

Synthesis of 2,5-Disubstituted Tetrahydrofurans by Stereospecific Elimination–Cyclization of 1-Iodomethyl-1,5-bis-epoxides

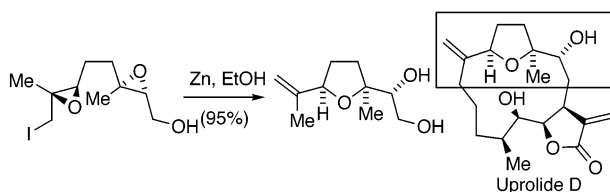
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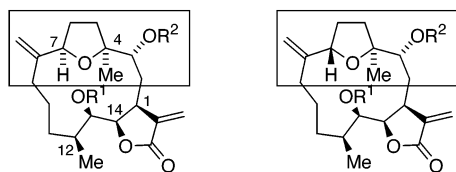
Received March 24, 2003

ABSTRACT



Treatment of 1-iodomethyl-1,5-bis-epoxides with zinc in refluxing ethanol affords cis or trans 2-vinyl-5-(1-hydroxyethyl)-substituted tetrahydrofurans stereospecifically in high yield.

Uprolides D and E are diterpenoid lactones isolated in trace amounts from *Eunicea mammosa* (Lamouroux), a variety of soft coral indigenous to the Caribbean (Figure 1).¹ These



Uprolide D, $R^1 = R^2 = H$ Uprolide E acetate; $R^1 = Ac$, $R^2 = H$
Uprolide D diacetate, $R^1 = R^2 = Ac$
Uprolide D acetate; $R^1 = Ac$, $R^2 = H$

Figure 1. Structures for uprolides D and E.

structurally unique diterpenes of the cembranolide family show IC_{50} levels of $\mu g/mL$ against leukemia, colon, and breast cancer cells. In view of their interesting structural features, limited availability, and potential as chemothera-

peutic agents, we considered these compounds to be likely targets for total synthesis.

Synthetic planning for the uprolides must address assembly of the stereotetrad array at C12–C13–C14–C1, the embedded tetrahydrofuran ring with attached substituents at C2–C9, and the macrocyclic ring. The first of these we felt could be easily dealt with by use of chiral allenylmetal additions.² The second is the subject of this report, and the third awaits future investigations.

In our initial plan for the C2–C9 segment of uprolides D and E, outlined in Figure 2, we envisioned the use of Sharpless methodology³ for stereodirected epoxidations ($A \rightarrow B$ and $D \rightarrow E$) and an acid-catalyzed cyclization ($E \rightarrow F$) to construct the tetrahydrofuran ring. The exo methylene would be introduced through a reductive elimination of a halo epoxide ($C \rightarrow D$).

Numerous examples of acid-catalyzed intramolecular etherifications have been reported for the construction of 2,5-disubstituted and 2,2,5-trisubstituted tetrahydrofuran rings

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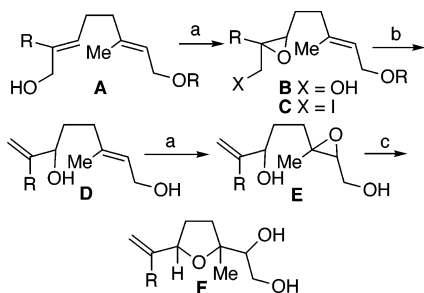
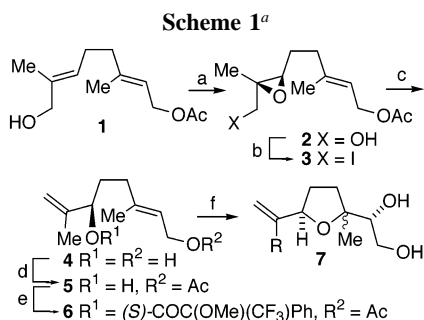


Figure 2. Synthetic plan for the tetrahydrofuran moiety of uprolides D and E. (a) Sharpless asymmetric epoxidation; (b) Zn; (c) acid.

with varying degrees of success.⁴ Most of these are initiated by protic acids, including HCl, trifluoroacetic acid, acetic acid, and camphorsulfonic acid. Despite the possibility of carbocation intermediates, reported stereoselectivities are high even for cyclizations at the more substituted position of a trisubstituted epoxide.

As a test of concept, we examined the sequence shown in Scheme 1 in which the SeO₂ oxidation product of geranyl

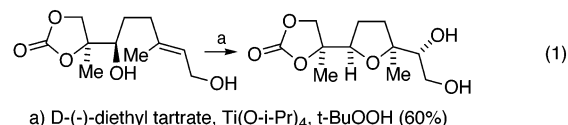


^a Conditions: (a) D-(−)-DET, Ti(O-*i*-Pr)₄, *t*-BuOOH (93%, er = 95:5); (b) Ph₃P•I₂, Im (82%); (c) Zn, EtOH (93%); (d) Ac₂O, Et₃N (50%); (e) (*S*)-ClCOC(OMe)(CF₃)Ph, pyr (95%); (f) D-(−)-DET, Ti(O-*i*-Pr)₄, *t*-BuOOH (42% ~1:1 mixture of diastereoisomers).

acetate, hydroxy acetate **1**, was employed as a model substrate.⁵ Epoxidation catalyzed by the Ti complex of D-(−)-diethyl tartrate (D-(−)-DET) proceeded in 93% yield affording epoxy alcohol **2**. Conversion to iodide **3** and treatment with Zn in ethanol led to the bis-allylic alcohol **4** in 80% yield for the two steps. The enantiopurity of this alcohol was established as 95% on the basis of the ¹H NMR

spectrum of the (*S*)-Mosher ester **6**.⁶ To achieve this level of enantiomeric purity, it was necessary to employ 60 mol % of the Ti–tartrate complex. A catalyst loading of 10 mol % afforded epoxide of 90% enantiopurity in only 56% yield.

Exposure of bis-allylic alcohol **4** to a second Sharpless epoxidation led not to the expected epoxy alcohol but to tetrahydrofuran **7** as a nearly 1:1 mixture of stereoisomers. Evidently, the titanium alkoxides present in this reaction catalyze cyclization of the intermediate epoxide. An analogous cyclization reported by Wuts⁷ afforded the S_N2 stereoisomer in 60% yield (eq 1). Examples of in situ VO(acac)₂-catalyzed epoxidation–cyclizations have also been recorded.^{8,9}



This turn of events necessitated a change in strategy in order to prevent the nonselective cyclization accompanying the Sharpless epoxidation. We expected that this goal might be accomplished by forestalling the reductive elimination of the iodo epoxide **3** until the second epoxidation was accomplished as in Figure 3. In that case, the allylic alcohol

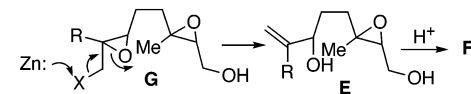


Figure 3. Revised plan for the tetrahydrofuran moiety of uprolides D and E.

intermediate **E** might be isolable, and various acid-catalyzed protocols for cyclization to the tetrahydrofuran **F** could be explored.

To implement this plan we effected cleavage of acetate **3** with methanolic potassium carbonate, which afforded allylic alcohol **8** in high yield. Epoxidation of this allylic alcohol catalyzed by the D-(−)-tartrate-titanium complex yielded the bis-epoxide **9** as a 90:10 mixture of diastereoisomers. This ratio represents a composite of the stereoisomeric ratios of both epoxidations. Remarkably, treatment of iodo bis-epoxide **9** with zinc in refluxing ethanol led directly to the tetrahydrofuran **10** in near-quantitative yield. This product was obtained as a 90:10 mixture, essentially that of the starting bis-epoxide, suggestive of a stereospecific process. The stereochemistry of the tetrahydrofuran ring was confirmed by a NOE experiment, which showed a 4% enhancement of the allylic carbonyl proton upon irradiation of the carbonyl Me substituent.

(4) (a) Reviews: Koert, U. *Synthesis* **1995**, 115. Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 5312. (c) Paterson, I.; Boddy, I.; Mason, I. *Tetrahedron Lett.* **1987**, *28*, 5205. (d) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *Tetrahedron Lett.* **1988**, *29*, 5947. (e) Ebenezer, W.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4053. (f) Patterson, I.; Tillyer, R. D.; Smail, J. B. *Tetrahedron Lett.* **1993**, *34*, 7137. (g) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9328.

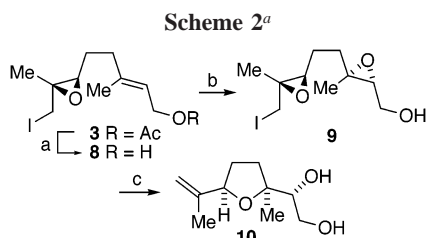
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(6) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(7) Wuts, P. G. M.; D'Costa, R.; Butler, W. *J. Org. Chem.* **1984**, *49*, 2582.

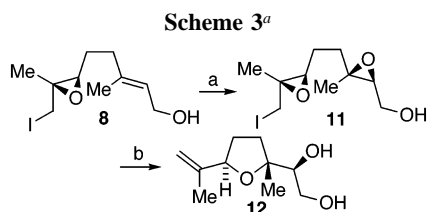
(8) Hanessian, S.; Cooke, N. G.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276.

(9) Hashimoto, M.; Yanagiya, M.; Shirahama, H. *Chem. Lett.* **1988**, 645.



^a Conditions: (a) K_2CO_3 , MeOH (94%); (b) D-(–)-DET, $\text{Ti}(\text{O}-i\text{-Pr})_4$, *t*-BuOOH (86%, dr = 90:10); (c) Zn, EtOH (95%, dr = 90:10).

To test the specificity of the elimination–cyclization cascade, we prepared the bis-epoxide **11**, an isomer of **9**, by epoxidation of allylic alcohol **8** with the L-(+)-tartrate complex (Scheme 3). This epoxide was obtained as a >90:

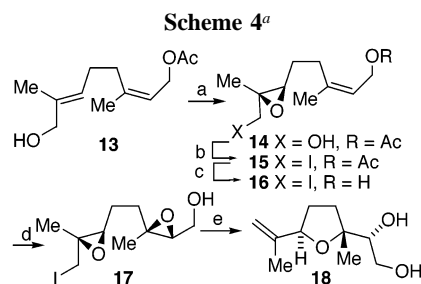


^a Conditions: (a) L-(+)-DET, $\text{Ti}(\text{O}-i\text{-Pr})_4$, *t*-BuOOH (86%, dr > 90:10); (b) Zn, EtOH (94%, dr > 90:10).

10 mixture of diastereomers. Exposure to zinc dust in refluxing ethanol gave rise to the tetrahydrofuran **12** in near-quantitative yield as a >90:10 mixture of diastereomers. In accordance with the stereospecificity of the process, the ¹H NMR signals of the minor tetrahydrofuran product derived from **9** overlapped with those of **12**, the major isomer from epoxide **11**, and vice versa. No NOE enhancement was seen for the allylic carbinyl proton of **12** upon irradiation of the carbinyl Me group, in accordance with the trans stereochemistry of those substituents.

To complete these studies, the elimination–cyclization cascade was extended to the remaining two stereoisomeric bis-epoxides. These were conveniently prepared from allylic alcohol **13**, the SeO_2 oxidation product of neryl acetate.¹⁰ Epoxidation of **13** with the D-(–)-tartrate complex gave the epoxy alcohol **14** as a 95:5 mixture of enantiomers (Scheme 4). The stereoselectivity of this reaction was evaluated by ¹H NMR analysis of the Mosher ester derivative of the secondary alcohol, obtained along the lines of Scheme 1. The second Sharpless epoxidation, carried out on allylic alcohol **16**, afforded an 85:15 mixture of diastereomers favoring **17**. This mixture, upon treatment with zinc in ethanol, gave the tetrahydrofuran product **18** in high yield

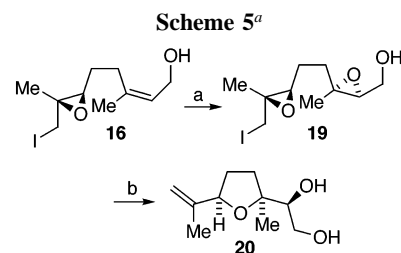
(10) Nacro, K.; Baltas, M.; Escudier, J.-M.; Gorrichon, L. *Tetrahedron* **1996**, *52*, 9047.



^a Conditions: (a) D-(–)-DET, $\text{Ti}(i\text{-PrO})_4$, *t*-BuOOH (>95%, er = 95:5); (b) $\text{Ph}_3\text{P}\cdot\text{I}_2$, Im (70%); (c) K_2CO_3 , MeOH (98%); (d) D-(–)-DET, $\text{Ti}(\text{O}-i\text{-Pr})_4$, *t*-BuOOH (88%, dr 85:15); (e) Zn, EtOH (86%, dr = 85:15).

as an 85:15 mixture. A NOE experiment showed no enhancement of the allylic carbinyl proton of **18**.

The final tetrahydrofuran stereoisomer was prepared from the iodo bis-epoxide **19**, a 90:10 mixture of diastereomers (Scheme 5). Exposure to zinc in ethanol afforded the cis-



^a Conditions: (a) L-(+)-DET, $\text{Ti}(\text{O}-i\text{-Pr})_4$, *t*-BuOOH (85%, dr = 90:10); (b) Zn, EtOH (89%, dr = 90:10).

tetrahydrofuran **20** in 89% yield as a 90:10 mixture of stereoisomers. The cis stereochemistry was confirmed by a 4% NOE enhancement of the allylic carbinyl proton. An overlay of the ¹H NMR spectra of the two tetrahydrofuran isomer mixtures obtained from bis-epoxides **17** and **19** confirmed the relationship of the two as major/minor and vice versa.

The foregoing cyclizations are noteworthy for their efficiency and stereospecificity. Although we speculate that these reactions are catalyzed by an iodozinc species resulting from the initiating reductive elimination, mechanistic confirmation awaits future studies.

Acknowledgment. Support for this research was provided by Grant R01 CA 090383 from the National Cancer Institute. H.R.C thanks Dr. Mark T. Valahovic for his valuable assistance with the NOE experiments.

Supporting Information Available: Experimental procedures and ¹H MNR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL034509L