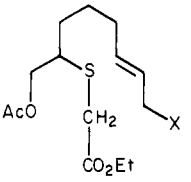
Studies in Macrolide Synthesis: Sulfur-Bridged Lactones from Ring Expansion via Intramolecular S-Alkylation

Summary: Sulfur-bridged 10- and 11-membered lactones have been prepared by [2,3] sigmatropic ring expansion methods from acyclic precursors **4**, **11**, and **18**.

Sir: Previous reports from our laboratory describe [2,3]-sigmatropic ring-expansion reactions involving intermolecular S-alkylation of cyclic α-vinyl sulfides followed by deprotonation.[1] A typical example is the hitherto unreported conversion of **1**[2] into **3** (Scheme I).

In the case of more highly functionalized systems of interest in natural product synthesis, preparation of the starting sulfur heterocycle can be tedious. We have therefore examined an alternative sequence with greater potential for convergent synthesis of complex sulfonium intermediates. The new method depends on the intramolecular S-alkylation of an allylic iodide, **4**, in the presence of base, resulting in ylide formation and rearrangement to **3**.



4, X = I
5, X = OTHP

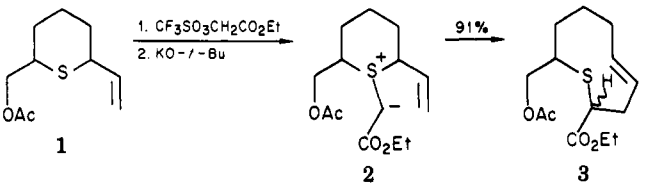
The key starting material **5** can be prepared by alkylation of $THPSCH(Li)CO_2C_2H_5$ with halide **6**[3] (Scheme II). After conversion of **7** to the acetate **8**, the STHP group is cleaved by using $Hg(OAc)_2$ followed by $NaBH_4$/ethanol. This procedure affords a mercaptan which is immediately alkylated ($BrCH_2CO_2Et/K_2CO_3/CH_3CN$) to give **5** (71%).

The transformation of tetrahydropyranyl ether **5** into iodide **4** is possible in a single step by using $(CH_3)_3SiI$.[4] The in situ method 4b (Me_3SiCl + NaI and CH_3CN, 2.1 mol/mol of **5**) proceeds at 20 °C (30 min) to give the sensitive iodide (85%). Upon being heated with K_2CO_3 in acetonitrile (2 h, reflux), the crude iodide is converted into **3**[5] in 60% overall yield based on the sequence **5** → **4** → **2** → **3**.

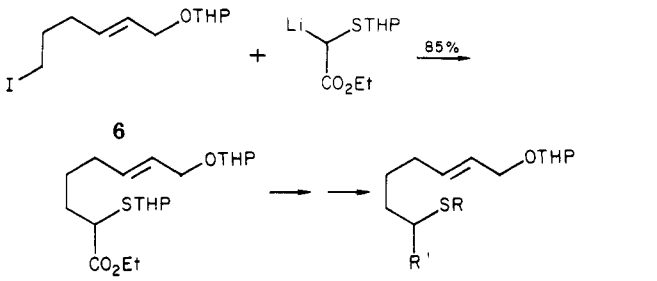
An important potential advantage of the intramolecular cyclization route to ring-expansion substrates is that the starting sulfide can be incorporated into a ring. In this case, internal S-alkylation would form a bicyclic sulfonium salt, and the [2,3] shift would produce a sulfur-bridged medium or large ring. To test this possibility, we have converted **5** into the sulfide lactone **10** (Chart I).

Lactonization of the precursor hydroxy acid (**9**, Scheme II) is surprisingly difficult. Standard methods such as simple acid catalysis (toluene, 105 °C) or EtO_2CCl/Et_3N serve only to destroy the substrate. The DCC method does work, but better results are achieved with DCC and (dimethylamino)pyridine[6] (72% for the sequence **5** → **10**). Conversion of **10** to allylic iodide **11** as before (Me_3SiCl/

Scheme I



Scheme II[a]



5, R′ = CH_2OAc; R = CH_2CO_2Et
8, R′ = CH_2OAc; R = THP
9, R′ = CH_2OH; R = CH_2CO_2H

[a] **7** → **8**: (1) $LiAlH_4$; (2) Ac_2O, Et_3N, DMAP. **8** → **5**: (1) $Hg(OAc)_2$, $NaBH_4$, EtOH; (2) $BrCH_2CO_2Et/K_2CO_3/CH_3CN$; 71% yield.

Scheme III

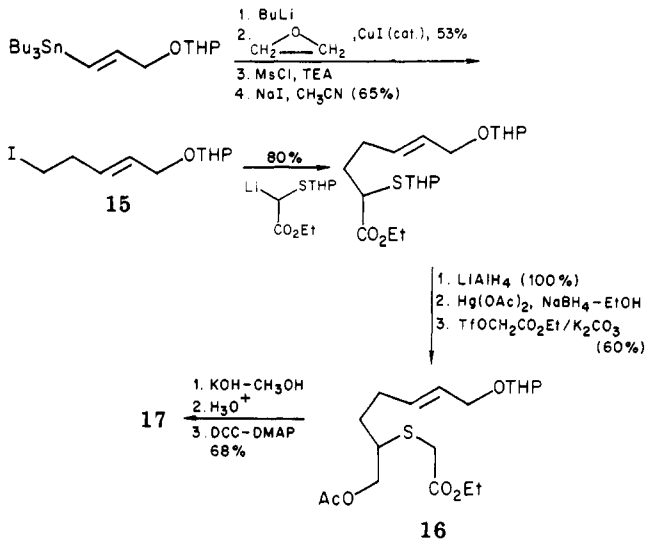
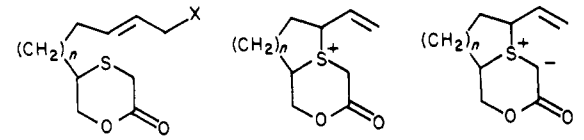


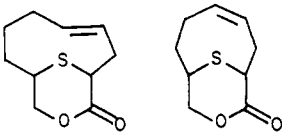
Chart I



10, n = 2; X = OTHP
11, n = 2; X = I
17, n = 1; X = OTHP
18, n = 1; X = I

12, n = 2
19, n = 1

13, n = 2
20, n = 1



14 **21**

(1) (a) Vedejs, E.; Arco, M. J.; Powell, D. W.; Renga, J. M.; Singer, S. P. *J. Org. Chem.* **1978**, *43*, 4831. (b) Vedejs, E.; Hagen, J. P.; Roach, B. L.; Spear, K. L. *Ibid.* **1978**, *43*, 1185.

(2) Prepared from the known α-vinyl-α'-carbethoxythiane[3] by ester reduction and acetylation.

(3) Vedejs, E.; Arnost, M. J.; Hagen, J. P. *J. Org. Chem.* **1979**, *44*, 3230.

(4) (a) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761. (b) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *Ibid.* **1979**, *44*, 1247.

(5) Characterization of **3**[10] (oil after preparative TLC, silica gel): IR (neat) 1730 (s), 1445 (m), 980 (m) cm^{-1}; NMR (CCl_4, major diastereomer) δ 5.7 (1 H, m), 5.2 (1 H, m), 4.1 (2 H, q, J = 7 Hz), 4.1–3.2 (3 H, m), 3.05 (1 H, dd, J = 9, 4 Hz), 3.0–1.4 (8 H, m), 2.0 (3 H, s), 1.28 (3 H, t, J = 7 Hz).

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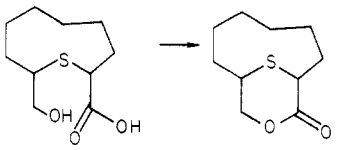
NaI–CH_3CN) followed by treatment with 2,6-lutidine (CH_3CN, reflux) affords the sulfur-bridged undecanolide **14**,[7] in 30% yield from **10** (iodide formation, cyclization to bicyclic salt **12**, rearrangement of ylide **13**). Although the yield is modest, it is nevertheless significant that bicyclic ylide **13** is capable of normal ring expansion. No products of competing Stevens rearrangement have been detected.

A closely parallel series of experiments has been performed with the sulfide lactone **17**, having one fewer methylene group in the side chain than in **10**. The acyclic precursor **16** can be prepared by the usual alkylation sequence starting from the iodide **15** (Scheme III). In this series, the yield of ring-expansion product from tetrahydropyranyl ether **17** to the sulfur-bridged decanolide **21**[8] is 33%. As in simpler, monocyclic systems, rearrangement via an ylide which incorporates a five-membered sulfur-containing ring leads to a ring-expansion product having a cis double bond.[1b] No isomeric products have been found.

The low material recovery from both of the bicyclic ylide rearrangements is probably due to the high reactivity of bridged sulfide lactones. This complication is also apparent in attempts to lactonize the monocyclic hydroxy acid **22**, available from **3** by saponification and reduction



22 **23**

with diimide. The Corey–Mukaiyama lactonization procedure[9] gives the lactone **23** under conditions of high dilution, which is identical with material prepared from **14** by diimide reduction, but the yield is only 56% after much effort. All of the classical lactonization procedures examined, including DCC/DMAP, afford only intractable materials assumed to be polyesters. Likewise, exposure of **23** to acid catalysts results in rapid degradation. The high reactivity of sulfur-bridged medium-ring lactones **14**, **21**, and **23** can be attributed to a combination of transannular effects and the inherent sensitivity of the six-membered sulfide lactone mentioned previously in connection with **10**.

We have shown that ring expansion can be achieved via monocyclic and bicyclic ylides originating from intramolecular S-alkylation. The technique has been used to prepare labile sulfur-bridged lactones **14** and **21**.[10] Subsequent publications will describe related applications for synthesis of medium-ring carbocycles.

Acknowledgment. This work was supported by a grant from the National Science Foundation (CHE-8113026).

(6) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475.

(7) Characterization of **14**[10]: mp 87–88 °C (recrystallized from ether/hexane); IR ($CDCl_3$) 1712 (s), 1440 (m), 975 (m), 962 (m) cm^{-1}; NMR ($CDCl_3$) δ 5.8 (1 H, ddd, J = 16, 11, 6 Hz), 5.15 (1 H, ddd, J = 16, 11, 4 Hz), 4.85 (1 H, dd, J = 10.5, 2 Hz), 4.44 (1 H, dd, J = 10.5, 2 Hz), 3.92 (1 H, dd, J = 4.5, 2.5 Hz), 3.25 (1 H, d, J = 12.5 Hz), 2.65 (1 H, d, J = 12 Hz), 2.46 (1 H, m), 1.76 (6 H, m).

(8) Characterization of **21**:[10] oil after preparative TLC, silica gel; IR ($CHCl_3$) 1735, 1655, 1455, 915 cm^{-1}; NMR ($CDCl_3$) δ 6.04 (dt, J = 9.5, 7.6 Hz, 1 H), 5.59 (dt, J = 9.5, 7.9 Hz, 1 H), 4.62 (ABX, J_{AB} = 12.3 Hz, J_{AX} = 9.4 Hz, J_{BX} = 7.7 Hz, 2 H), 3.67 (t, J = 5.7 Hz, 1 H), 1.90 (m, 2 H).

(9) (a) Corey, E. J.; Nicolau, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. (b) Mukaiyama, T.; Matsueda, R.; Suzuki, M. *Tetrahedron Lett.* **1970**, 1901. (c) Mukaiyama, T.; Matsueda, R.; Marayma, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1271. (d) Corey, E. J.; Brunelle, D. J. *Tetrahedron* Lett. **1976**, 3409.

(10) Correct high-resolution m/e values were obtained for all sulfur heterocycles.

Registry No. **1**, 79815-75-1; **2**, 79827-16-0; **3**, 79815-76-2; **4**, 79815-77-3; **5**, 79815-78-4; **6**, 79815-79-5; **7**, 79815-80-8; **8**, 79815-81-9; **9**, 79815-82-0; **10**, 79815-83-1; **11**, 79815-84-2; **12**, 79815-85-3; **13**, 79815-86-4; **14**, 79815-87-5; **15**, 79815-88-6; **16**, 79815-89-7; **17**, 79815-90-0; **18**, 79815-91-1; **19**, 79815-92-2; **20**, 79815-93-3; **21**, 79815-94-4; **22**, 79815-95-5; **23**, 79815-96-6.

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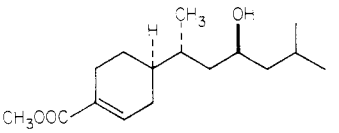
A Synthesis of the Juvabiols

Summary: Synthetic studies utilizing condensations of α-sulfinyl carbanions, have provided (+)-juvabiol and its analogous diastereoisomers.

Sir: Throughout the last several years, new synthetic methodologies have been developed and illustrated by preparation of (±)-juvabione and (±)-epijuvabione.[1] The wood of balsam fir (*Abies balsamea* (L.) Mill.) also contains a mixture of alcohols identified as (+)-juvabiol (**1**) and (+)-isojuvabiol (**2**), whereas alpine fir produces (+)-juvabiol (**1**) and (+)-epijuvabiol (**3**).[2] All of these constituents demonstrate insect juvenile hormone activity. The remaining isomer, (+)-isoepijuvabiol (**4**), is recognized as a reduction product from (+)-epijuvabione. These alcohols have identical ^1H NMR, IR, mass spectra, and chromatographic properties, complicating the analysis of unresolved mixtures. However, ^{13}C NMR information is advantageous for recognition of each of the diastereoisomers.[2a]



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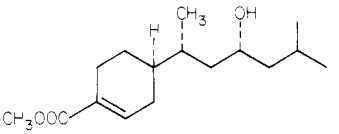

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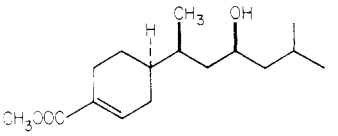

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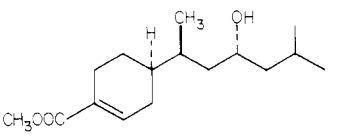

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(1) For some leading references, see the following: Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774. Trost, B. M.; Tamaru, Y. *Ibid.* **1977**, *99*, 3101. Ficini, J.; d'Angelo, J.; Noire, J. *Ibid.* **1974**, *96*, 1213.

(2) (a) Manville, J. F.; Kriz, C. D. *Can. J. Chem.* **1977**, *55*, *2547*. (b) Manville, J. F. *Ibid.* **1976**, *54*, 2365.

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