mp 32.0–33.0 °C (lit.[16] mp 34 °C). Centrifugal chromatography of the distillation residue eluting with 10% ethyl acetate in dichloromethane resulted in recovery of 15.0 mg of **9**. Thus, the yield of **13** based upon recovered starting material was 62%: ^{1}H NMR[18] (80 MHz, $CDCl_3$) δ 1.91–2.14 (m, 2 H), 2.28–2.62 (m, 4 H), 5.95 (br s, 1 H), 6.14 (t, J = 4.6 Hz, 1 H).

In an alternative procedure, method A in Table I, a solution of **9** (40.3 mg, 0.148 mmol) in acetonitrile was treated with *tert*-butyl hypochlorite (19.3 μL, 0.162 mmol). After 2 min, this solution was cooled to 0 °C and treated with 0.5 mL of water and 34 μL (0.252 mmol) of triethylamine and stirred for 45 min at 0 °C. Isolation as described above afforded only 3.7 mg (0.033 mmol, 22%) of **13**.

Finally, when **9** is treated with cyclopentadiene following the addition of *tert*-butyl hypochlorite, the Diels–Alder adduct **23** can be isolated from the final reaction mixture.

Preparation of Ethyl 2,3-Dioxobutanoate (24) from Ethyl 2-(4-Phenylurazolyl)-3-oxobutanoate (10). The urazole **10** (212 mg, 0.695 mmol) was dissolved in 8 mL of acetonitrile and treated with *tert*-butyl hypochlorite (83.0 μL, 0.697 mmol). After about 30 s, four drops of a saturated solution of Na_2CO_3 in DMSO was added, and the solution warmed to 50 °C for 1 h. Upon cooling, the yellow solution was poured into water, and the aqueous mixture extracted twice with ether. The combined ether layers were washed with water, dried with $MgSO_4$, and evaporated to dryness. Kugelrohr distillation of the residue at 60 °C at 1 mmHg of pressure afforded the tricarbonyl product **24** as a bright yellow oil (45.3 mg, 0.315 mmol, 45%), bp 70 °C (12 mmHg) [lit.[6b] bp 68 °C (12 mmHg)]: IR ($CHCl_3$) 1745, 1728 cm^{-1} (lit.[6b] 1748, 1730 cm^{-1}); mass spectrum, m/e 144 (M^+), 116.

Treatment of urazole **10** (34.0 mg, 0.111 mmol) with *tert*-butyl hypochlorite (13.3 μL, 0.111 mmol) in 2.5 mL of acetonitrile followed by 30 μL of 0.1 M Na_2CO_3 afforded a pink–orange solution that contained no **24** as judged by TLC and NMR. Heating at 45 °C for 10 h afforded a red–pink solution. This color was discharged immediately by the addition of cyclopentadiene (5 μL). The only product that could be isolated from this reaction mixture (thick-layer chromatography eluting with CH_2Cl_2) was **23** (3.3 mg, 0.0137 mmol, 12%).

Preparation of 2-(4-Phenylurazolyl)-2-cycloocten-1-one (31). The urazole **30** (42.9 mg, 0.142 mmol) was dissolved in 1.5 mL of benzene at 45 °C and treated with *tert*-butyl hypochlorite (17.0 μL, 0.143 mmol). Three drops of distilled water was added, and the mixture stirred for 1 h. Upon cooling, the reaction mixture was dried over $MgSO_4$ and evaporated to dryness. Centrifugal chromatography of the residue eluting with 10% ethyl acetate in dichloromethane resulted in recovery of 15.1 mg of urazole starting material **30** and 7.6 mg (0.025 mmol, 28% based on recovered **30**) of the unsaturated urazole **31** as a colorless oil: ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.55–1.90 (m, 6 H), 2.59–2.93 (m, 4 H), 6.85 (t, J = 7 Hz, 1 H), 7.45–7.56 (m, 5 H); mass spectrum, m/e 299 (M^+, base peak), 257, 177.

Acknowledgment. The financial support of the National Science Foundation (CHE-8312691) and the University of Cincinnati for the award of a fellowship to A.C.H. is gratefully acknowledged. In addition we thank the National Science Foundation for grants used to purchase the NMR (CHE-810274) and mass spectrometry (PCM-8219912) facilities used in this research.

Registry No. **3**, 103865-85-6; **4**, 5257-24-9; **5**, 107798-93-6; **6**, 123209-00-7; **7**, 123209-01-8; **8**, 123209-02-9; **9**, 98186-09-5; **10**, 72708-74-8; **11**, 72708-78-2; **12**, 643-75-4; **13**, 10316-66-2; **23**, 15971-63-8; **24**, 1723-25-7; **30**, 123209-06-3; **31**, 123209-07-4; PhCHO, 100-52-7; $PhCH_2OH$, 100-51-6; $Ph(CO)_2Ph$, 134-81-6; $Ph(CO)_2CH_2Ph$, 23464-17-7; cyclopentadiene, 542-92-7; isatin, 91-56-5; 3-(4-phenylurazolyl)-2-hepten-4-one, 123209-04-1; 2-(4-phenylurazolyl)cycloheptanone, 123209-05-2.

Supplementary Material Available: Experimental procedures and spectroscopic data for the ylide formation and conversion to carbonyl compounds from urazoles **7**, **8**, and **11**, as well as for the formation of 3-(4-phenylurazolyl)-2-hepten-4-one (4 pages). Ordering information is given on any current masthead page.

(18) *Aldrich Library of NMR Spectra*, 2nd ed.; Aldrich Chemical Co.: Milwaukee, WI, 1983; Vol. 1, p 390B.

Total Synthesis of (±)-Gnididione and (±)-Isognididione

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(±)-Gnididione (**1**) and (±)-isognididione (**2**) have been prepared in a totally stereospecific fashion beginning with the oxazole aldehyde **20**, which was efficiently elaborated to the tertiary alcohols **3Z-R** and **3E-R** by a chelation controlled addition of 1-propynylmagnesium bromide to the intermediate enones **24Z** and **24E**. Alcohol **3Z-R** was converted in a single step to **1** via a process involving sequential chemoselective oxy-Cope reaction to produce the acetylenic ketone **5**, intramolecular Diels–Alder reaction of **5** to afford gnididione ketal **7**, and acid hydrolysis. In identical fashion, **3E-R** was directly converted to **2** with 100% stereoselectivity.

Introduction

During the course of a search for plant-based tumor inhibitors, Kupchan et al. isolated the furanosesquiterpene gnididione (**1**) from ethanolic extracts of *Gnidia latifolia* and proposed the structure **1** for this material on the basis of chemical and spectroscopic evidence.[1] At the time, **1** was the only known example of a guaiane type sesquiterpene incorporating a furan ring.[2] As a part of these studies, **1** was equilibrated with HCl to afford an approximately 50:50 mixture of **1** and an isomeric material formulated as the C-1 epimer, isognididione (**2**, Figure 1). This assignment was based mainly on an upfield shift of the C-10 methyl group in the NMR spectrum of **2**, relative to **1**, due to its close proximity to the 6,7 double bond. The

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

(2) One other example of a furanoguaiane has subsequently been reported: (a) Li, M. K. W.; Sheuer, P. J. *Tetrahedron Lett.* **1984**, *25*, 2109. (b) Imre, S.; Thomson, R. H.; Yalhi, B. *Experientia* **1981**, *37*, 442.

0022-3263/90/1955-0202$02.50/0

Figure 1.

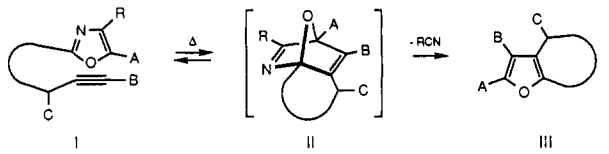
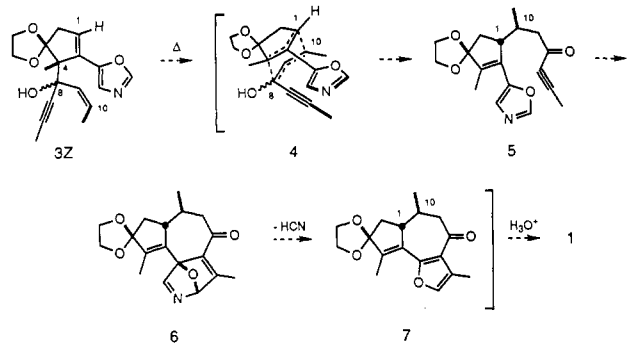


Figure 2.

Scheme I



optical rotations of 1 and 2 were also consistent with this interpretation.

Subsequently, the stereochemical assignments for C-1 and C-10 were questioned on the basis of biosynthetic considerations, and it was suggested that 2 might be the proper formulation for gnididione.[3] This ambiguity is understandable in view of the paucity of model systems available for comparison. Furthermore, similar difficulties have been encountered in synthetic efforts directed toward the guaianolides, and at least one structural assignment pertaining to C_1–C_{10} stereochemistry has required revision.[4] To address these issues, we have developed unequivocal syntheses of both 1 and 2 that confirm the structures originally proposed.[5a] The methodology employed should be of general utility for the synthesis of other members of the guaiane class of sesquiterpenes, which have received considerably less attention than the closely related pseudoguaianes.[6]

Discussion and Results

In an ongoing series of papers we have described an unequivocal approach to the synthesis of furanosesquiterpenes and related materials, the most notable feature of which is the use of an intramolecular Diels–Alder reaction of acetylenic oxazoles of general structure I to afford

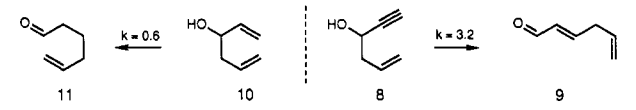


Figure 3.

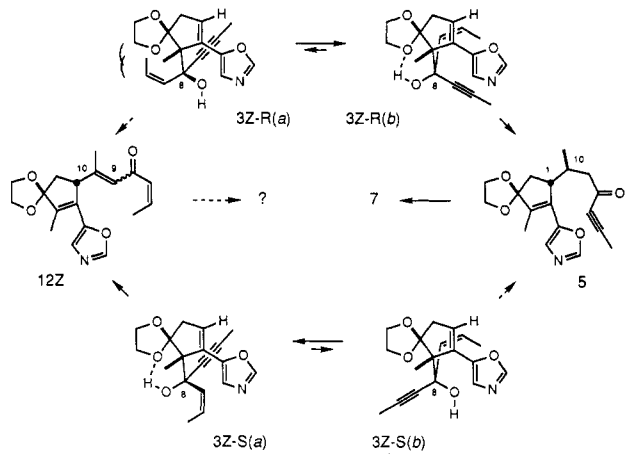


Figure 4.

fused ring furan derivatives of type III (Figure 2).[7] Transformations of this type are of considerable synthetic utility, since the appended groups A, B, and C are transposed in an unequivocal fashion, via intermediate II, to the final annulated product III. The vast majority of furanosesquiterpenes are functionalized at C-3 (B) and C-4′ (C) of the furan ring (cf. 1), and a proper choice of substituent A allows for the transformation of III to butenolides or lactones.[7e,j]

Our projected application of this strategy to the synthesis of gnididione (1) is diagrammed in Scheme I. The key intermediate in this approach is the acetylenic oxazole 5, which should be convertible in a single step to gnididione ketal 7 (vide supra). Simple acid hydrolysis would then complete the synthesis. Several approaches were considered for the stereospecific synthesis of 5. However, we were particularly attracted to the possibility that 5 might be prepared from the tertiary alcohol 3Z by an oxy-Cope transformation proceeding via the intermediacy of the chair transition state 4. In this way, relative stereochemistry at C-1 and C-10 would ultimately be controlled by the geometry of the alkene component in 3. A (*Z*)-propenyl substitutent at C-8 would produce the cis-relative stereochemistry found in 5, while alternatively, an (*E*)-propenyl group would lead to trans-relative stereochemistry. Thus, minor variations in the synthetic scheme might also allow for the unambiguous synthesis of 2. Finally, it seemed possible that 3Z might be directly converted to 1 by thermolysis followed by deprotection. In that event, all of the stereochemical and regiochemical challenges associated with the synthesis of 1 would be met in a single step.

As attractive as this scheme appeared, we realized that difficulties might arise in the chemoselective oxy-Cope

(3) Ramsey, H. D. Ph.D. Thesis, Texas Tech University, Lubbock, TX, 1980; *Chem. Abstr.* **1980**, *95*, 6933q; *Diss. Abstr. Int. B* **1981**, *41*(7), 2616–2617; University Microfilms International, Ann Arbor, MI, No. 8102458.

(4) Metz, P.; Schäfer, H.-J. *Tetrahedron Lett.* **1983**, *24*, 1959.

(5) (a) A preliminary communication describing portions of this work has appeared.[7g] (b) For an alternative synthesis of 1 see: Dell, C. P.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1987**, 349.

(6) For leading references, see: (a) Rigby, J. H.; Senanayake, C. *J. Am. Chem. Soc.* **1987**, *109*, 3147. (b) Rigby, J. H.; Wilson, J. Z. *J. Org. Chem.* **1987**, *52*, 34; *J. Am. Chem. Soc.* **1984**, *106*, 8217. (c) See also footnote 5 in 7g below.

(7) (a) Jacobi, P. A.; Craig, T. *J. Am. Chem. Soc.* **1978**, *100*, 7748. (b) Jacobi, P. A.; Ueng, S. N.; Carr, D. *J. Org. Chem.* **1979**, *44*, 2042. (c) Jacobi, P. A.; Walker, D. G.; Odeh, I. M. A. *J. Org. Chem.* **1981**, *46*, 2065. (d) Jacobi, P. A.; Walker, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 4611. (e) Jacobi, P. A.; Frechette, R.; Arrick, B.; Walker, D.; Craig, T. *J. Am. Chem. Soc.* **1984**, *106*, 5585. (f) Jacobi, P. A.; Weiss, K.; Egbertson, M. *Heterocycles* **1984**, *22*, 281. (g) Jacobi, P. A.; Selnick, H. G. *J. Am. Chem. Soc.* **1984**, *106*, 3041. (h) Jacobi, P. A.; Kaczmarek, C. S. R.; Udodong, U. E. *Tetrahedron Lett.* **1984**, 4859. (i) Jacobi, P. A.; Frechette, R. F. *Tetrahedron Lett.* **1987**, 2937. (j) Jacobi, P. A.; Kaczmarek, C. S. R.; Udodong, U. E. *Tetrahedron* **1987**, *43*, 5475. (k) Jacobi, P. A.; Egbertson, M.; Frechette, R. F.; Miao, C. K.; Weiss, K. T. *Tetrahedron* **1988**, *44*, 3327.

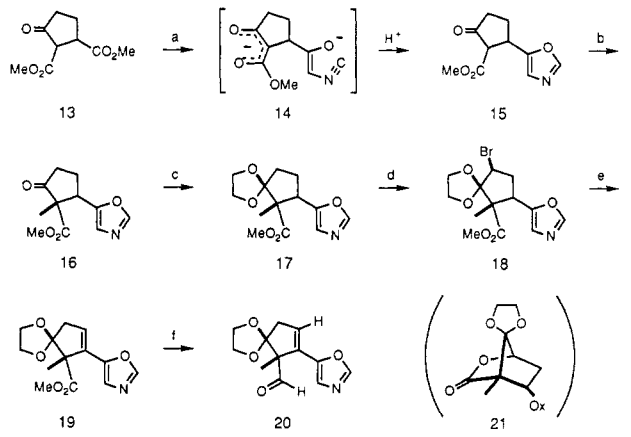
transformation of **3Z** to **5**. In particular, it is frequently observed that acetylenic π-bonds undergo this transformation at a substantially faster rate than the corresponding vinylic substituents.[8] For example, Viola et al. reported that the acetylenic alcohol **8** is transformed to **9** at a rate ~5 times greater than that for the analogous conversion of **10** to **11** (Figure 3).[9] In Scheme I, we represented only one of two possible conformations of **3Z** that might participate in an oxy-Cope transformation. An alternative conformation, derived by rotation about the C_4–C_8 bond, would bring the propyne residue into proper orientation for oxy-Cope reaction, in which case the precedent above would suggest that reaction with triple-bond participation would be energetically favored.[8,9] In the present example, however, we believed that chemoselectivity might be influenced by overriding differences in conformational stabilities, themselves dependent upon the relative configurations at C-4 and C-8. Our analysis that led to this hypothesis is summarized below.

Four stereoisomers can be derived by varying chirality at C-4 and C-8. Two of these isomers arise from mirror image relationships and need not be considered further. If one sets the *R* configuration at C-4, the remaining two possibilities consist of **3Z-R** and **3Z-S** (Figure 4). Each of these diastereomers, in turn, could undergo an oxy-Cope reaction via either conformation a or b. In the absence of any biasing factors, one would predict that the acetylenic oxy-Cope reaction would be favored, affording the cross-conjugated enone **12Z**,[8,9] presumably as a mixture of stereoisomers at the C_9–C_{10} double bond. However, models indicate that conformations a and b should differ markedly in ground-state energy for both **3Z-R** and **3Z-S**. Thus, **3Z-R(a)** should be highly destabilized by steric interactions involving the (*Z*)-propenyl group and the adjacent spirocyclic dioxolane ring, while **3Z-R(b)** should derive considerable stabilization from the hydrogen bonding indicated. In analogous fashion, **3Z-S(b)** should be less stable than **3Z-S(a)** (strong hydrogen bond), although steric interactions do not appear to be as important in this pair of conformations. To a first approximation, these energy differences should also be manifested in the transition states for 3,3-sigmatropic shift, *leading to the prediction that the S configuration at C-8 would favor acetylenic oxy-Cope product* ***12Z****, while the R configuration would favor the desired product* ***5***.

To summarize, we anticipated that regiochemical control in our synthesis of **1** would be ensured by the geometrical constraints imposed by an intramolecular Diels–Alder reaction (**5** → **7**), stereochemical control would be exercised through the use of an oxy-Cope reaction (**3Z-R** → **5**), and chemoselectivity would be governed by conformational stabilities relating to the relative configurations at C-4 and C-8 (vide supra).

The key intermediate for our syntheses of both **3Z-R** and **3Z-S** was the oxazole aldehyde **20**, which was readily prepared in gram scales and larger from the known diester **13**[10] (Scheme II). Thus, **13** was first treated with 2.8 equiv of lithiomethyl isocyanide, which afforded a 75% yield of the oxazole ester **15**. In this reaction, excess lithiomethyl isocyanide functions to produce the enolate anion **14**, in which the ketone carbonyl and the β-ester are protected against nucleophilic addition. Standard Schöllkopf cyclization of the isocyano ketone derived from the unprotected ester then produces the desired oxazole ring.[11] Next, methylation of **15** and formation of the dioxolane derivative **17** were readily carried out under standard conditions (77% overall yield). Of a variety of procedures investigated for introducing the cyclopentene double bond required in **20**, the most satisfactory involved bromination of **17** with phenyltrimethylammonium tribromide (PTAT),[12] which afforded a 93% yield of **18** as a single isomer. Dehydrobromination of **18** with DBU then gave a 54% yield of the unsaturated ester **19**, together with 25% of the bicyclo derivative **21**. It is interesting to note that the only unsaturated compound formed in this reaction is that in which the double bond has migrated into conjugation with the oxazole ring. The formation of **21**, which presumably occurs by initial demethylation of the ester functionality in **18**,[13] followed by intramolecular S_N2 displacement of bromide, serves to confirm the stereochemistry of **18** as indicated. Finally, reduction of **19** with 2.6 equiv of DIBAL provided a 79% yield of the desired aldehyde **20**.

Scheme II[a]



[a] (a) 2 equiv of $LiCH_iNC$, THF, −78 °C, 75%; (b) NaH, THF/HMPA, MeI, RT, 83%; (c) EG, Bz, TsOH, Δ, 93%; (d) PTAT, $CHCl_3$, Δ, 93%; (e) DBU, 60 °C, 54% **19**, 25% **21**; (f) 2 equiv of DIBAL, CH_2Cl_2, −78 °C, 79%.

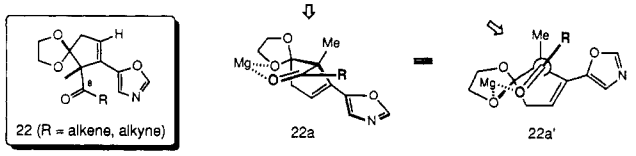
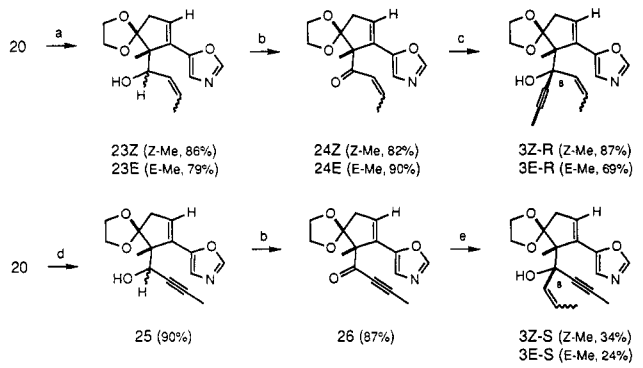


Figure 5.

We expected that the relative configurations at C-4 and C-8 could be efficiently controlled via a chelation-mediated addition of an appropriate Grignard reagent to ketones of general structure **22** (Figure 5, R = alkene, alkyne).[14] Under these conditions, magnesium should chelate between the syn dioxolane oxygen and the ketone carbonyl group, thereby affording the reactive intermediate **22a**, which most likely exists in a flattened chair conformation (Newman projection **22a'**). It appeared likely that nu-

(8) Viola, A.; Collins, J. J.; Filipp, N. *Tetrahedron* **1981**, *37*, 3765.
(9) (a) Viola, A.; MacMillan, J. H. *J. Am. Chem. Soc.* **1970**, *92*, 2404. (b) Viola, A.; MacMillan, J. H.; Proverb, R. J.; Yates, B. L. *J. Chem. Soc., Chem. Commun.* **1971**, 936.
(10) White, W. L.; Anzeveno, P. B.; Johnson, F. J. *J. Org. Chem.* **1982**, *47*, 2379, and references therein.
(11) (a) Schöllkopf, U.; Schröder, R. *Angew. 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. Proc. Int.* **1979**, *11*, 293. See also ref 7c and 7d above.
(12) (a) Eaton, P. E. *J. Am. Chem. Soc.* **1962**, *84*, 2344. (b) Johnson, W. S.; Bass, J. D.; Williamson, T. *Tetrahedron* **1963**, *19*, 861. (c) Visweswariah, S.; Prakash, G.; Bhushan, V.; Chandrasekaran, S. *Synthesis* **1982**, *309*.
(13) Parish, E. J.; Miles, E. H. *J. Org. Chem.* **1973**, *38*, 1223.
(14) (a) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1958**, *81*, 2748. (b) Still, W. C.; McDonald, J. H., III *Tetrahedron Lett.* **1980**, 1031.

Scheme III[a]



[a] (a) *cis*- or *trans*-1-lithiopropene, THF, −78 °C; (b) oxaloyl chloride, DMSO, CH_2Cl_2, NEt_3, −78 °C; (c) 1-propynylmagnesium bromide, THF, 0 °C; (d) 1-lithiopropyne, THF, −78 °C; (e) *cis*- or *trans*-1-propenylmagnesium bromide, THF, −78 °C.

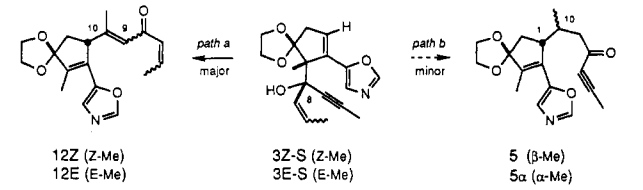


Figure 6.

cleophilic addition would then occur from the *Re* face (arrows), since the *Si* face is shielded by the oxazole ring. Thus, stereochemistry at C-8 would ultimately be determined by the order of addition of organometallic reagents to aldehyde **20**; the second group added should always approach from the *Re* face. This turned out to be the case (Scheme III).

Both (*Z*)- and (*E*)-1-lithiopropene[15] readily added to **20** to give the allylic alcohols **23Z** (86%) and **23E** (79%), each of which was obtained as a ~3:1 mixture of C-8 epimers (configurations not assigned). These epimeric mixtures were directly oxidized, without separation, to the corresponding ketones **24Z** and **24E** with Swern's reagent.[16] It is not surprising that only modest diastereoselectivity was observed in the additions of organolithiums to aldehyde **20** (nonchelation conditions[14b]). In contrast, however, 1-propynylmagnesium bromide[17] added to both **24Z** and **24E** in a highly stereoselective fashion, affording the tertiary alcohols **3Z-R** (87%) and **3E-R** (69%) together with only traces of the corresponding *S* isomers (<4%). The structures of the minor *S* isomers obtained were confirmed by the results which follow. Thus, in analogous fashion, but reverse order of addition, **20** reacted with 1-lithiopropyne to give the acetylenic alcohol **25** (90% yield, 4:1 mixture of epimers), which was oxidized with Swern's reagent to afford the acetylenic ketone **26** (87%). This last material then gave the tertiary alcohols **3Z-S** (34%) and **3E-S** (24%) upon condensation with (*Z*)- and (*E*)-1-propenylmagnesium bromide[18] (>98% diastereoselectivity). A contributing factor in the low yields obtained for **3Z-S** and **3E-S** is the ease of proton abstraction from the acetylenic ketone **26**. Also, however, no effort was made to optimize these yields, since we believed that both of

Scheme IV

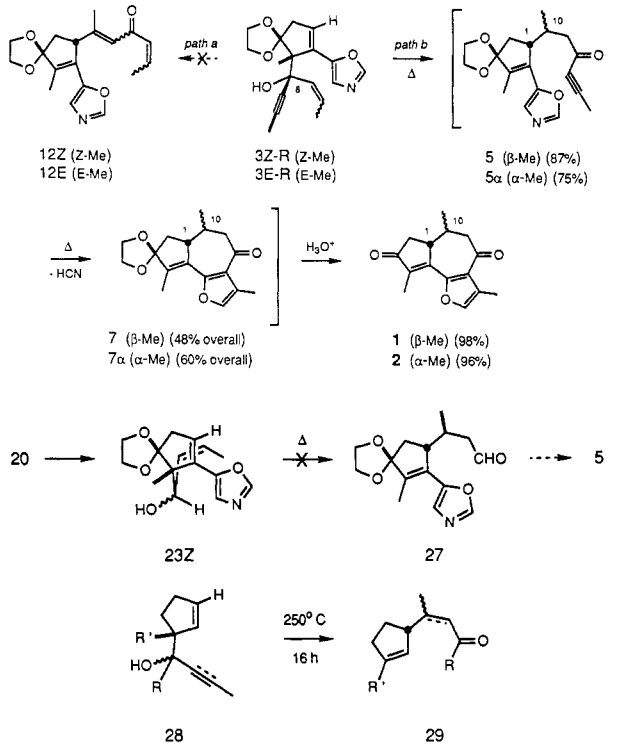


Figure 7.

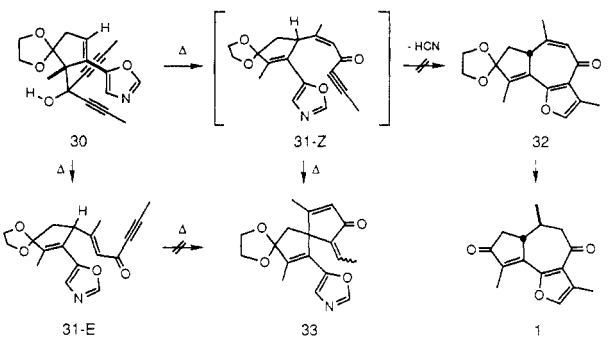
these materials would favor the undesired acetylenic oxy-Cope reaction pathway (vide supra).

Our initial oxy-Cope experiments were carried out with **3Z-S** and **3E-S**, and the results obtained substantiated our analysis given in Figure 4. Upon thermolysis (110 °C, toluene, reflux), **3Z-S** gave a ~2:1 mixture of **12Z** and **5**, and **3E-S** gave a ~2:1 mixture of **12E** and **5α** (Figure 6). Thus, the acetylenic oxy-Cope reaction, proceeding via path a, was favored (cf. also Figure 4). In each case the derived cross-conjugated enones **12Z** and **12E** were obtained as ~1:1 mixtures of *Z* and *E* isomers at the C_9–C_{10} double bond. Importantly, however, there was no detectable crossover in the minor reaction pathways leading to acetylenic ketones **5** and **5α** (path b). Enynol **3Z-S** gave only **5**, having the β-configuration at C-10, while **3E-S** afforded only **5α**. Therefore, the vinylic oxy-Cope reaction, although unfavorable, takes place exclusively through a chair conformation.

We next turned our attention to the thermolysis of **3Z-R** and were gratified to find that this material behaved exactly as predicted (Scheme IV). Thus, **3Z-R** gave an 87% yield of the desired acetylenic ketone **5** upon heating at 110 °C for 4 h (path b, toluene, reflux). No trace of either the acetylenic oxy-Cope product **12Z** (path a) or the isomeric vinylic oxy-Cope product **5α** could be detected in the crude reaction mixtures. *Furthermore, at higher temperatures* ***3Z-R*** *was directly converted to gnididione ketal* ***7*** *(158 °C, mesitylene, 48% yield), which upon mild acid hydrolysis afforded a 98% yield of gnididione* (***1***).[19] The material thus obtained had spectral data and TLC behavior identical with those of an authentic sample of **1**.[20] Finally, in identical fashion, **3E-R** gave a 60% yield of isognididione ketal **7α**, which was readily hydrolyzed to isognididione (**2**, 96%). This last material was identical

(15) (a) Seyferth, D.; Vaughan, L. G. *J. Am. Chem. Soc.* **1964**, *86*, 883. (b) Linstrumelle, G.; Krieger, J. K.; Whitesides, G. M. *Org. Synth.* **1976**, *55*, 103.
(16) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(17) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: New York, 1971.
(18) Beak, P.; Yamamoto, J.; Upton, C. G. *J. Org. Chem.* **1975**, *40*, 3052.
(19) Alternatively, **1** was obtained in 58% overall yield when hydrolysis of ketal **5** was carried out prior to the Diels–Alder reaction.
(20) We are grateful to Professor John Marx, of Texas Tech University, for providing us with an authentic sample of gnididione (**1**).

Scheme V



in all respects with a sample of **2** prepared by acid-catalyzed isomerization of **1**.[1] The structures of both **1** and **2** are thus confirmed as originally reported.[1]

Note added in proof: During the course of our studies culminating in the total synthesis of **1** and **2**, we made a number of observations pertaining to substituent effects on the rates for oxy-Cope rearrangement in systems related to **3**. As one example, it is worth noting that allylic alcohol **23Z**, derived by addition of (*Z*)-1-lithiopropene to aldehyde **20** (cf. Scheme III), was much less reactive toward 3,3-sigmatropic shift than the corresponding tertiary alcohols **3Z-R(S)** or **3E-R(S)** (Figure 7). It will be recognized that the anticipated product **27** would provide an alternative means for the synthesis of the key acetylenic oxazole **5**. However, **23Z** was totally unreactive under conditions that smoothly transformed **3Z-R** and **3E-R** to the respective acetylenic ketones **5** and **5α** and under more vigorous conditions suffered extensive decomposition. This observation is in general agreement with the reactivity trend noted by Viola et al.,[8] in which increased substitution at C-3 lowers the energy of activation for sigmatropic rearrangement.

In addition, we have evidence to suggest that the oxy-Cope rearrangements of **3Z-R(S)** and **3E-R(S)** are accelerated by steric compression involving the adjacent spirocyclic dioxolane ring and/or hydrogen bonding of the type depicted for **3Z-R(b)** and **3Z-S(a)** in Figure 4. Thus, in an extensive series of model studies,[21] we found that substrates of general structure **28** require substantially higher temperatures for conversion to **29** as compared to the analogous transformations leading to **12** or **5** (>250 °C/16 h vs 110 °C/4 h; Figure 7; see also Scheme V).

Finally, we briefly explored the possibility that dehydrognididione ketal **32** might be derived from the acetylenic enone **31-Z**, itself presumably available via bis-acetylenic oxy-Cope transformation of the tertiary alcohol **30** (Scheme V).[8] In fact, thermolysis of **30** provided an excellent yield of the expected mixture of **31-Z** and **31-E** at temperatures between 80 and 90 °C. At higher temperatures, however, we were surprised to find that **31-Z** gave none of the desired furan **32** but rather was cleanly converted to the spirocyclic methylenecyclopentenone **33**. The mechanism for this unusual transformation has been discussed elsewhere,[21a] and we believe that transformations of this type have considerable synthetic potential.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary appratus and are uncorrected. Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6E spectrometer. NMR spectra were obtained on a Varian XL200 spectrometer, and are expressed as ppm downfield from tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrometer.

2-Carbomethoxy-3-(5-oxazolyl)cyclopentan-1-one (15). Dry THF (900 mL) was placed in a flame-dried, 2-L flask under N_2 and cooled to −78 °C. Then 60 mL (0.14 mol, 2.8 equiv) of 2.3 N *n*-BuLi in hexane was then added in one portion, and the resulting solution was treated in a dropwise fashion, with vigorous stirring, with 7.4 mL (0.14 mol, 2.8 equiv) of freshly distilled methyl isocyanide. After stirring for an additional 10 min at −78 °C, the resulting suspension was treated in dropwise fashion with a solution of 10.0 g (0.05 mol, 1.0 equiv) of diester **13** in 100 mL of THF while a temperature of −78 °C was maintained. The reaction mixture was then allowed to warm slowly to 0 °C over a period of 3 h before quenching with 350 mL of pH 7 buffer and enough 2 N HCl to bring the aqueous phase to pH 7. The phases were separated, and the aqueous phase was extracted with 3 × 100 mL of CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and chromatographed (silica gel, ether) to afford 7.6 g (75%) of **15** as a viscous, pale orange oil that solidified on standing. Recrystallization from ether/petroleum ether then gave **15** as a colorless solid, mp 62–64 °C; R_f 0.32 (silica gel, ether); mass spectrum, *m/e* 209 (M^+); IR (KBr) 3128, 1753, 1725, 1511 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06 (m, 1 H), 2.48 (m, 4 H), 3.34 (d, *J* = 12 Hz, 1 H), 3.75 (s, 3 H), 6.88 (s, 1 H), 7.82 (s, 1 H). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.69. Found: C, 57.66; H, 5.21; N, 6.49.

2-Carbomethoxy-2-methyl-3-(5-oxazolyl)cyclopentan-1-one (16). A solution of 7.1 g (0.033 mol) of oxazole ester **15** in 50 mL of dry THF was added dropwise, under N_2, to a stirring suspension of 1.79 g (50% oil dispersion, 0.037 mol, 1.1 equiv) of NaH in 350 mL of dry THF at 0 °C. The reaction mixture was stirred at 0 °C for an additional 15 min until the hydrogen evolution had ceased. Then 12 mL of HMPA was added, followed immediately by 25 g (0.17 mol, 5.1 equiv) of iodomethane. The reaction was allowed to warm slowly to room temperature and was then stirred under N_2 for 7 h. The resulting solution was quenched by the addition of 250 mL of pH 7 buffer, and approximately half of the THF was evaporated at reduced pressure. Then 500 mL of water and 100 mL of CH_2Cl_2 were added, and the layers separated. The aqueous phase was extracted with 3 × 100 mL of CH_2Cl_2, and the combined organic layers were washed with 2 × 25 mL of brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to a pale yellow oil. Chromatography (silica gel, ether) then afforded 6.2 g (83%) of **16** as a viscous, colorless oil that solidified upon standing. Recrystallization from ether/petroleum ether gave **16** as a colorless solid, mp 51–52 °C; R_f 0.37 (silica gel, ether); mass spectrum, *m/e* 223 (M^+); IR (KBr) 3125, 2950, 1730, 1599 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 3 H), 2.42 (m, 3 H), 2.74 (m, 1 H), 3.33 (t, *J* = 4 Hz, 1 H), 3.54 (s, 3 H), 6.90 (s, 1 H), 7.82 (s, 1 H). Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87. Found: C, 58.84; H, 5.82.

6-Carbomethoxy-6-methyl-7-(5-oxazolyl)-1,4-dioxaspiro[4.4]nonane (17). A mixture of 4.69 g (0.020 mol) of oxazole ester **16**, 2.0 mL (0.035 mol, 1.8 equiv) of ethylene glycol, 350 mL benzene, and 0.30 g (1.57 mmol) of *p*-toluenesulfonic acid was heated at reflux for a period of 48 h with a Dean–Stark trap to remove water as formed. After cooling to room temperature, the reaction mixture was poured into 100 mL of saturated $NaHCO_3$, and the layers were separated. The organic phase was washed once with 50 mL of saturated $NaHCO_3$, and the layers were separated. The organic phase was washed once with 50 mL of saturated $NaHCO_3$ and the combined aqueous layers were back extracted with 2 × 30 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and chromatographed (silica gel, ether) to afford 5.1 g (93%) of **17** as a colorless oil, R_f 0.48 (silica gel, ether). The analytical sample, prepared by bulb-to-bulb distillation showed the following: bp 125 °C (0.35 Torr); mass spectrum, *m/e* 267 (M^+); IR (film) 3105, 2951, 1728, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 2.04 (m, 2 H), 2.38 (m, 2 H), 3.25 (t, *J* = 9 Hz, 1 H), 3.61 (s, 3 H), 3.96 (m, 4 H), 6.80 (s, 1 H), 7.74 (s, 1 H). Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.44; N, 5.25. Found: C, 58.38; H, 6.26; N, 4.88.

(21) (a) Jacobi, P. A.; Armacost, L. M.; Kravitz, J. I.; Martinelli, M. J.; Selnick, H. G. *Tetrahedron Lett.* **1988**, 6865. (b) Jacobi, P. A.; Armacost, L. M.; Kravitz, J. I.; Martinelli, M. J. *Ibid.* **1988**, 6869. (c) Jacobi, P. A.; Kravitz, J. I. *Ibid.* **1988**, 6873.

9-Bromo-6-carbomethoxy-6-methyl-7-(5-oxazolyl)-1,4-dioxaspiro[4.4]nonane (18). A solution of 6.20 g (0.023 mol) of ketal **17** and 8.65 g (0.023 mol, 1 equiv) of phenyltrimethylammonium tribromide in chloroform was heated at reflux for a period of 1 h. After cooling to room temperature, the reaction was poured into a mixture of 100 mL of saturated $NaHCO_3$ and 100 mL of 5% sodium thiosulfate. The layers were separated, and the aqueous phase was extracted with 2 × 30 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and chromatographed (silica gel, ether) to afford 7.34 g (93%) of **18** as a pale yellow oil: R_f 0.54 (silica gel, ether); mass spectrum, m/e 345 (M^+), 347 (M^{2+}); IR (film) 3130, 2899, 1721, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (s, 3 H), 2.41 (m, 1 H), 2.74 (m, 1 H), 3.49 (t, J = 9 Hz, 1 H), 3.54 (s, 3 H), 4.19 (m, 4 H), 5.08 (dd, J = 7.2, 10.8 Hz, 1 H), 6.80 (s, 1 H), 7.37 (s, 1 H).

6-Carbomethoxy-6-methyl-7-(5-oxazolyl)-1,4-dioxaspiro[4.4]non-7-ene (19). A solution of 5.0 g (0.014 mol) of α-bromoketal **18** in 15 mL of dry benzene was treated with stirring with 15 mL of DBU. The resulting dark brown solution was heated at 80 °C for 3 days. After cooling to room temperature, the reaction mixture was diluted with 200 mL of CH_2Cl_2 and poured into 400 mL of pH 7 buffer, and the pH adjusted to 7 with 2 N HCl. The layers were separated, and the aqueous phase was extracted with 4 × 75 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and chromatographed (silica gel, ether) to afford 2.5 g (54%) of **19** as a pale yellow oil that solidified upon standing. Recrystallization from ether/petroleum ether gave **19** as a colorless solid: mp 83–84 °C; R_f 0.45 (silica gel, ether); mass spectrum, m/e 265 (M^+); IR (KBr) 3030, 2890, 1721, 1635, 1499 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 3 H), 2.68 (dd, J = 16, 2.5 Hz, 1 H), 2.86 (dd, J = 16, 2.5 Hz, 1 H), 3.67 (s, 3 H), 4.00 (m, 4 H), 6.24 (t, J = 2.5 Hz, 1 H), 6.85 (s, 1 H), 7.78 (s, 1 H). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.87; H, 5.66; N, 5.28. Found: C, 58.67; H, 5.63; N, 5.27.

The major byproduct of this reaction, lactone **21**, was isolated in 25% yield as a colorless, crystalline solid: mp 147–48 °C; R_f 0.21 (silica gel, ether); mass spectrum, m/e 251 (M^+); IR (KBr) 3118, 2991, 1785, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (s, 3 H), 1.99 (dd, J = 5.5, 14 Hz, 1 H), 2.30 (ddd, J = 2.5, 10, 14 Hz, 1 H; collapses to a dd upon irradiation at 4.47), 3.53 (dd, J = 5.5, 10 Hz, 1 H; collapses to a doublet upon irradiation at 1.99), 4.04 (m, 4 H), 4.47 (d, J = 2.5 Hz, 1 H), 6.88 (s, 1 H), 7.77 (s, 1 H). Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.63; H, 5.15; N, 5.81.

6-Methyl-7-(5-oxazolyl)-1,4-dioxaspiro[4.4]non-7-ene-6-carboxaldehyde (20). A solution of 2.01 g (7.58 mmol) of oxazole ester **19** in 100 mL of dry CH_2Cl_2 was cooled to −78 °C under N_2 and treated in a dropwise fashion, with vigorous stirring, with 20 mL (2.6 equiv) of 1 N DIBAL in CH_2Cl_2. After this stirred for an additional 1 h at −78 °C, excess DIBAL was destroyed by the slow addition of MeOH. The resulting deep yellow solution was then poured into 600 mL of water, and enough 1 N NaOH was added to destroy any emulsion. The layers were separated, and the aqueous phase was extracted with 4 × 50 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and chromatographed (silica gel, ether) to afford 1.41 g (79%) of **20** as a viscous, pale orange oil that solidified upon standing. Recrystallization from EtOAc/ether gave **20** as a colorless solid, mp 72–73 °C; R_f 0.62 (silica gel, ether); mass spectrum, m/e 235 (M^+); IR (KBr) 3115, 2875, 2730, 1705, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3 H), 2.82 (d, J = 3 Hz, 2 H; collapses to a singlet upon irradiation at 6.43), 3.90 (m, 4 H), 6.43 (t, J = 3 Hz, 1 H; collapses to a singlet upon irradiation at 2.82), 6.84 (s, 1 H), 7.79 (s, 1 H), 9.68 (s, 1 H). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.47. Found: C, 61.32; H, 5.75; N, 5.65.

6-Methyl-7-(5-oxazolyl)-α-1-(*Z*)-propenyl-1,4-dioxaspiro[4.4]non-7-ene-6-methanol (23Z). A total of 3.0 mL (1.4 equiv) of a 1 M solution of (*Z*)-1-lithiopropene in ether was added in dropwise fashion to a stirring solution of 518 mg (2.2 mmol) of oxazole aldehyde **20** in 40 mL of dry THF at −78 °C under N_2. The reaction was warmed slowly to 0 °C and quenched by pouring into 100 mL of pH 7 buffer and 40 mL of CH_2Cl_2. After the layers were separated, the aqueous phase was extracted with 3 × 40 mL of CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and chromatographed (silica gel, ether) to afford 526 mg (86%) of **23Z** as an inseparable 3:1 mixture of epimers at C-8 (pale yellow oil). The major isomer had R_f 0.47 (silica gel, ether); mass spectrum, m/e 277 (M^+); IR ($CHCl_3$) 3520, 3000, 1497, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.42 (d, J = 5.2 Hz, 3 H), 2.50 (dd, J = 3, 18 Hz, 1 H), 2.68 (dd, J = 2.5, 18 Hz, 1 H), 2.77 (d, J = 9 Hz, 1 H), 3.99 (m, 4 H), 4.63 (t, J = 9 Hz, 1 H), 5.52 (m, 2 H), 6.35 (t, J = 3 Hz, 1 H), 7.02 (s, 1 H), 7.97 (s, 1 H).

6-Methyl-7-(5-oxazolyl)-α-1-(*E*)-propenyl-1,4-dioxaspiro[4.4]non-7-ene-6-methanol (23E). In a fashion identical with that described above for **23Z**, **23E** was obtained in 79% yield from oxazole aldehyde **20** and (*E*)-1-lithiopropene (pale yellow oil, 3:1 mixture of epimers at C-8). The major isomer had R_f 0.47 (silica gel, ether) and bp 140 °C (0.35 Torr); mass spectrum, m/e 277 (M^+); IR ($CHCl_3$) 3522, 3002, 1496, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (s, 3 H), 1.61 (d, J = 5 Hz, 3 H), 2.49 (dd, J = 3, 17 Hz, 1 H), 2.64 (dd, J = 2.5, 17 Hz, 1 H), 2.91 (d, J = 8 Hz, 1 H), 3.97 (m, 4 H), 4.19 (t, J = 8 Hz, 1 H), 5.51 (m, 2 H), 6.24 (dd, J = 2.5, 3.0 Hz, 1 H), 6.97 (s, 1 H), 7.98 (s, 1 H). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.90; N, 5.04. Found: C, 64.72; H, 6.74; N, 4.89.

6-Methyl-7-(5-oxazolyl)-α-1-propynyl-1,4-dioxaspiro[4.4]non-7-ene-6-methanol (25). A solution of 200 mg (0.81 mmol) of triphenylmethane in 20 mL of dry THF was cooled to −78 °C under N_2 and treated in a dropwise fashion with 4.8 mL (11.45 mmol) of a 2.35 N solution of *n*-butyllithium in hexane. The red color of the triphenylmethyl anion appeared almost immediately. Propyne gas was then bubbled into the solution with efficient stirring until the red color disappeared. A total of 10 mL of the resulting suspension was then added via syringe to a stirring solution of 540 mg (2.3 mmol) of oxazole aldehyde **20** in 60 mL of THF at −78 °C under N_2. After addition was complete, the reaction mixture was allowed to warm to room temperature over 1 h, and was then poured into 120 mL of pH 7 buffer. Most of the THF was evaporated under reduced pressure, and the remaining aqueous phase was extracted with 4 × 40 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and chromatographed (silica gel, ether) to afford 574 mg (90%) of **25** as a viscous, pale yellow oil (4:1 mixture of epimers at C-8). The major isomer had R_f 0.41 (silica gel, ether), bp 130 °C (0.6 Torr); mass spectrum, m/e 275 (M^+); IR ($CHCl_3$) 3516, 3001, 2230, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3 H), 1.72 (d, J = 3.0 Hz, 3 H), 2.29 (dd, J = 3.5, 18 Hz, 1 H), 2.80 (dd, J = 2.5, 18 Hz, 1 H), 3.15 (d, J = 8 Hz, 1 H), 3.97 (m, 4 H), 4.52 (dq, J = 8, 3 Hz, 1 H), 6.51 (dd, J = 2.5, 3.5 Hz, 1 H), 7.13 (s, 1 H), 7.77 (s, 1 H).

1-[6-Methyl-7-(5-oxazolyl)-1,4-dioxaspiro[4.4]non-7-en-6-yl]-(*Z*)-2-buten-1-one (24Z). A solution of 493 mg (3.65 mmol, 1.2 equiv) of oxalyl chloride in 50 mL of dry CH_2Cl_2 was cooled to −78 °C under N_2 and was treated in a dropwise fashion, with efficient stirring, with 563 mg (511 μL, 7.61 mmol) of DMSO. After this stirred for an additional 5 min at −78 °C, a solution of 843 mg (3.04 mmol) of (*Z*)-propenyl alcohol **23Z** in 5 mL of CH_2Cl_2 was added in one portion. The reaction was kept at −78 °C for 40 min and was then treated with 1.2 mL of NEt_3 and allowed to warm to room temperature. The resulting dark brown reaction mixture was poured into 100 mL of pH 7 buffer, and the layers were separated. The aqueous layer was extracted with 3 × 20 mL of CH_2Cl_2, and the combined organic extracts were dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and chromatographed (silica gel, ether) to afford 689 mg (82%) of **24Z** as a viscous, pale yellow oil that solidified on standing. Recrystallization from ether gave **24Z** as a colorless solid, mp 93–94 °C; R_f 0.62 (silica gel, ether); mass spectrum, m/e 275 (M^+); IR (KBr) 1684, 1614 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 2.03 (dd, J = 2.0, 7.0 Hz, 3 H; collapses to a doublet upon irradiation at 6.31), 2.82 (d, J = 3 Hz, 2 H), 3.90 (m, 4 H), 6.04 (m, 2 H), 6.31 (m, 1 H), 6.75 (s, 1 H), 7.76 (s, 1 H). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.08. Found: C, 65.05; H, 6.27; N, 5.01.

1-[6-Methyl-7-(5-oxazolyl)-1,4-dioxaspiro[4.4]non-7-en-6-yl]-(*E*)-2-buten-1-one (24E). In a fashion identical with that described above for **24Z**, **24E** was obtained in 90% yield as a pale yellow oil, R_f 0.62 (silica gel, ether), from (*E*)-propenyl alcohol **23E**; mass spectrum, m/e 275 (M^+); IR ($CHCl_3$) 3014, 2892, 1686, 1623, 1494, 1442 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.63 (dd,

J = 1.5, 7.0 Hz, 3 H), 2.8 (br s,2 H), 3.83 (m, 4 H), 6.31 (m, 2 H), 6.72 (s, 1 H), 6.79 (m, 1 H), 7.74 (s, 1 H). **24E** gave a 1:1 mixture of **24E** and **24Z** upon equilibration with potassium *tert*-butoxide/*tert*-butyl alcohol.

1-[6-Methyl-7-(5-oxazolyl)-1,4-dioxaspiro[4.4]non-7-en-6-yl]-2-butyn-1-one (26). In a fashion identical with that described above for **24Z**, **26** was obtained in 87% yield by oxidation of acetylenic alcohol **25**. Crystallization from ether/petroleum ether gave **26** as a colorless solid, mp 113–14 °C; R_f 0.48 (silica gel, ether); mass spectrum, m/e 273 (M^+); IR (KBr) 3100, 2210, 1664 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 3 H), 1.90 (s, 3 H), 2.73 (dd, J = 3.0, 18 Hz, 1 H), 2.94 (dd, J = 3.0, 18 Hz, 1 H), 3.97 (m, 4 H), 6.33 (t, J = 3 Hz, 1 H), 6.85 (s, 1 H), 7.87 (s, 1 H). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.12. Found: C, 65.71; H, 5.52; N, 4.93.

(*R,*R**)-6-Methyl-7-(5-oxazolyl)-α-1-(*Z*)-propenyl-α-1-propynyl-1,4-dioxaspiro[4.4]non-7-ene-6-methanol (3Z-R).** Propyne gas was bubbled into a solution consisting of 1.8 mL (3.6 mmol, 2 equiv) of 2 N ethylmagnesium bromide/THF in 10 mL of dry THF at room temperature for 15 min. The resulting solution of 1-propynylmagnesium bromide was then added via syringe to a stirring solution of 484 mg (1.76 mmol) of (*Z*)-enone **24Z** in 20 mL of dry THF maintained at 0 °C under N_2. The reaction mixture was stirred for an additional 1 h at 0 °C and was then allowed to warm slowly to room temperature. Excess propynylmagnesium bromide was quenched with 100 mL of pH 7 buffer, and the aqueous phase was extracted with 3 × 30 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and chromatographed (silica gel, ether) to afford 485 mg (87%) of enynol **3Z-R** as a pale yellow oil, R_f 0.46 (silica gel, ether), and 21 mg (4%) of the epimeric enynol **3Z-S**; mass spectrum, m/e 315 (M^+); IR ($CHCl_3$) 3492, 2225, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53 (s, 3 H), 1.70 (s, 3 H), 1.76 (d, J = 6 Hz, 3 H), 2.45 (dd, J = 4.0, 18 Hz, 1 H), 2.79 (dd, J = 3.0, 18 Hz, 1 H), 3.99 (m, 5 H), 5.48 (m, 2 H), 6.16 (dd, J = 3.0, 4.0 Hz, 1 H), 7.13 (s, 1 H), 7.74 (s, 1 H).

(*R,*R**)-6-Methyl-7-(5-oxazolyl)-α-1-(*E*)-propenyl-α-1-propynyl-1,4-dioxaspiro[4.4]non-7-ene-6-methanol (3E-R).** In a fashion identical with that described above for **3Z-R**, **3E-R** was obtained in 69% yield (4% **3E-S**) as a pale yellow oil, R_f 0.45 (silica gel, ether), from (*E*)-enone **24E**; mass spectrum, m/e 315 (M^+); IR ($CHCl_3$) 3486, 2225, 1656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.48 (s, 3 H), 1.61 (dd, J = 1.0, 6.5 Hz, 3 H), 1.72 (s, 3 H), 2.44 (dd, J = 4.0, 18 Hz, 1 H), 2.70 (dd, J = 3.0, 18 Hz, 1 H), 4.01 (m, 5 H), 5.60 (dq, J = 16, 1.0 Hz, 1 H), 5.83 (dq, J = 16, 6.5 Hz, 1 H), 6.19 (dd, J = 3.0, 4.0 Hz, 1 H), 7.01 (s, 1 H), 7.74 (s, 1 H).

(*R,*S**)-6-Methyl-7-(5-oxazolyl)-α-1-(*Z*)-propenyl-α-1-propynyl-1,4-dioxaspiro[4.4]non-7-ene-6-methanol (3Z-S).** A flame-dired 50-mL three-neck flask equipped with a N_2 inlet, reflux condenser, and a pressure-equalizing addition funnel was charged with 240 mg (10.0 mmol) of magnesium turnings and 5 mL of dry THF. A solution of 1.2 g (0.86 mL, 10.0 mmol) of (*Z*)-1-bromopropene in 5 mL of THF was placed in the addition funnel, and 0.5 mL of this solution was added rapidly to the stirring magnesium turnings along with 100 μL of iodomethane to initiate the reaction. The reaction mixture was warmed gently until the THF began to boil. The remainder of the (*Z*)-1-bromopropene solution was then added dropwise over 1 h at such a rate as to keep the reaction at, or near, reflux. The resulting clear, light brown solution of (*Z*)-1-propenylmagnesium bromide was cooled to room temperature and used directly. A solution of 21.3 mg (0.07 mmol) of acetylenic ketone **26** in 2 mL of dry THF maintained at −78 °C was treated with vigorous stirring, under N_2, with 500 μL of the Grignard solution prepared as described above. After addition was complete, the reaction was allowed to warm to 0 °C and quenched by pouring into 20 mL of pH 7 buffer. The aqueous phase was extracted with 4 × 10 mL of CH_2Cl_2, and the combined extracts were dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and purified by preparative TLC. Collection of the band of R_f 0.53 (silica gel, ether) gave 7.5 mg (34%) of **3Z-S** as a viscous, pale yellow oil: mass spectrum, m/e 315 (M^+); IR ($CHCl_3$) 3486, 2222, 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 3 H), 1.78 (s, 3 H), 1.82 (d, J = 7 Hz, 3 H), 2.48 (dd, J = 4.0, 18 Hz, 1 H), 3.14 (dd, J = 2.5, 18 Hz, 1 H), 4.04 (m, 5 H), 5.45 (m, 2 H), 6.38 (dd, J = 2.5, 4.0 Hz, 1 H), 7.04 (s, 1 H), 7.76 (s, 1 H). None of the epimeric enynol **3Z-R** could be detected by TLC or NMR analysis.

(*R,*S**)-6-Methyl-7-(5-oxazolyl)-α-1-(*E*)-propenyl-α-1-propynyl-1,4-dioxaspiro[4.4]non-7-ene-6-methanol (3E-S).** In a fashion identical with that described above for **3Z-S**, **3E-S** was obtained in 24% yield as a pale yellow oil, R_f 0.52 (silica gel, ether), from acetylenic ketone **26** and (*E*)-1-propenylmagnesium bromide; mass spectrum, m/e 315 (M^+); IR ($CHCl_3$) 3486, 2225 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, 3 H), 1.62 (dd, J = 1.5, 6.5 Hz, 3 H), 1.79 (s, 3 H), 2.48 (dd, J = 4.0, 17.5 Hz, 1 H), 3.18 (dd, J = 2.5, 17.5 Hz, 1 H), 4.03 (m, 5 H), 5.45 (dq, J = 16, 1.5 Hz, 1 H), 5.84 (dq, J = 16, 6.5 Hz, 1 H), 6.37 (dd, J = 2.5, 4.0 Hz, 1 H), 6.91 (s, 1 H), 7.75 (s, 1 H). None of the epimeric enynol **3E-R** could be detected by TLC or NMR analysis.

(*R,*S**)-6-[9-Methyl-8-(5-oxazolyl)-1,4-dioxaspiro[4.4]non-8-en-7-yl]-2-heptyn-4-one (5).** A solution of 70 mg (0.22 mmol) of tertiary alcohol **3Z-R** in 8 mL of dry, degassed toluene was heated at reflux under N_2 for 4 h. The resulting pale yellow solution was cooled to room temperature, concentrated under reduced pressure, and purified by preparative TLC to afford 61 mg (87%) of oxy-Cope product **5** as a pale yellow oil: R_f 0.44 (silica gel, 30% EtOAc/CH_2Cl_2); mass spectrum, m/e 315 (M^+); IR ($CHCl_3$) 2219, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66 (d, J = 7.0 Hz, 3 H), 1.83 (dd, J = 4.0, 14.5 Hz, 1 H; collapses to a doublet upon irradiation at 3.19), 1.87 (d, J = 2.0 Hz, 3 H), 2.01 (s, 3 H), 2.08 (dd, J = 8.0, 14.5 Hz, 1 H; collapses to a doublet upon irradiation at 3.19), 2.37 (m, 2 H), 2.65 (m, 1 H), 3.19 (m, 1 H), 4.01 (m, 4 H), 7.18 (s, 1 H), 7.88 (s, 1 H). None of the acetylenic oxy-Cope product **12Z** or the isomeric vinylic oxy-Cope product **5α** could be detected by TLC or NMR analysis.

(*R,*R**)-6-[9-Methyl-8-(5-oxazolyl)-1,4-dioxaspiro[4.4]non-8-en-7-yl]-2-heptyn-4-one (5α).** A solution of 49 mg (0.16 mmol) of tertiary alcohol **3E-R** in 5 mL of dry, degassed toluene was heated at reflux under N_2 for 3 h. The resulting pale yellow solution was cooled to room temperature, concentrated under reduced pressure, and purified by preparative TLC to afford 37 mg (75%) of oxy-Cope product **5α** as a pale yellow oil: R_f 0.44 (silica gel, 30% EtOAc/CH_2Cl_2); mass spectrum, m/e 315 (M^+); IR ($CHCl_3$) 2220, 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 7.0 Hz, 3 H), 1.81 (dd, J = 3.5, 4.5 Hz, 1 H), 1.87 (d, J = 2.0 Hz, 3 H), 1.89 (s, 3 H), 2.19 (m, 3 H), 2.60 (m, 1 H), 3.14 (m, 1 H), 4.01 (m, 4 H), 7.13 (s, 1 H), 7.88 (s, 1 H). None of the acetylenic oxy-Cope product **12E** or the isomeric vinylic oxy-Cope product **5** could be detected by TLC or NMR analysis.

Gnididione Ketal (7). Method A. Thermolysis of 5. A solution of 24 mg (0.076 mmol) of oxy-Cope product **5** in 10 mL of dry, degassed mesitylene was treated with a trace of $NaHCO_3$ and hydroquinone, and the resulting mixture was heated at reflux for 60 h under N_2. Concentration under reduced pressure and purification by preparative TLC then afforded 10 mg (45%) of **7** as a colorless, crystalline solid: mp 103–04 °C; R_f 0.64 (silica gel, ether); mass spectrum, m/e 288 (M^+); IR ($CHCl_3$) 2970, 2880, 1654, 1520, 1435 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, J = 6.50 Hz, 3 H), 1.75 (dd, J = 8.0, 13.0 Hz, 1 H), 1.94 (m, 1 H), 2.03 (d, J = 2.3 Hz, 3 H), 2.16 (d, J = 1.0 Hz, 3 H), 2.29 (dd, J = 6.5, 13.0 Hz, 1 H), 2.68 (m, 3 H), 4.05 (m, 4 H), 7.18 (q, J = 1.0 Hz, 1 H). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.79; H, 7.21.

Method B. Direct Thermolysis of 3Z-R. A solution of 47.4 mg (0.150 mmol) of tertiary alcohol **3Z-R** in 10 mL of dry, degassed mesitylene was treated with a trace of $NaHCO_3$ and hydroquinone, and the resulting mixture was heated at reflux for 72 h under N_2. Concentration under reduced pressure and purification by preparative TLC then afforded 20.6 mg (48%) of **7**, identical with that prepared by method A above.

Isognididione Ketal (7α). Method A. Thermolysis of 5α. A solution of 19 mg (0.060 mmol) of oxy-Cope product **5α** in 8 mL of dry, degassed mesitylene was treated with a trace of $NaHCO_3$ and hydroquinone, and the resulting mixture was heated at reflux for 24 h under N_2. Concentration under reduced pressure and purification by preparative TLC then afforded 13 mg (74%) of **7α** as a pale yellow oil: R_f 0.63 (silica gel, ether); mass spectrum, m/e 288 (M^+); IR ($CHCl_3$) 2968, 2885, 1650, 1511, 1416 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (d, J = 7.0 Hz, 3 H), 1.80 (dd, J = 7.0, 14.0 Hz, 1 H), 2.00 (d, J = 2.0 Hz, 3 H), 2.02 (m, 1 H), 2.16 (d, J = 1.3 Hz, 3 H), 2.29 (dd, J = 7.5, 14.0 Hz, 1 H), 2.73 (dd, J = 5.5,

16.0 Hz, 1 H), 2.87 (dd, J = 5.4, 16.0 Hz, 1 H), 3.19 (m, 1 H), 4.04 (m, 4 H), 7.16 (q, J = 1.3 Hz, 1 H).

Method B. Direct Thermolysis of 3E-R. A solution of 25.2 mg (0.080 mmol) of tertiary alcohol **3E-R** in 3 mL of dry, degassed mesitylene was treated with 6 mg of $NaHCO_3$, and the resulting mixture was heated at reflux for 24 h under N_2. Concentration under reduced pressure and purification by preparative TLC then afforded 13.0 mg (60%) of **7α**, identical with that prepared by Method A above.

(±)-Gnididione (1). A solution of 27.2 mg (0.094 mmol) of gnididione ketal (**7**) in 4 mL of acetone was treated with ~2 mg of *p*-toluenesulfonic acid at room temperature with stirring. After stirring for 15 min, the reaction was quenched with 10 mL of saturated $NaHCO_3$ and extracted with 3 × 5 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and purified by preparative TLC to afford 22.5 mg (98%) of **1** as a colorless cyrstalline solid, R_f 0.55 (silica gel, ether), which had identical NMR, IR, UV, mass spectral, and TLC behavior as an authentic sample.[20] Recrystallized from MeOH, synthetic **1** had mp 108–09 °C (lit. mp 102–03 °C, synthetic;[5b] 110–11 °C, (+)-**1**[1]).

(±)-Isognididione (2). A solution of 12.9 mg (0.045 mmol) of isognididione ketal (**7α**) in 2 mL of acetone was treated with ~2 mg of *p*-toluenesulfonic acid at room temperature with stirring. After stirring for 1 h, the reaction was quenched with 10 mL of saturated $NaHCO_3$ and extracted with 3 × 5 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and purified by preparative TLC to afford 10.5 mg (96%) of **2** as a colorless, crystalline solid, R_f 0.50 (silica gel, ether), which had identical NMR, IR, UV, mass spectral, and TLC behavior as an authentic sample.[1,20] Recrystallized from ether/petroleum ether, synthetic **2** had mp 130–31 °C (lit. (−)-**2**,[1] amorphous solid).

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Registry No. (±)-**1**, 89999-21-3; (±)-**2**, 89999-22-4; (±)-**3*Z*-*R***, 123597-42-2; (±)-**3*E*-*R***, 123621-26-1; (±)-**3*Z*-*S***, 123597-43-3; (±)-**3*E*-*S***, 123597-44-4; (±)-***S***, 89999-23-5; (±)-**5α**, 89999-24-6; (±)-**7**, 89999-25-7; (±)-**7α**, 89999-26-8; (±)-**13**, 81159-11-7; **15**, 123597-45-5; (±)-**16**, 123597-46-6; (±)-**17**, 123597-47-7; (±)-**18**, 123597-48-8; (±)-**19**, 123597-49-9; (±)-**20**, 89999-31-5; (±)-**21**, 123597-50-2; (±)-**23*Z*-*R***, 123597-51-3; (±)-**23*E*-*R***, 123621-27-2; (±)-**23Z-*S***, 123597-52-4; (±)-**23E-*S***, 123597-53-5; (±)-**24*Z***, 89999-33-7; (±)-**24*E***, 89999-34-8; (±)-**25-*R***, 89999-35-9; (±)-**25-*S***, 89999-36-0; (±)-**26**, 89999-37-1; CH_3NC, 593-75-9.

Selective Photoelectrochemical Oxidation of Vicinal Cyclohexanedicarboxylic Acids: A Mechanistic Study

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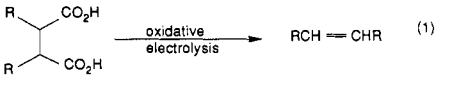
The course of photooxidation of vicinal diacids on irradiated TiO_2 suspensions proceeds via one-electron oxidative decarboxylation rather than two-electron oxidative bis-decarboxylation (which occurs on poised metal electrodes). The formation of a monocarboxylic acid as the major product indicates that trapping of an intermediate radical is competitive with further oxidation. The observed regiochemical preference in unsymmetrical diacids is rationalized by the conformational preference of the diacid adsorbed onto the photoactivated catalyst surface.

Introduction

The semiconductor-mediated photocatalyzed oxidation of many organic substrates proceeds through interfacial electron transfer, with an appropriate adsorbate trapping the photogenerated hole.[1-3] In several cases, clear evidence exists for surface-confined organic cation radicals formed in this manner.[4,5] Since the occurrence of single vs multiple electron transfer redox reactivity remains one of the pressing problems in synthetic organic electrochemistry, we sought to determine whether photoelectrochemical methods using semiconductor powders could be used to selectively achieve a desired single-electron oxidative route.

Photoexcitation of semiconductor particles such as titanium dioxide with light of energy greater than the band gap produces electron-hole pairs[2] (Figure 1). These electrons and holes serve as reductants and oxidants, respectively, for compounds adsorbed to the semiconductor surface. Chemical selectivity of these photoelectrochemical transformations is influenced by three different factors: (1) the accessible electrochemical potentials (defined by the potential of the band edges of the semiconductor); (2) preferential adsorption of donors and/or acceptors to the catalytic surface; and (3) the rate at which charge carriers (electrons and holes) are delivered to the adsorbed donor or acceptor. All three effects have demonstrable consequence in the selectivity observed in this study.

We report herein our investigation of the TiO_2-photocatalyzed oxidation of several vicinal dicarboxylic acids. Mild two-electron oxidation of these compounds at an inert electrode causes bis-decarboxylation, producing an alkene, eq 1.[6] In contrast, we find that in several cases photoe-



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