where A is the area of the electrode in the thin-layer cell, D_A is the diffusion coefficient, and C_A^* is the concentration of A. D_A for **2** at 373 K was estimated from the known[4a] diffusion coefficient of **1** at 294 K and the viscosity of DMF using the Stokes-Einstein relation. The value of k_{BA} at 373 K was estimated from its measured value[4d] at 294 K and the assumption that the entropy of activation was negligible. The observed initial current for reduction of **2** gave $K_{AB} = 2 \times 10^{-5}$ when calculated by eq 4.

Bis Heteroannulation. 7. Total Syntheses of (±)-Gnididione and (±)-Isognididione

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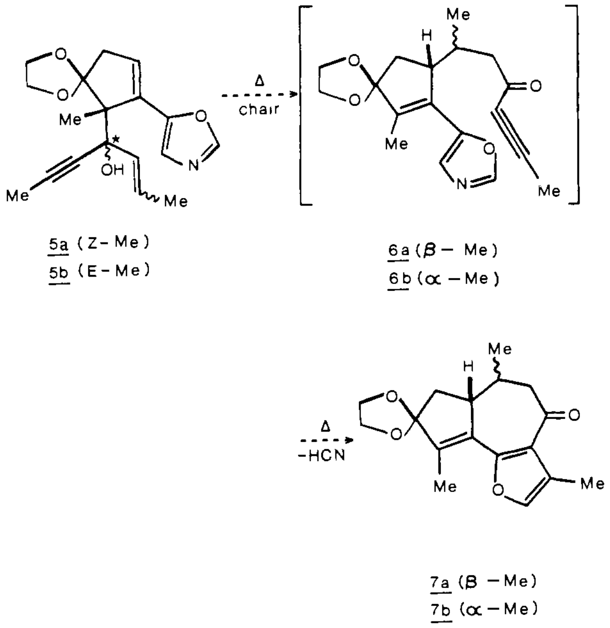
During the course of a search for plant-based tumor inhibitors Kupchan et al. isolated the furanosesquiterpene gnididione from the antileukemic fractions of *Gnidia latifolia* and proposed the structure **1** for this material on the basis of chemical and spectroscopic evidence (Figure 1).[1] This compound has a number of structural features that make it an attractive synthetic target, not the least of these being the furan ring, the first example of this functionality occurring in a guaiane sesquiterpene, and the cis relationship between H-1 and Me-10. This last substitution pattern is quite rare among members of this class[2] and has led to the suggestion that the alternative structure **2** might better fit the experimental data.[3] In addition, the guaiane skeleton itself represents a distinct synthetic challenge. These materials have attracted considerably less attention than the biogenetically related pseudoguaianes[4] and there have been only scattered reports describing the total synthesis of naturally occurring members of this class.[5] In this paper we report on an unequivocal synthesis of both **1** and **2** which firmly establishes the structure of gnididione as **1**.

Gnididione (1) Isognididione (2)

Figure 1.

Scheme I



For some time now we have been developing a general synthetic approach to the furanosesquiterpenes and this strategy appeared to be particularly well suited for the synthesis of **1** and **2** ("bis heteroannulation").[6] Thus, we envisioned that acetylenic oxazoles **6a** and **6b** should be directly convertable to the annulated derivatives **7a** and **7b**, which upon mild acid hydrolysis would provide the desired target compounds (Scheme I). As one advantage of this approach *regio*chemical control is assured by the geometrical constraints of the intramolecular Diels-Alder reaction,[6] and, furthermore, it occurred to us that *stereo*chemical control in the preparation of **6a** and **6b** might be established through the use of an oxy-Cope reaction[7] if certain criteria could be met. It was our hope, in particular, the *chemo*selectivity in the conversin of **5a,b** to **6a,b** might be effectively controlled by conformational factors relating to the relative configuration at C-8 (*), thereby overriding the usual tendency of such reactions to proceed at a faster rate with acetylenic π-bond participation (Scheme II).[8] Thus, of the four possible diastereomers of general structure **5** models clearly indicate that **8** and **9** should be strongly biased in favor of conformations **8a** and **9a**, while **10** and **11** should react preferentially through conformations **10b** and **11b**. In the event, these predictions were readily tested by experiment.

The key intermediate for our synthesis of **8-11** was the oxazole aldehyde **18**, which was readily prepared as indicated and further elaborated as follows (Scheme III).[9] Thus, **18** was first treated with *cis*-lithiopropene[12] to give an 86% yield of the allylic alcohol **19a** which was directly oxidized with Swern's reagent[13] to the corresponding enone **20a** (82%). This material, upon condensation

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(1) Kupchan, S. M.; Shizuri, Y.; Baxter, R. L.; Haynes, H. R. *J. Org. Chem.* **1977**, *42*, 348.

(2) Yoshioka, H.; Mabry, T. J.; Timmermann, B. B. "Sesquiterpene Lactones"; University of Tokyo Press: Tokyo, 1973.

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(4) For a complete survey of activity in the pseudoguaiane area through 1981, see: Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In "The Total Synthesis of Natural Products"; ApSimon, J. W., Ed.; Wiley: New York, 1982; Vol. 5. See also: (a) Heathcock, C. H. *Ibid.* Vol. 2. (b) Heathcock, C. H.; DelMar, E. G.; Graham, S. L. *J. Am. Chem. Soc.* **1982**, *104*, 1907 and references cited therein.

(5) Recent examples include: (a) Sammes, P. G.; Street, L. J. *J. Chem. Soc., Chem. Commun.* **1983**, 666. (b) Devreese, A. A.; Demuynck, M.; De Clercq, P. J.; Vandewalle, M. *Tetrahedron* **1983**, *39*, 3049. (c) Oppolzer, W.; Weglie, R. D. *Helv. Chim. Acta* **1980**, *63*, 1198. For a general survey of synthetic methodology in this area, see ref 4. Recent papers of interest include: (d) Hudlicky, T.; Reddy, D. B.; Govindan, S. V.; Kulp, T.; Still, B.; Sheth, J. P. *J. Org. Chem.* **1983**, *48*, 3422. (e) Kozikowski, A. P.; Mugrage, B. B.; Wang, B. C.; Xu, Z.-b. *Tetrahedron Lett.* **1983**, 3705. (f) Metz, P.; Schäfer, H.-J.; Henkel, G.; Krebs, B. *Ibid.* **1983**, 1959. (g) Rigby, J. H. *Ibid.* **1982**, 1863. (h) Posner, G. H.; Babiak, K. A.; Loomis, G. L.; Frazee, W. J.; Mittal, R. D.; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 7498.

(6) Jacobi, P. A.; Craig, T. A. *J. Am. Chem. Soc.* **1978**, *100*, 7748. (b) Jacobi, P. A.; Walker, D. G.; Odeh, I. *J. Org. Chem.* . **1981**, *46*, 2065. (c) Jacobi, P. A.; Walker, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 4611. (d) Jacobi, P. A.; Craig, T. A.; Arrick, B. A. *Ibid.*, in press. (e) Jacobi, P. A.; Walker, D. G.; Frechette, R. F. *Ibid.*, submitted for publication. (f) Jacobi, P. A.; Weiss, K. T.; Egbertson, M. *Heterocycles*, in press.

(7) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765 and references cited therein. See also: (b) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774.

(8) Viola, A.; Collins, J. J.; Filipp, N. *Tetrahedron*, **1981**, *37*, 3765.

(9) Satisfactory elemental analyses and spectral data were obtained for all new compounds reported. All yields refer to isolated and purified materials.

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(11) Schöllkopf, U.; Schröder, R. *Agnew. Chem., Int. Ed. Engl.* **1971**, *10*, 333. (b) Hoppe, D. *Ibid.* **1974**, *13*, 789. (c) Schöllkopf, U. *Pure* Appl. *Chem.* **1979**, *51*, 1347. (d) Walborsky, H. M.; Peresasamy, M. P. *Org. Prep. Proceed. Int.* **1979**, *11* 293. (e) Kozikowski, A. P.; Ames, A. *J. Am. Chem. Soc.* **1980**, *102*, 860. See also ref 6b.

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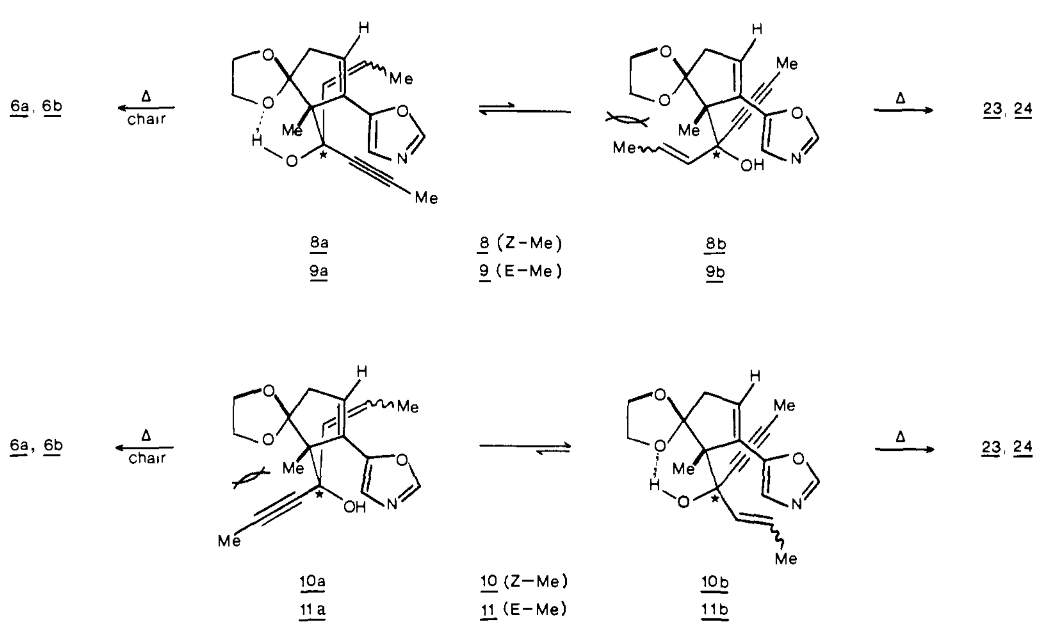
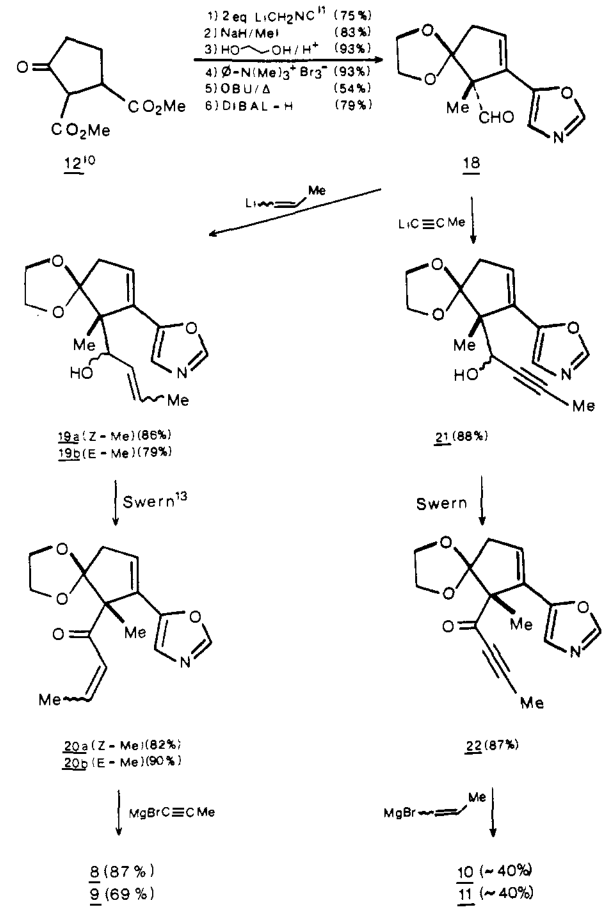
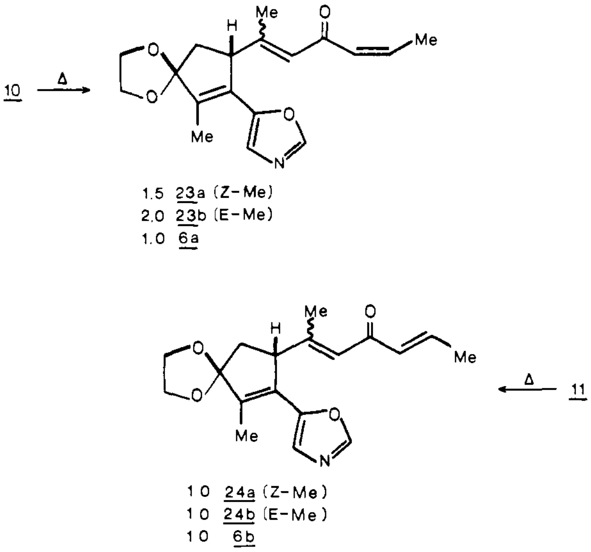
Scheme II



Scheme III



Scheme IV



with propynylmagnesium bromide[14] gave an 87% yield of the acetylenic alcohol **8** accompanied by <4% of the diastereomer **10**. Selectivity in this case is presumably a result of chelation control in the transition state leading from **20a** to **8**.[15] In similar fashion trans enone **20b**, prepared in 72% overall yield from **18** via *trans*-lithiopropene,[16] gave a 69% yield of **9** with >95% stereocontrol, and, finally, diastereomers **10** and **11** were conveniently prepared by simply reversing the reaction sequence described above. Thus, **18** gave an 88% yield of the acetylenic alcohol **21** upon condensation with lithiopropyne, and this latter material was cleanly oxidized[13] (87%) and reacted with either *cis*- or *trans*-propenylmagnesium bromide[19] to give **10** and **11** respectively, with excellent (~100%) stereocontrol.

The results obtained upon thermolysis of **8**–**11** were rather dramatic and fully substantiated our earlier predictions (Scheme IV). Thus, compounds **10** and **11** reacted predominantly through conformations **10b** and **11b** and afforded the expected products,[8] **23** and **24** together with smaller amounts of the acetylenic ketones **6a** and **6b** (toluene, reflux, ratios as indicated). In contrast, however, compound **8** gave an 87% yield of **6a** upon warming in mesitylene to 110 °C and under identical conditions **9** afforded 76% of the diastereomeric material **6b**.[17] A careful search of

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(16) Linstrumelle, G.; Krieger, J. K.; Whitesides, G. M. *Org. Synth.* **1976**, *55*, 103.

(17) All of these reactions exhibit a substantial acceleration due to the relief of steric crowding, and it is interesting to note that simpler model systems derived from methyl 3-cyclopentenecarboxylate could not be induced to undergo analogous conversions at temperatures <250 °C. These studies and others pertaining to acetylenic oxy-Cope transformations will be reported in due course.

the crude reaction mixtures indicated that <2% of crossover had occurred via boat-like transition states in these latter conversions, and no evidence could be found for the presence of enones **23** and **24**.

Finally, *at higher temperatures (~160 °C)* **8** *and* **9** *were directly converted to the ketal derivatives* **7a** *and* **7b**, *respectively, which upon mild acid hydrolysis afforded gnididione* (**1**) *and isognididione* (**2**) *in overall yields of 45% and 57%.*[20] The materials thus obtained were identical in all respects with authentic samples of **1** and **2**[1,18] and were isomerically pure to the limits of NMR and TLC detection. We believe this to be the first example of a sequential (oxy-Cope)-(Diels-Alder)-(retro-Diels-Alder) reaction, and we might only add that similar schemes can be envisioned for the synthesis of other guaiane and pseudoguaiane derivatives. This last possibility is currently under active tigation.

Acknowledgment. Financial support of this work by the National Science Foundation (Grant CHE81-08984) is gratefully acknowledged. The Varian XL-200 spectrometer used in this work was financed in part by the National Science Foundation (Grant CHE-7908593), the Dreyfus Foundation, and Wesleyan University.

Supplementary Material Available: Physical and chemical properties of compounds **6–11** and **13–24** (5 pages). Ordering information is given on any current masthead page.

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[18] We are grateful to Professor John Marx, of Texas Tech University, for providing us with an authentic sample of gnididione (**1**). Isognididione (**2**) was derived from **1** following the published procedure.[1]

[19] Beak, P.; Yamamoto, J.; Upton, C. J. *J. Org. Chem.* **1975**, *40*, 3052.

[20] The somewhat lower yield obtained for gnididione (**1**) appears to be associated with an inherent instability of ketal **7a**. For example, the overall yield for **1** was raised to 58% when hydrolysis of intermediate **6a** was carried out prior to the Diels–Alder reaction.

Templated Synthesis of Interlocked Macrocyclic Ligands: The Catenands

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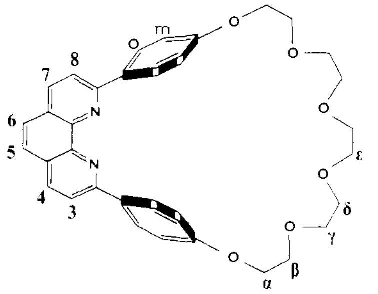
The synthesis of molecules displaying novel topological properties has long been a challenge. In particular catenanes were discussed several decades ago,[1,2] but the development of synthetic procedures of practical significance is still very limited.

The directed synthesis of catenanes has been performed by Schill et al.;[1] statistical methods have also been used.[3-7] Another approach, taking advantage of the synthesis of a molecular Möbius strip, seems to be very promising.[8]

This report deals with an extremely short and convenient synthetic route to catenanes. The principle of the synthesis is based on a generalized template effect around a metal ion,[9] leading to a metallocatenane as intermediate. After demetalation, the new ligand obtained contains two interlocked macrocycles. We therefore propose the name catenand for this new class of coordinating molecules. We also report some of the exceptional properties of the cuprocatenane, which clearly demonstrate a strong catenand effect.

Recently, we described the synthesis of a cuprocatenane from a macrocyclic compound.[10] We have now developed a one-step synthesis of cuprocatenane $\mathbf{4}^+$ from $\mathbf{1}$[10] and 1,14-diiodo-3,6,9,12-tetraoxatetradecane (**3**),[11] as shown in Figure 1. $Cu(CH_3CN)_4{}^+{\cdot}BF_4{}^-$ forms, with 2 equiv of the diphenol **1**, a very stable, deep red complex, $\mathbf{2}^+$. Reacting $\mathbf{2}^+$ and **3** in *N,N'*-dimethylformamide (DMF), under high dilution conditions, in the presence of Cs_2CO_3, affords $\mathbf{4}^+$ in 27% yield. The monocyclic compound **5**[12] is also obtained (20% isolated), as well as open-



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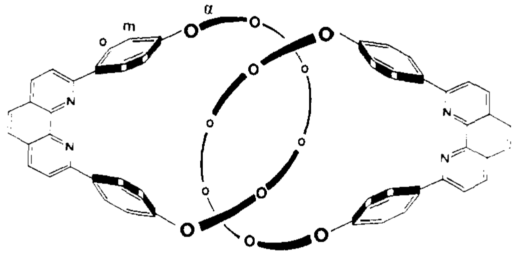

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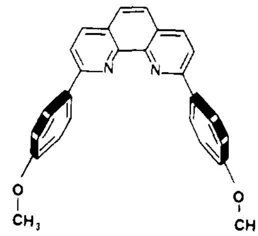

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[9] Another example of three-dimensional template effect is furnished by the synthesis of cobalt(III) sepulchrate: Creaser, I. I.; Geue, R. J.; Harrowfield, J. McB; Hertl, A. J.; Sargeson, A. M.; Snow, M. R.; Springborg, J. *J. Am. Chem. Soc.* **1982**, *104*, 6016 and references cited.

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[11] **3** was obtained by NaI treatment of the ditosylate of pentaethylene glycol; the latter was purified according to: Fenton, D. E.; Parkin, D.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 449.