A Novel Sulfoxide-Directed Route to Enantiopure Tetrahydrofurans: Application to the Expedient Formal Synthesis of (+)-*trans*-Kumausyne and (+)-Kumausallene[1,†]

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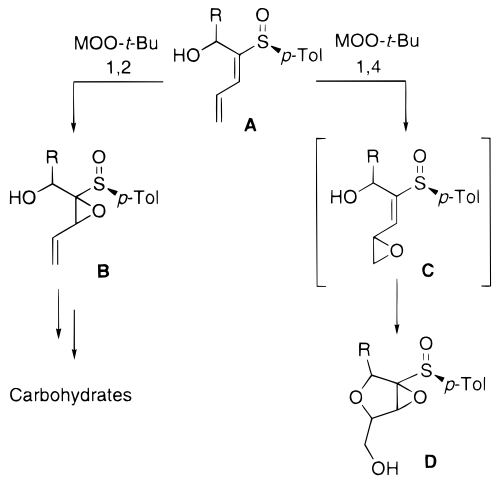
In previous reports from this laboratory, the nucleophilic epoxidation of simple vinyl sulfoxides has been documented as a general and efficient route to enantiopure sulfinyl and sulfonyl oxiranes,[2] versatile synthetic intermediates.[3] Furthermore, the epoxidation of vinyl sulfoxides bearing oxygenated substituents at allylic positions was found to be primarily directed by the chiral sulfur atom.[4] Seeking to apply our methodology to the synthesis of carbohydrate derivatives, the nucleophilic epoxidation of hydroxy dienyl sulfoxides **A** (Scheme 1) was explored with the expectation that oxiranes **B** should be amenable to straightforward manipulations to produce carbohydrates.[5] The 1,4 conjugate addition pathway was perceived as a potential hurdle to our approach,[6] which in the unlikely event of selectively producing oxiranes **C** could be of synthetic relevance as a simple route to tetrahydrofurans.[7] Herein, we describe a novel strategy for the expedient preparation of enantiopure highly substituted tetrahydrofurans **D**, which presumably takes place by sequential remote nucleophilic epoxidation of dienes **A**, ring closure of vinyl oxiranes **C**, and further nucleophilic epoxidation in a single synthetic operation. In addition, this methodology has been successfully applied to the enantioselective formal synthesis of (+)-*trans*-kumausyne and (+)-kumausallene.

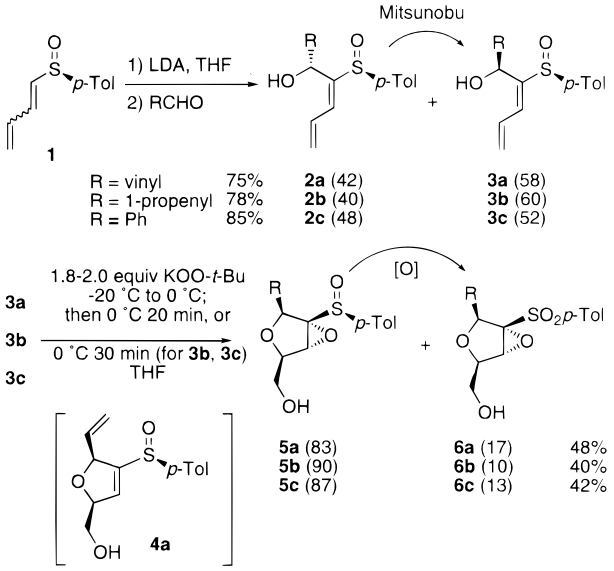
The initial stage of our investigation was carried out on readily available dienols **2a** and **3a** (Scheme 2), prepared by lithiation of the mixture of dienes **1**,[8,9] trapping with acrolein, and chromatographic separation. Dienol **2a** proved to be very unreactive to the standard nucleophilic epoxidation protocol and under forcing conditions led to intractable mixtures of products that were not investigated in detail. In sharp contrast, diastereomeric dienol **3a** reacted with KOO-*t*-Bu to afford a low yield (ca. 10%) of a product **5a** for which a detailed NMR analysis suggested a tetrahydrofuran structure **D** (Scheme 1). This assignment, as well as the relative and absolute configuration of **5a**, was subsequently confirmed by an X-ray diffraction analysis of the *p*-nitrobenzoate ester of **5a**.

After considerable experimentation, a 48% yield of a separable 83:17 mixture of sulfoxide **5a** and sulfone **6a**, as practically single isomers, was obtained by carefully monitoring the reaction parameters (temperature, time, stoichiometry, etc.),[10] and the structure of sulfone **6a** was secured by independent oxidation of the known **5a** (MMPP, MeOH, 71%) to **6a**. To gain insight on the reaction pathway of this remarkable process, the isolation of the proposed reaction intermediates **C** (Scheme 1) and dihydrofuran **4a** (Scheme 2) was attempted. Under optimal reaction conditions and at short reaction times (10 min), a small amount of an intermediate

Scheme 1



Scheme 2



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(1) Presented in part at the 12th International Conference on Organic Synthesis (ICOS-12), Venice, Italy, June 28−July 2, 1998.

(2) Fernández de la Pradilla, R.; Castro, S.; Manzano, P.; Martín-Ortega, M.; Priego, J.; Viso, A.; Rodríguez, A.; Fonseca, I. *J. Org. Chem.* **1998**, *63*, 4954−4966.

(3) For reviews, see: (a) Satoh, T.; Yamakawa, K. *Synlett* **1992**, 455−468. (b) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303−3325.

(4) Fernández de la Pradilla, R.; Manzano, P.; Priego, J.; Viso, A.; Martínez-Ripoll, M.; Rodríguez, A. *Tetrahedron Lett.* **1996**, *37*, 6793−6796.

(5) For a review on the synthesis of carbohydrate derivatives from acyclic precursors, see: Ager, D. J.; East, M. B. *Tetrahedron* **1993**, *49*, 5683−5765.

(6) For 1,4-additions of lithiated protected cyanohydrins to a dienyl sulfoxide, see: (a) Guillet, E.; Julia, S. *Tetrahedron Lett.* **1978**, *37*, 1155−1158. (b) Guillet, E.; Julia, S. *Synth. Commun.* **1981**, *11*, 697−708. (c) Guillet, E.; Julia, S. *Synth. Commun.* **1981**, *11*, 709−722.

(7) For a review see: Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711−1754.

(8) Prepared in one step by the method of Craig. Craig, D.; Daniels, K.; MacKenzie, A. R. *Tetrahedron* **1993**, *49*, 11263−11304. Lithiation of *Z* vinyl sulfoxides yields *E* lithio derivatives; there are conflicting reports on the configurational stability at sulfur in this process; see: (a) Posner, G. H. In *Asymmetric Reactions and Processes in Chemistry*; Eliel, E. L., Otsuka, S., Eds.; ACS Symposium Series No. 185; Washington, DC, 1982; p 142. (b) Fawcett, J.; House, S.; Jenkins, P. R.; Lawrence, N. J.; Russell, D. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 67−73.

(9) All new products have been fully characterized. See the Supporting Information.

(10) The reaction conditions should be strictly controlled to avoid a larger degree of overoxidation of sulfoxide **5a** to sulfone **6a** in the reaction medium.

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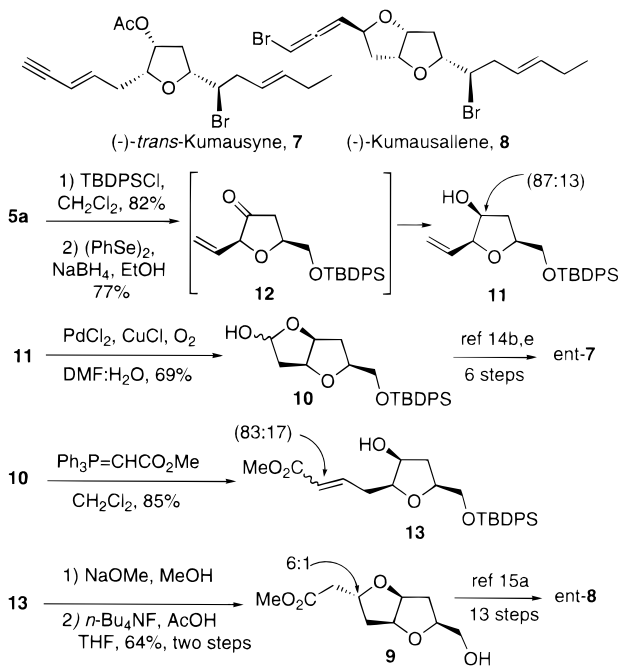
Scheme 3



of general structure **C** (ca. 7%) was isolated; alternatively, with 0.8 equiv of KOO-*t*-Bu at 4 °C for 18 h, a 35:35:5:25 mixture of **3a**, **5a**, **6a**, and the elusive dihydrofuran **4a** (ca. 10% isolated yield) was obtained. The epoxidation of **4a** under standard conditions produced **5a** smoothly. These findings support a highly stereoselective reaction pathway in which an unprecedented remote nucleophilic epoxidation is followed by a 5-*exo*-*trig* cyclization and further epoxidation to afford sulfinyl tetrahydrofuran **5a**, which is partially oxidized to sulfone **6a** in the reaction medium.[11]

To explore the scope of the methodology, the reactions between **2b**, **2c**, **3b**, and **3c** and KOO-*t*-Bu were examined with results very similar to those described above, and sulfinyl tetrahydrofurans **5b** and **5c** were obtained in fair yields considering the complexity of the process (Scheme 2).[12] Next, the transformation of the "unreactive" diastereomer **2c** into **3c** was briefly examined with acceptable results via a Mitsunobu protocol (DIAD, Ph_3P, $PhCO_2H$, toluene; NaOMe, MeOH, 59%, two steps).[13]

At this stage of the project, an application of the methodology was pursued, and we focused our attention on the red algal metabolites (−)-*trans*-kumausyne, **7**, and (−)-kumausallene, **8** (Scheme 3), which possess a 2,5-cis-disubstituted tetrahydrofuran core. On the basis of previous syntheses of these marine products,[14,15] lactol **10** was envisioned as an appropriate precursor for both target molecules, but since our efforts had begun with (−)-menthyl sulfinate, the unnatural enantiomers would be derived from this research.[16]

Smooth protection of the primary alcohol of **5a** as a TBDPS ether, subsequent oxirane cleavage and concurrent carbonyl reduction by treatment with $(PhSe)_2$ in the presence of a large excess of $NaBH_4$ led to alcohol **11** (Scheme 3) as a separable 87:13 mixture of epimers at C-4.[17] Next, **11** was transformed into the desired lactol **10** by a regiocontrolled Wacker protocol in good yield.[18] A subsequent Wittig reaction ($Ph_3P{=}CHCO_2Me$) gave unsaturated ester **13** as an 83:17 mixture of isomers that was cyclized with catalytic NaOMe/MeOH and deprotected in good overall yield with *n*-Bu_4NF/AcOH to produce **9** (6:1 mixture of epimers at C-2). Our synthetic lactol **10** and ester **9** had spectral features identical to those reported in the literature.[14e,15a] Since the enantiomers of **10**[14b,e] and (±)-**9**[15a] have been transformed into the natural products, **7** and **8**, respectively, this approach constitutes a formal synthesis of the kumausynes and kumausallene.

In conclusion, we have developed an extremely concise and unified formal synthesis of enantiopure kumausynes and kumausallene. The key step of this novel entry to the tetrahydrofuran core is likely to be an unprecedented highly stereoselective remote nucleophilic epoxidation of the sulfinyl diene moiety. We are currently studying the scope of this remarkable process as well as additional applications of the methodology to the synthesis of natural products.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds and X-ray diffraction analysis data for the *p*-nitrobenzoate of **5a** (24 pages).

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(11) Under these conditions a sulfonyl diene related to **3a** gave a more complex mixture of inseparable sulfonyl tetrahydrofurans (62:29:9) in which **6a** was the major component. This demonstrates that the sulfinyl functionality plays a crucial role in the observed stereocontrol.

(12) It should be pointed out that phenyl-substituted tetrahydrofuran **5c** was produced with diminished selectivity (74:14:12).

(13) Hughes, D. L. *Org. React.* **1992**, *42*, 335−669.

(14) For previous syntheses of *trans*-kumausyne, see: (a) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378−5384. First total synthesis of (±)-**7** in 18 steps from 2-cyclopentylidenecyclopentanone. An optically enriched intermediate (84% ee) was prepared in just one additional step using (*S*)-*O*-methylprolinol as chiral controller. (b) Osumi, K.; Sugimura, H. *Tetrahedron Lett.* **1995**, *36*, 5789−5792. First enantioselective synthesis of of (−)-**7** in 18 steps from L-arabinose; 12 steps are required to lactol **10**, our key synthetic intermediate. (c) Martín, T.; Soler, M. A.; Betancort, J. M.; Martín, V. S. *J. Org. Chem.* **1997**, *62*, 1570−1571. Total synthesis of (+)-*trans*-deacetylkumausyne in 22 steps from propargyl alcohol. (d) Lee, E.; Yoo, S.-K.; Cho, Y.-S.; Cheon, H.-S.; Chong, Y. H. *Tetrahedron Lett.* **1997**, *38*, 7557−7558. Total synthesis of (−)-**7** in 22 steps from D-xylose. (e) When this work was in progress Boukouvalas reported an improved synthesis of (−)-**7** in 13 steps: Boukouvalas, J.; Fortier, G.; Radu, I.-I. *J. Org. Chem.* **1998**, *62*, 9916−917. This approach produces lactol **10** in seven steps from dimethyl (*R*)-malate.

(15) Previous syntheses of kumausallene. (a) Grese, T.; Hutchinson, K.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468−2477. First total synthesis of (±)-**8** in 21 steps from 2-cyclopentylidenecyclopentanone. Ester **9** was prepared in eight steps. (b) More recently, Lee has published an enantioselective synthesis of intermediate **9** in 16 steps from (−)-diethyl D-tartrate; see: Lee, E.; Yoo, S.-K.; Choo, H.; Song, H. Y. *Tetrahedron Lett.* **1998** *39*, 317−318.

(16) The enantiomeric (1*S*,2*R*,5*S*)-(+)-menthyl (*R*)-*p*-toluenesulfinate is commercially available.

(17) Satoh, T.; Kaneko, Y.; Izawa, T.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1983−1990.

(18) Mereyala, H. B.; Gadikota, R.; Krishnan, R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3567−3571.