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Medium Ring Ethers by Ring Expansion–Ring Contraction: Synthesis of Lauthisan

Mark J. Coster and James J. De Voss*

Department of Chemistry, University of Queensland, Brisbane 4072, Australia

devoss@chemistry.uq.edu.au

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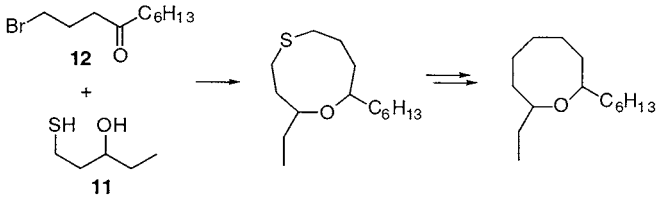
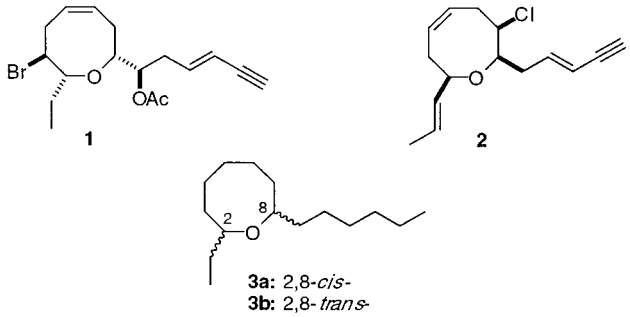
ABSTRACT



A new general method for the construction of medium ring ethers has been developed. This involves the ring expansion of halo-*O,S*-acetals followed by a Ramburg–Bäcklund ring contraction reaction with concomitant extrusion of the sulfur atom. This methodology has been utilized for the synthesis of *cis*- and *trans*-lauthisan.

Medium-ring ethers are widespread in nature, occurring in red algal metabolites such as laurencin (**1**)[1,2] and laurenyne (**2**)[3,4] and as substructures of various toxins, such as the brevetoxins[5,6] and ciguatoxins.[7] Considerable effort has been applied to the development of general methods for the construction of oxocenes and oxocanes; however, there remains a need for more efficient and general methods for medium ring ether formation. Herein we report a concise racemic synthesis of *cis*-lauthisan (**3a**) and *trans*-lauthisan (**3b**),[8] targets that have often served as the exemplars for efficient oxocane construction.[9]



Medium rings are generally difficult to synthesize via standard cyclization methodologies.[10] Fragmentation of a

(1) Isolation and characterisation: (a) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron Lett.* **1965**, 1091. (b) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, *24*, 4193. (c) Cameron, A. F.; Cheung, K. K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc., Chem. Commun.* **1965**, 638.

(2) Synthesis: (a) Masamune, T.; Matsue, H.; Murase, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 127. (b) Masamune, T. Murase, H.; Matsue, H.; Murai, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 135. (c) Murai, S.; Murase, H.; Matsue, H.; Masamune, T. *Tetrahedron Lett.* **1977**, 2507. (d) Masamune, T.; Matsue, H. *Chem. Lett.* **1975**, 895. (e) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345. (f) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958. (g) Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Synlett* **1996**, 983. (h) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483. (i) Krueger, J.; Hoffmann, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499. (j) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029. (k) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653.

(3) Isolation: Falshaw, C. P.; King, T. J.; Imre, S.; Islimyeli, S.; Thomson, R. H. *Tetrahedron Lett.* **1980**, *21*, 4951.

(4) Synthesis: Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248.

(5) Synthesis of brevetoxin A: Nicolaou, K. C.; Yang, Z.; Shi, G.-Q.; Gunzner, J. L.; Agrios, K. A.; Gartner, P. *Nature* **1998**, *392*, 264.

(6) Synthesis of brevetoxin B: (a) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1995**, *117*, 1171. (b) Nicoloau, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 1173.

(7) Synthesis of ciguatoxin CTX3C: Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904.

(8) For the coining of the name lauthisan, see: Blunt, J. W.; Lake, R. J.; Munro, M. H. G.; Yorke, S. C. *Aust. J. Chem.* **1981**, *34*, 2393.

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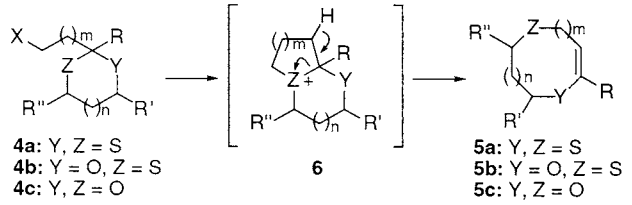
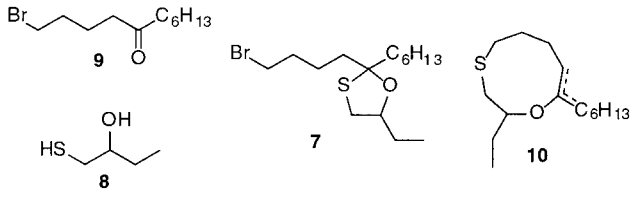
more easily synthesized intermediate bicyclic system overcomes many of the enthalpic and entropic barriers associated with direct formation of the medium size ring. Recently, we introduced methodology that employs this strategy for the synthesis of 8-, 9-, and 10-membered dithia-, oxathia-, or dioxacycloalkenes (**5a**−**c**). The synthesis employs the ring expansion of halothioacetals (**4a**),[11] halo-*O*,*S*-acetals (**4b**), and haloacetals (**4c**)[12] (Scheme 1) under mild conditions (*i*-Pr_2NEt, refluxing DMF). The reaction is believed to proceed via intramolecular alkylation of the nucleophilic heteroatom, to form a bicyclic sulfonium or oxonium ion intermediate (**6**). Removal of the β-proton by *i*-Pr_2NEt initiates fragmentation to afford the corresponding medium ring thioenol ether or enol ether.

Scheme 1



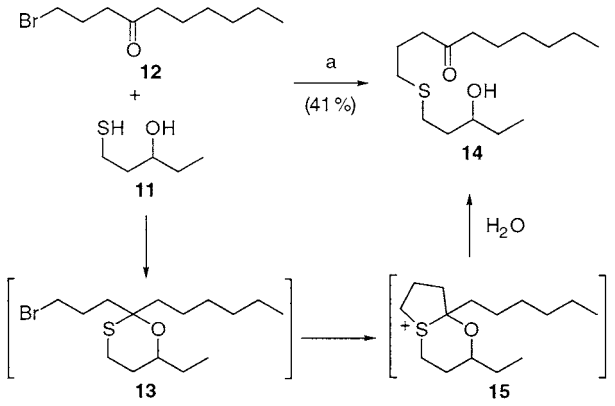
The present approach for medium ring ether synthesis exploits the ring-expansion reaction of halo-*O*,*S*-acetals. We envisioned that the product oxathia-cycloalkenes could be converted to useful medium ring ether structures by extrusion of the sulfur atom with concomitant ring-contraction. Among the available methods for this task, the Stevens[13] and Ramburg−Bäcklund[14] reactions have been used to good effect in the synthesis of strained cyclic systems. Additionally, each of these reactions would provide a functional handle of potential use for the synthesis of more complex medium ring ether compounds.

Our initial approach to lauthisan relied on the ring expansion of bromooxathiolane **7**, formed by $BF_3{\cdot}OEt_2$-promoted condensation of mercapto alcohol **8** with ketone **9**, to the mixture of enol ethers **10**. After reduction to the corresponding saturated nine-membered ethers, ring contraction by the Stevens and Ramburg−Bäcklund procedures was investigated. The Ramburg−Bäcklund reaction on the analogous chloro sulfones gave only fragmentation products and none of the desired medium ring ether. Similarly, attempted Stevens rearrangement of the *S*-methyl sulfonium salts led only to fragmentation affording acyclic alkenes. Boekelheide[15] reported a benzyne-induced Stevens rearrangement as an alternative protocol that was useful in minimizing side reactions, particularly eliminations. However, this too only produced acyclic alkenes.



We reasoned that the ether oxygen positioned β to the sulfur atom in the above approach was providing a leaving group and thus leading to the undesired fragmentation processes. Our revised approach therefore placed the oxygen atom γ to the sulfur atom. This synthesis began with the $BF_3{\cdot}OEt_2$-promoted condensation of 3-hydroxy-1-pentanethiol (**11**)[16] with 1-bromo-4-decanone (**12**)[17] (Scheme 2).

Scheme 2[a]



[a] Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 16 h.

However, upon aqueous workup, none of the desired bromooxathiane **13** was obtained. Instead the acyclic hydroxy ketone **14** (41%) was isolated along with recovered **12** (22%).

Although the formation of **14** could be the result of direct intermolecular *S*-alkylation of thiol **11** by bromoketone **12**, it seems unlikely given the reaction conditions and the absence of products of this type in previous work.[11,12] An alternative explanation would involve initial formation of the desired *O*,*S*-acetal, followed by rapid intramolecular *S*-alkylation to give the corresponding sulfonium ion **15** in situ.

(9) Other syntheses of the lauthisans: (a) Carling, R. W.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1986**, 565. (b) Carling, R. W.; Clark, J. S.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 83. (c) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Veale, C. A.; Furst, G. T. *J. Am. Chem. Soc.* **1987**, *109*, 2504. (d) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. H.; Ogilvie, W. W.; Yiannikouros, G.; Prasad, C. V. C.; Veale, C. A.; Hark, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6263. (e) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1989**, *54*, 5153. (f) Paquette, L. A.; Sweeney, T. J. *J. Org. Chem.* **1990**, *55*, 1703. (g) Paquette, L. A.; Sweeney, T. J. *Tetrahedron* **1990**, *46*, 4487. (h) Tsushima, K.; Murai, A. *Chem. Lett.* **1990**, 761. (i) Udding, J. H.; Giesselink, J. P. M.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1994**, *59*, 6671. (j) Hoffmann, H. M. R.; Brandes, A. *Tetrahedron* **1995**, *51*, 155. (k) Kim, H.; Ziani-Cherif, C.; Oh, J.; Cha, J. K. *J. Org. Chem.* **1995**, *60*, 792. (l) Suh, Y.-G.; Koo, B.-A.; Kim, E.-N.; Choi, N.-S. *Tetrahedron Lett.* **1995**, *36*, 2089.

(10) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

(11) Sui, Z.; Furth, P. S.; De Voss, J. J. *J. Org. Chem.* **1992**, *57*, 6658.

(12) De Voss, J. J.; Sui, Z. *Tetrahedron Lett.* **1994**, *35*, 49.

(13) For a review, see: Olsen, R. K.; Currie, J. O. In *The Chemistry of the Thiol Group, Part 2*; Patai, S., Ed.; Wiley: New York, 1974; pp 561−566.

(14) For a review, see: Paquette, L. A. *Org. React.* **1977**, *25*, 1.

(15) Otsubo, T.; Boekelheide, V. *Tetrahedron Lett.* **1975**, *45*, 3881.

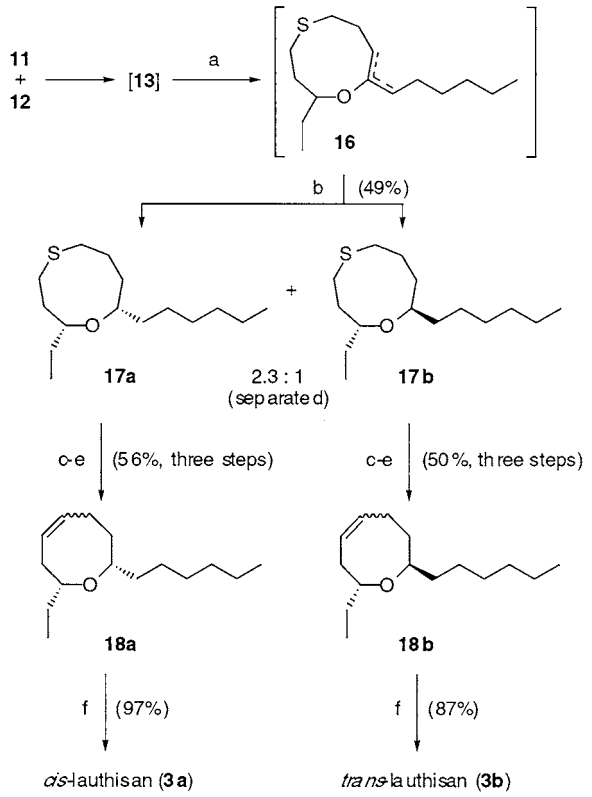
(16) Synthesised in two steps from 1-penten-3-one via Michael addition of potassium thioacetate and reduction with $LiAlH_4$.

(17) Generated from 4-bromobutyryl chloride by reaction with *N*,*O*-dimethylhydroxylamine followed by addition of *n*-hexylmagnesium bromide.

Reaction of this species with water would lead to a nine-membered cyclic hemiacetal, which would collapse to hydroxy ketone **14**.

With this possibility in mind, we investigated a one-pot procedure for the in situ ring expansion of bromo oxathiane **13** (Scheme 3). Thus, treatment of **11** and **12** with $BF_3{\cdot}OEt_2$

Scheme 3[a]



[a] Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, 3 Å molecular sieves, CH_2Cl_2, 2 h; then Et_3N, 1 h; (b) $NaBH_3CN$, TFA, THF, 15 min; (c) NCS, CCl_4, 4−6 h; (d) *m*-CPBA, CH_2Cl_2, 16 h; (e) *t*-BuOK, THF, 4−16 h; (f) H_2, Pd/C, THF, 1−3 h.

(1.5 equiv), in the presence of powdered 3 Å molecular sieves, was followed by the addition of Et_3N (5 equiv) to give the ring-expanded enol ethers **16** in situ. Reduction of enol ethers of this type had previously been best achieved by reaction with $NaBH_3CN$ in the presence of TFA.[12] Thus, reduction of **16** under these conditions led smoothly to the corresponding saturated ethers. This three-step, one-pot procedure provided a mixture (ca. 2.3:1) of the desired 1,5-oxathionanes **17a** and **17b** in 49% yield, which were readily separated by column chromatography (SiO_2). The relative stereochemistry of **17a** and **17b** was assigned after separate conversion of these compounds to the corresponding lauthisans and comparison with literature spectroscopic data (vide infra). These results indicated a significant *cis* selectivity for the reduction, even under these unoptimized conditions.

The facile nature of the above intramolecular alkylation was surprising, considering that standard conditions for reactions of this type involve heating in DMF. However, **13** is particularly well suited for an intramolecular *S*-alkylation. The use of bromide as the leaving group and the formation of a five-membered ring in the alkylation step are notable. Additionally, the sulfur atom of **13** resides in a six-membered ring, which is thought to be more nucleophilic than the corresponding five-membered ring compounds. An analogous explanation has been suggested to account for differences in complex formation of tetrahydrofuran and tetrahydropyran with dimethylzinc.[12,18] The present combination of oxathiane with a sulfur atom as the nucleophile, a C_3 side chain and a bromide as the leaving group had not been previously investigated.

With the required 1,5-oxathionanes in hand, we next examined extrusion of the sulfur atom. Initial attempts to effect a Stevens rearrangement, via *S*-alkylation of **17a** with Me_3OBF_4, followed by treatment with *t*-BuOK, again resulted in the formation of acyclic elimination products. This approach was not pursued further and we turned our attention to the use of a Ramburg−Bäcklund rearrangement.

A number of methods for the production of the desired α-chloro sulfone from the sulfide **17a** were successful, e.g., oxidation to the corresponding sulfone, deprotonation with *n*-BuLi, and reaction with SO_2Cl_2. However, reaction of **17a** with *N*-chlorosuccinimide followed by sulfur oxidation with *m*-CPBA to yield a mixture of all four possible α-chloro sulfones was found to be the most efficient and convenient. The Ramburg−Bäcklund rearrangement of the α-chloro sulfone proceeded smoothly with *t*-BuOK to yield the desired alkene **18a** as a ca. 9:1 mixture of (*Z*)- and (*E*)-double bond isomers, respectively (56%, three steps). The predominance of the (*Z*)-isomer is in line with the selectivity normally seen for this rearrangement but production of the (*E*)-isomer is not surprising, as the reaction has been well utilized in the synthesis of strained systems. The assignment of the alkene streochemistry was made on the basis of ^1H NMR coupling constants for the vinylic hydrogens, the (*E*)-isomer having $^3J = 15.0$ Hz and the (*Z*)-isomer having $^3J = 8.9$ Hz. In agreement with our assignment, the (*E*)-isomer was found to isomerize rapidly to the (*Z*)-form in $CDCl_3$ which had not been pretreated with basic alumina to remove acid. To our knowledge, this constitutes both the first report of an eight-membered cyclic ether containing an (*E*)-double bond and the smallest such cycle yet synthesized. Simple calculations on the 2,8-dimethyl analogue of **18a** suggested the (*E*)-isomer to be 13.0 kcal/mol less stable than the (*Z*)-isomer.[19] A value of 12.2 kcal/mol for (*E*)- vs (*Z*)-cyclooctene was calculated via a similar method.[20] Hydrogenation of **18a** (H_2, Pd/C) provided *cis*-lauthisan (**3a**) as the sole isolated product

(18) Searles, S., Jr.; Tamres, M. Basicity and Complexing Ability of Ethers. In *The Chemistry of the Ether Linkage*; Patai, S. Ed.; Interscience Publishers: New York, 1967; pp 295−297.

(19) Calculations were performed using MacSpartan Pro 2.0, by AM1 energy minimisation of conformers generated by a Monte Carlo conformational search. Quoted energy differences are for the lowest energy conformers for each molecule.

(20) This compares with the difference in strain energy, 11.4 kcal/mol, estimated from experimental heats of hydrogenation: Rogers, D. W.; von Voithenberg, H.; Allinger, N. L. *J. Org. Chem.* **1978**, *43*, 360.

(97%), which gave spectroscopic data (^{1}H and ^{13}C NMR, HRMS) consistent with that reported in the literature.[9e,9g]

Conversion of **17b** to the corresponding mixture of α-chloro sulfones and subsequent Ramburg−Bäcklund rearrangement provided **18b** (50%, three steps) as a mixture of (*Z*)- and (*E*)-double-bond isomers (ca. 9:1, respectively). Hydrogenation of **18b** provided *trans*-lauthisan (**3b**) (87%), which gave spectroscopic data (^{1}H and ^{13}C NMR, HRMS) in excellent agreement with that reported in the literature.[9g]

The present work demonstrates a concise new strategy for the synthesis of medium ring ethers. The ring expansion−ring contraction sequence employed herein should be amenable to the generation of 7- to 10-membered cyclic ethers, by adjusting the length of the halo-alkyl chain and suitable choice of either oxathiane or oxathiolane systems. Additionally, the use of enantiomerically enriched mercapto-alcohols, e.g., **11**, would lead to enantioselective syntheses of medium ring ether compounds.

Supporting Information Available: Experimental procedures and full characterization for compounds **3**, **11**, **12**, **17**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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