization of the allylic methyl substituent when **i** was subjected to hydrogenation using palladium on carbon as catalyst. In the present study, we observed no evidence of epimerization during hydrogenation of **9** (based on 500-MHz proton NMR of **10** and **11**). In contrast, hydrogenation of **18** in methanol resulted in significant epimerization of one (or both) allylic centers. This isomerization was eliminated when ethanol was employed as solvent for the reduction. Interestingly, hydrogenolysis of the allylic ether in **18** was also suppressed under these conditions.



(*S*)-**i**

R = H, Et

(12) ^{13}C NMR analysis of synthetic **1** revealed no trace of the diastereomer. Analysis of an authentic mixture of **1** and its diastereomer (prepared by hydrogenation of farnesol) by 62-MHz ^{13}C NMR clearly reveals individual resonances; see ref 7f.

(13) Jewett, D. M.; Matsumura, F.; Coppel, H. C. *Science (Washington, D.C.)* **1976**, *192*, 51.

(14) For a review of recent syntheses of **2**, see: Mori, K. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley-Interscience: New York, 1984; Vol. 4, p 123.

(15) Takahashi, T.; Miyazawa, M.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 5139.

carboxyl-assisted[17] transformation of acyclic olefins will facilitate further functionalization of intermediates such as **18**, enabling us to rapidly develop the polyketide-derived acyclic systems of biologically important macrolides. Efforts to further define the scope of the iterative scheme and applications of this strategy to the synthesis of complex, naturally occurring acyclic systems are in progress.

Acknowledgment. We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work. High-field NMR spectra were obtained at the NIH Research Resource facility (RR-01317) in this department.

Registry No. (±)-**1**, 87247-04-9; (±)-**2**, 102680-34-2; (±)-**3**, 64727-70-4; (±)-**4**, 102616-10-4; (±)-**5**, 102616-11-5; (±)-**6**, 102616-12-6; (±)-**7**, 102616-13-7; (±)-**8**, 102616-14-8; (±)-**9**, 102616-15-9; (±)-**10**, 102616-16-0; (±)-**11**, 102616-17-1; (±)-**12**, 102616-18-2; (±)-**13**, 102616-19-3; (±)-**14**, 102616-20-6; (±)-**15**, 102616-21-7; (±)-**16**, 102616-22-8; (±)-**17**, 102616-23-9; (±)-**18**, 102616-24-0; (±)-**19**, 102616-25-1; $PhCH_2OCH_2C(O)Cl$, 19810-31-2; $((E)\text{-}CH_3CH{=}CH)_2CuLi$, 33462-38-3; $MeOCH_2C(O)Cl$, 38870-89-2.

(16) (a) Rositer, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733. (b) Bartlett, P. A.; Jernstedt, K. K. *J. Am. Chem. Soc.* **1977**, *99*, 4829. (c) Still, W. C.; Darst, K. P. *Ibid.* **1980**, *102*, 7385. (d) Evans, D. A.; Morrissey, M. M.; Dow, R. L. *Tetrahedron Lett.* **1985**, *26*, 6005. (e) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259. (f) Cha, J. K.; Christ, W. J.; Kishi, Y. *Ibid.* **1983**, *105*, 3943, 3947. (g) Stork, G.; Kahn, M. *Ibid.* **1983**, *105*, 3951. (h) Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Ibid.* **1978**, *100*, 2741.

(17) See: Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 411.

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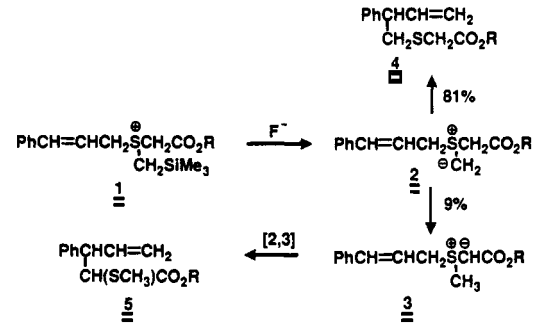
[2,3]-Sigmatropic Rearrangement of Sulfur Ylides Derived from Trimethylsilyl Sulfonium Salts

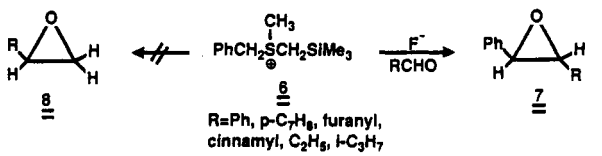
Summary: The [2,3]-sigmatropic rearrangement of sulfur ylides derived via the desilylation of several α-trimethylsilyl benzylsulfonium salts has been studied. The initially formed ylide was found to rapidly equilibrate with the thermodynamically more stable ylide. In the absence of trapping reagents, a Sommelet–Hauser-type rearrangement occurs.

Sir: Desilylation of α-trimethylsilyl onium salts by fluoride ion has been widely utilized in recent years as a convenient method for preparing nitrogen and sulfur ylides.[1-10] Relatively little work has been done, however, using the trimethylsilyl functionality as a leaving group in the generation of ylides for [2,3]-sigmatropic rearrangements.[1,2,11-13] In searching for new ways to utilize sulfur ylides in organic synthesis, we investigated the fluoride-induced desilylation reaction of several benzyl α-trimethylsilyl sulfonium salts. We report here the results of this study.

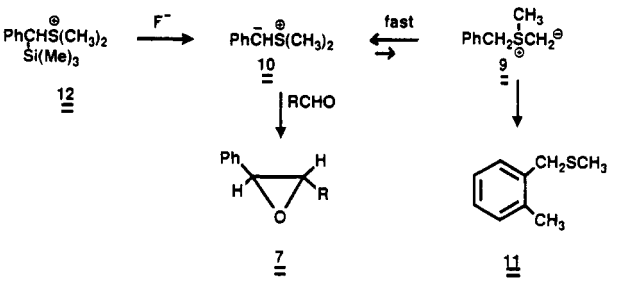
In 1979, Vedejs and Martinez reported that the fluoride-induced desilylation of **1** afforded 81% of the 2,3-sigmatropic shift product derived from the kinetic ylide **2** even though a more stabilized ester ylide **3** could have been produced by proton transfer.[1] Thus, we were somewhat



surprised to find that treatment of sulfonium salt **6** with fluoride ion in the presence of an aldehyde produced only the disubstituted trans epoxide **7**.[14] No signs of the monosubstituted epoxide **8** could be found in the crude reaction mixture. Evidently, the initially formed sulfur ylide



9 rapidly rearranged to the more stable ylide **10**, which reacted with the aldehyde to give the observed epoxide. This result contrasts with Vedejs' earlier observations wherein the predominant product is that obtained from the thermodynamically less stable ylide.[1] Attempts to trap ylide **10** with ketones or imines failed. The only material isolated in high yield corresponded to the [2,3]-sigmatropic rearranged product **11**. These results are understandable if one assumes that the initially formed ylide **9** undergoes a proton shift to give **10** at a faster rate than addition to the aldehyde carbonyl group.



The fact that *o*-[(methylthio)methyl]toluene (**11**) is isolated in the absence of a trapping agent is of considerable mechanistic interest. One possibility (path A) to account for this observation is that the thermodynamically more stable sulfur ylide **10** is in partial equilibrium with the less stable ylide **9**. In the absence of aldehyde, the small amount of **9** present in equilibrium rearranges via a [2,3]-sigmatropic shift, thereby driving the reaction to

(1) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452.
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(3) Schmidbauer, H. *Acc. Chem. Res.* **1975**, *8*, 62.
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(8) Tsuge, O.; Kanemasa, S.; Matsuda, K. *Chem. Lett.* **1985**, 1411.
(9) Achiwa, K.; Sekiya, M. *Heterocycles* **1983**, *20*, 167.
(10) Padwa, A.; Haffmanns, G.; Tomas, M. *J. Org. Chem.* **1984**, *49*, 3314.
(11) Gassman, P. G.; Miura, T. *Tetrahedron Lett.* **1981**, 4787.
(12) Sato, Y.; Sakakirbara, H. J. *J. Organomet.* **1979**, *166*, 303. Sato, Y.; Yagi, Y.; Koto, M. J. *J. Org. Chem.* **1980**, *45*, 613.
(13) Fleischmann, C.; Zbiral, E. *Tetrahedron* **1978**, *34*, 317.
(14) Yields ranged from (80–95%), and the structure of the epoxides were established by comparison with authentic samples.

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