or 10% Carbowax 20M on 100/120 Supelcoport (5 or 6 ft × 4 mm) in glass columns, 30-mL/min helium as the carrier gas at flow rates and temperatures as specified (Tables VI and X).

General Procedure for the Preparation of 14-(Primary alkyl)-5,6,8,9-tetrahydro-7-phenyldibenzo[*c*,*h*]acridinium Tetrafluoroborates (8-17) (Table I). Method A. 5,6,8,9-Tetrahydro-7-phenyldibenzo[*c*,*h*]-xanthylium tetrafluoroborate[18] (**6**) (4.48 g, 0.01 mol) and the corresponding amine (0.01 mol) were stirred in ethanol (20 mL) for 24 h at room temperature. The product was filtered and crystallized.

Method B. 5,6,8,9-Tetrahydro-7-phenyldibenzo[*c*,*h*]xanthylium tetrafluoroborate[18] (**6**) (4.48 g, 0.01 mol), the corresponding amine (0.01 mol), and triethylamine (1.01 g, 0.01 mol) were stirred in CH_2Cl_2 (30 mL) for 3 h at room temperature. AcOH (0.120 g, 0.002 mol) was added and the mixture was stirred for 48 h. After the solution was with washed water and 10% HCl, the organic layer was dried with $MgSO_4$. Addition of Et_2O gave the product (except for **11** and **12** where the petroleum ether was used). The product was purified by dissolving in CH_2Cl_2 and reprecipitating with Et_2O or petroleum ether. Compounds (Table I) were characterized by C, H, N analysis (Table XXVIII*), UV, NMR, and ^{13}C NMR (Table II*). **5,6,8,9-Tetrahydro-7-phenyldibenzo[*c*,*h*]acridine** (**7**) was prepared from 5,6,8,9-tetrahydro-7-phenylxanthylium tetrafluoroborate according to the literature method.[18]

Kinetic Measurements. Kinetics were followed by UV spectrophotometry monitoring the decrease of absorbance of the acridinium cation at fixed wavelength (386 nm) using the procedure already described.[19] In typical runs under pseudo-first-order conditions the concentration of acridinium compound was 6.4×10^{-5} M. A slightly different procedure was utilized for trifluoroacetic and acetic acids: the kinetic solutions of the acridinium compound (1.6×10^{-3} mol L^{-1}) were diluted to the UV concentration (6.4×10^{-5} mol L^{-1}) using a 4% (v/v) solution of triethylamine in ethanol before UV measurement (this converted acridine (**7**) into free base). Pseudo-first-order rate constants were calculated from the slope of conventional plots of ln $[(\epsilon_1 - \epsilon_2)/(\epsilon - \epsilon_2)]$ vs. time.[36] Such plots were linear to at least 80-90% completion, and k values were reproducible to ca. 5%.

Solvolysis Procedure by GC/MS Study. The acridinium compound (0.5 g) in 0.5 mL of solvent was heated in a sealed glass tube at 150 °C for 24-48 h. The tube was opened immediately before using for GC/MS study.

Acknowledgment. We thank the Department of Chemistry, A. Mickiewicz University, Pozan, Poland, for leave of absence to Zofia Dega-Szafran and the Commission for Educational Exchange between the United States and Spain for a Fulbright M.U.I. grant to Maria L. Lopez-Rodriguez.

Registry No. 6, 53217-56-4; **8**, 90886-02-5; **9**, 90886-03-6; **10**, 88125-57-9; **10A**, 557-17-5; **10B**, 109-60-4; **10C**, 108-21-4; **10D**, 115-07-1; **11**, 88125-58-0; **11A**, 628-80-8; **11B**, 6795-88-6; **11C**, 628-63-7; **11D**, 626-38-0; **11E**, 109-68-2; **11F**, 109-67-1; **12**, 90886-04-7; **12A**, 929-56-6; **12B**, 1541-09-9; **12C**, 54658-02-5; **12D**, 111-66-0; **12E**, 111-67-1; **12F**, 112-14-1; **12G**, 2051-50-5; **12H**, 4864-61-3; **12I**, 5921-87-9; **13**, 90886-05-8; **13A**, 625-44-5; **13B**, 115-11-7; **13C**, 540-88-5; **13D**, 105-46-4; **13E**, 110-19-0; **13F**, 107-39-1; **14**, 90886-07-0; **14A**, 994-05-8; **14B**, 513-35-9; **14C**, 625-16-1; **14D**, 926-41-0; **14E**, 5343-96-4; **15**, 81128-08-7; **16**, 82135-18-0; **17**, 90886-09-2.

Supplementary Material Available: Tables II (^{13}C NMR data for **8-17**), III (UV data for **7-17**), VIII, IX, XI-XX (mass spectral data for **10-14**), XXVI (solvolysis rate constants for **8-11**, **13**, **14**), and XXVII (analytical data for **8-17**) (16 pages). Ordering information is given on any current masthead page.

(36) Latham, J. L. "Elementary Reaction Kinetics"; Butterworths: London, 1969.

Bis Heteroannulation. 4. Facile Syntheses of Methylene Acids, Methylbutenolides, α-Methyl-γ-lactones, and Related Materials. Total Syntheses of (±)-Ligularone and (±)-Petasalbine

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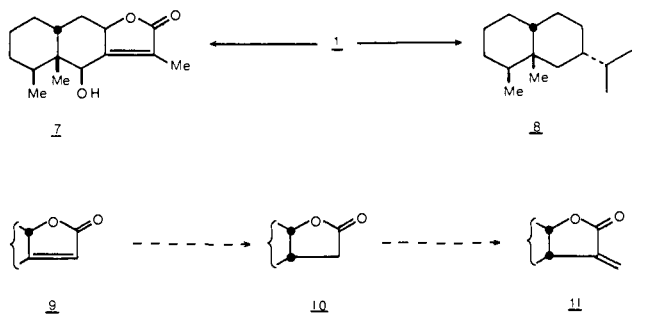
Contribution from the Hall-Atwater Laboratories, Wesleyan University, Middletown, Connecticut 06457. *Received December 5, 1983. Revised Manuscript Received March 26, 1984*

Abstract: Acetylenic oxazoles of proper design undergo an intramolecular Diels-Alder reaction leading directly to fused ring furan derivatives ("bis heteroannulation"). With 5-ethoxyoxazoles the corresponding 2-ethoxyfurans are obtained, and these latter materials are excellent precursors for methylene esters, methylene acids, methylbutenolides, α-methyl-γ-lactones, and β-methylfurans. In similar fashion, acetylenic oxazoles unsubstituted in the 2-position have been utilized for highly efficient syntheses of (±)-ligularone and (±)-petasalbine.

The structural diversity of the sesquiterpenes is renowned, and it is of little surprise that these materials have been a source of continuing fascination for synthetic chemists. With their myriad of skeletal types and their relatively large number of asymmetric centers, members of this class have served as an important testing ground for new synthetic methodology. Furthermore, many of these efforts have culminated in elegant total syntheses.[1]

(1) For representative examples see: (a) Ziegler, F. E.; Fang, J. M.; Tam, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 7174. (b) Schlessinger, R. H.; Kieczykowski, G. R.; Quesada, M. L. *Ibid.* **1980**, *102*, 782. (c) Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *Ibid.* **1977**, *99*, 6066. (d) Yoshikoshi, A.; Kumazawa, T.; Miyashita, M. *J. Org. Chem.* **1980**, *45*, 2945. (e) Grieco, P. A.; Nishizawa, M.; Oguri, T.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773. (f) Grieco, P. A.; Oguri, T.; Gilman, S.; DeTitta, G. T. *Ibid.* **1978**, *100*, 1616. (g) Schultz, A. G.; Godfrey, J. D. *Ibid.* **1980**, *102*, 2414. (h) Lansbury, P. T.; Hangauer, D. G.; Vacca, J. P. *Ibid.* **1980**, *102*, 3964. (i) Wender, P. A.; Lechleiter, J. C. *Ibid.* **1978**, *100*, 4321. (j) Wender, P. A.; Howbert, J. J. *Tetrahedron Lett.* **1983**, 5325.

Scheme I



Our own work in this area has focused on the observation that virtually all of these materials, regardless of their complexity, exhibit certain structural features in common (cf. Chart I).[2] That

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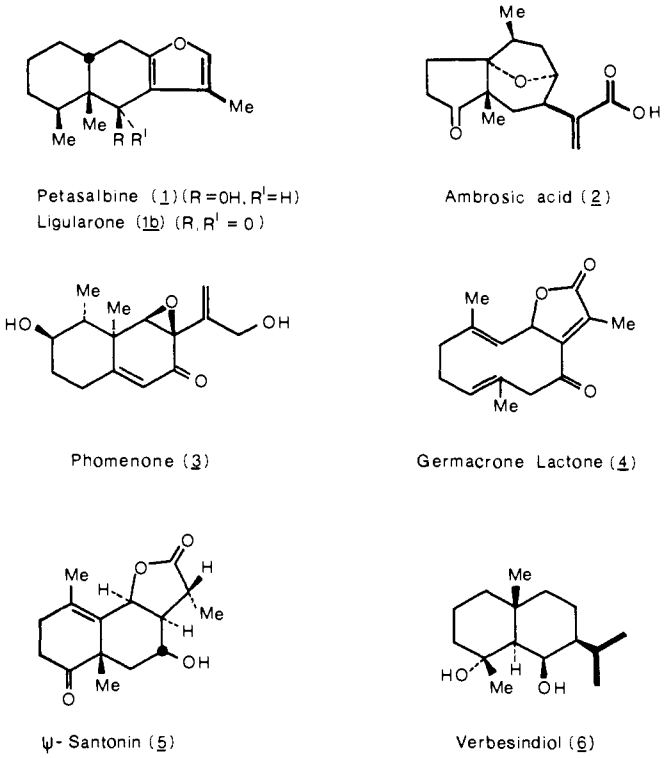
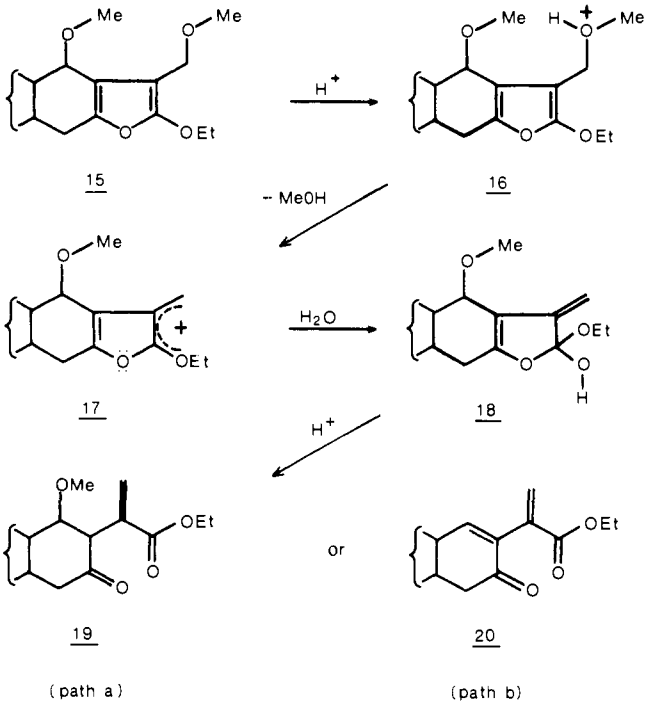
Chart I



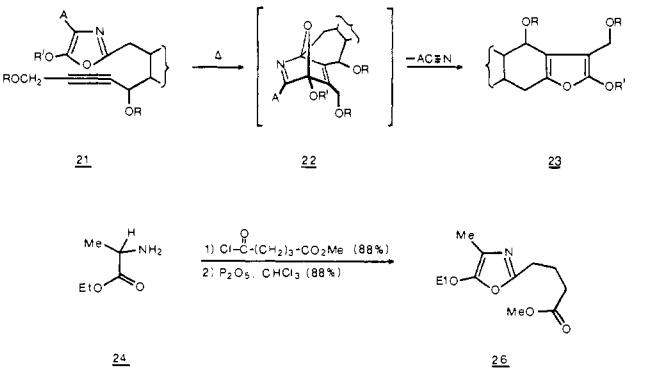
such should be the case is of course not surprising since all of these compounds can be traced to the same biological precursor.[3] Nevertheless, it is interesting to note that (1) most of these materials either contain a furan ring *or* a functionality *in principle* derivable from a furan ring and (2) many of the more biologically active compounds contain an oxygen functionality at a position adjacent to the furan or *furan-derived* ring juncture.[4]

In reference to point 1, it will be recognized that a properly constituted furan ring represents an extremely versatile synthon.[5] Pertinent examples include the oxidative conversion of petasalbine (**1**) to 6-hydroxyeremophilenolide (**7**) and the hydrogenolysis of this same material to give eremophilane (**8**) (Scheme I).[6] In addition, it is now well established that butenolides of type **9** can be selectively reduced to the corresponding γ-lactones **10**,[7] which in turn are useful precursors for elaboration to methylene lactones **11**.[8] Each of these transformations could be of considerable practical importance if methods could be developed for the regiospecific incorporation of furan rings within the confines of relatively complex molecular skeletons. In this paper we describe an efficient solution to the problem of regiochemical control in such systems, as illustrated by our total syntheses of petasalbine (**1**) and ligularone (**1b**), and we provide additional examples which further establish the synthetic utility of highly substituted furan derivatives.

Scheme II

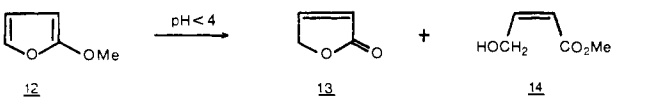


Scheme III



Discussion and Results

Our initial efforts in this area were stimulated by the report that 2-methoxyfuran (**12**) is rapidly hydrolyzed under acidic conditions (pH < 4) to give mixtures of 4-hydroxycrotonic acid lactone (**13**) and methyl 4-hydroxycrotonate (**14**).[9] Mechanistic



studies of this reaction now indicate that initial protonation takes place at C-5. One might expect, however, that this hydrolytic behavior could be modified by a proper choice of substituents about the furan ring,[10] and we were intrigued with the possibility that furans of type **15** might undergo initial protonation at the C-3′ substituent as indicated (Scheme II). Is such were the case, we believed, intermediate **16** should undergo a rapid heterolytic cleavage to generate the highly stabilized oxonium cation **17**, and this latter material could proceed via orthoester **18** to either of

(2) A preliminary communication describing portions of this work has appeared: (a) Jacobi, P. A.; Craig, T. *J. Am. Chem. Soc.* **1978**, *100*, 7748. For other papers in this series, see: (b) Jacobi, P. A.; Walker, D.; Odeh, I. *J. Org. Chem.* **1981**, *46*, 2065. (c) Jacobi, P. A.; Walker, D. *J. Am. Chem. Soc.* **1981**, *103*, 4611. (d) Jacobi, P. A.; Weiss, K. T.; Egbertson, M. *Heterocycles* **1984**, *22*, 281. (e) Jacobi, P. A.; Selnick, H. G. *J. Am. Chem. Soc.* **1984**, *106*, 3041. (f) Jacobi, P. A.; Kaczmarek, C. S. R.; Udodong, U. E. *Tetrahedron Lett.*, in press.

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

(4) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147.

(5) Meyers, A. I. "Heterocycles in Organic Synthesis"; Wiley: New York, 1974.

(6) (a) Ishii, H.; Tozyo, T.; Minato, H. *J. Chem. Soc. C* **1966**, 1545. (b) Ishii, H.; Tozyo, T.; Minato, H. *Tetrahedron* **1965**, *21*, 2605. (c) Novotný, L.; Herout, V.; Storm, F. *Collect. Czech. Chem. Commun.* **1964**, *29*, 2189.

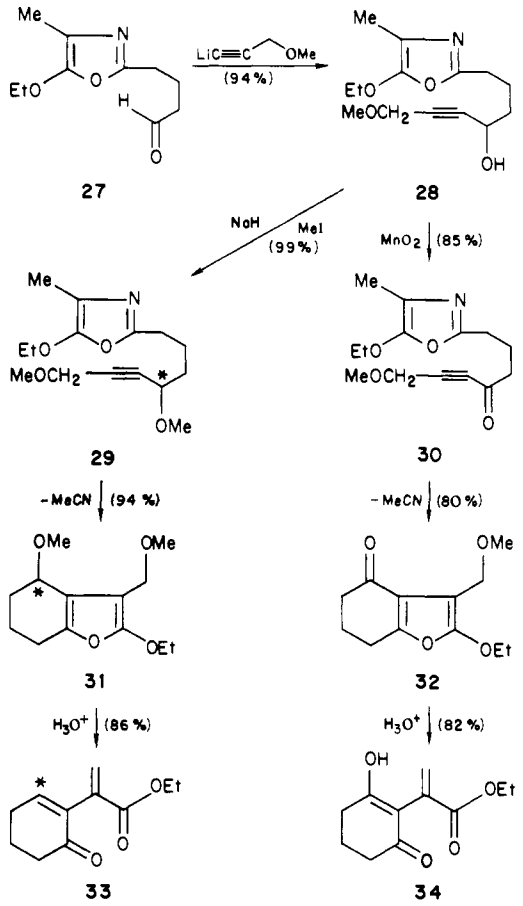
(7) Kido, F.; Tsutsumi, K.; Maruta, R.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1979**, *101*, 6420 and references cited therein.

(8) Grieco, P. A. *Synthesis* **1975**, 67.

(9) Garst, J. E.; Schmor, G. L. *J. Org. Chem.* **1974**, *39*, 2920.

(10) Acheson, R. M. "An Introduction to the Chemistry of Heterocyclic Compounds"; Interscience: New York, 1967.

Scheme IV

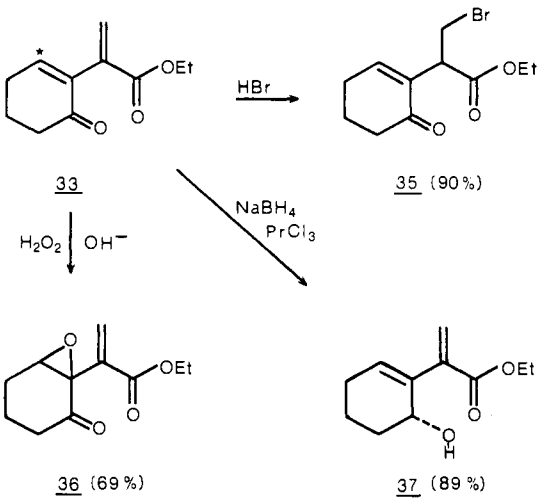


two likely products.[11] Protonation at C-4, for example, could lead via path a to β-methoxy ketone **19**, while protonation at the C-4′ substituent would presumably lead to enone **20** (path b).[12] It will be noted that both **19** and **20** contain an array of functionality which could be useful in the synthesis of highly oxygenated sesquiterpenes.

In order to test this hypothesis we have developed a remarkably efficient synthesis of furans of general structure **23** which takes advantage of the extraordinary reactivity of oxazoles in Diels–Alder reactions[13] ("bis heteroannulation",[2] Scheme III). Among other features,[2] this approach allows for an unambiguous positioning of the furan ring relative to other functionality.

The utility of this process was initially studied with the unsubstituted derivative **29** (Scheme IV). Thus, the readily available ester **26** was smoothly converted to aldehyde **27** which was immediately condensed with lithiomethyl propargyl ether to give acetylenic oxazole **28** in excellent overall yield. This latter material, in turn, could be methylated to give the target compound **29** (99%) or oxidized to give the acetylenic ketone **30** (85%). Both **29** and **30** proved to be excellent substrates for the bis heteroannulation process. Compound **29**, for example, gave a 94% yield

Scheme V

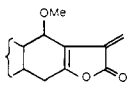


of ethoxyfuran **31** upon refluxing in ethylbenzene, while **30** required somewhat less vigorous conditions, giving **32** in 80% yield in refluxing benzene. The NMR spectrum of **31** in D_2O was revealing. At pH values ≥ 7 **31** was stable and showed all peaks expected for the assigned structure. Upon addition of 1 drop of 1 N H_2SO_4, however, the spectrum was instantly transformed to that expected for the methylene ester **33**. On a preparative scale this transformation could be routinely accomplished in 86% yield upon brief exposure of **31** to 1 N H_2SO_4,[14] and in analogous fashion ketone **32** gave an 82% yield of the corresponding methylene ester **34**. For compound **31** we could find no evidence for the formation of products derived from path a (Scheme II), although such a pathway might predominate in special circumstances.[15]

Methylene ester **33** proved to be highly selective in its reaction with a variety of nucleophilic and electrophilic reagents (Scheme V). Addition of HBr, for example, gave an excellent yield of bromomethyl derivative **35** (90%), while reaction with hydrogen peroxide, under basic catalysis, gave epoxide **36** as the only isolable product (69%). Also, reduction with $NaBH_4$, *in the presence of* $PrCl_3$,[16] proceeded normally to give hydroxy ester **37** in 89% yield.[17]

Of perhaps greater interest, however, **33** was also an excellent precursor for the synthesis of methylbutenolide **40** and closely related materials (Scheme VI). Thus, **33** was cleanly hydrolyzed to the methylene acid **38** (NaOH, 97%) which gave a 97% yield of **40** upon heating in 1 N H_2SO_4. Alternatively, **40** was also obtained upon prolonged acid hydrolysis of either the methylene ester **33** (88%) or ethoxyfuran **31** (64%). This latter sequence allowed for the two-step conversion of acetylenic oxazole **29** to methylbutenolide **40** in an overall yield of 60%.[18] Methyl-

(11) A third possibility, involving formation of the unsaturated lactone *i*,

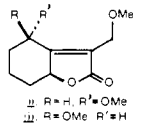


was deemed less likely because of the strain associated with the introduction of an additional sp^2 center (total of four) within a five-membered ring. See also ref 1a.

(12) See, for example: Novotný, L.; Kotva, K. *Collect. Czech. Chem. Commun.* **1974**, *39*, 2949.

(13) (a) Grigg, R.; Jackson, J. L. *J. Chem. Soc. C* **1970**, 552 and references cited therein. (b) Graf, F.; Konig, H. Deutsches Patentamt 1 935 009 (Jan 14, 1971). (c) Katritzky, A. R.; Boulton, A. J. Eds. "Advances in Heterocyclic Chemistry"; Academic Press: New York, 1974; Vol. 17.

(14) Interestingly, however, in aqueous acetic acid **31** gave only trace amounts of **33**, the major products being the isomeric butenolides ii and iii:



ii, R=H, R'=OMe
iii, R=OMe R'=H

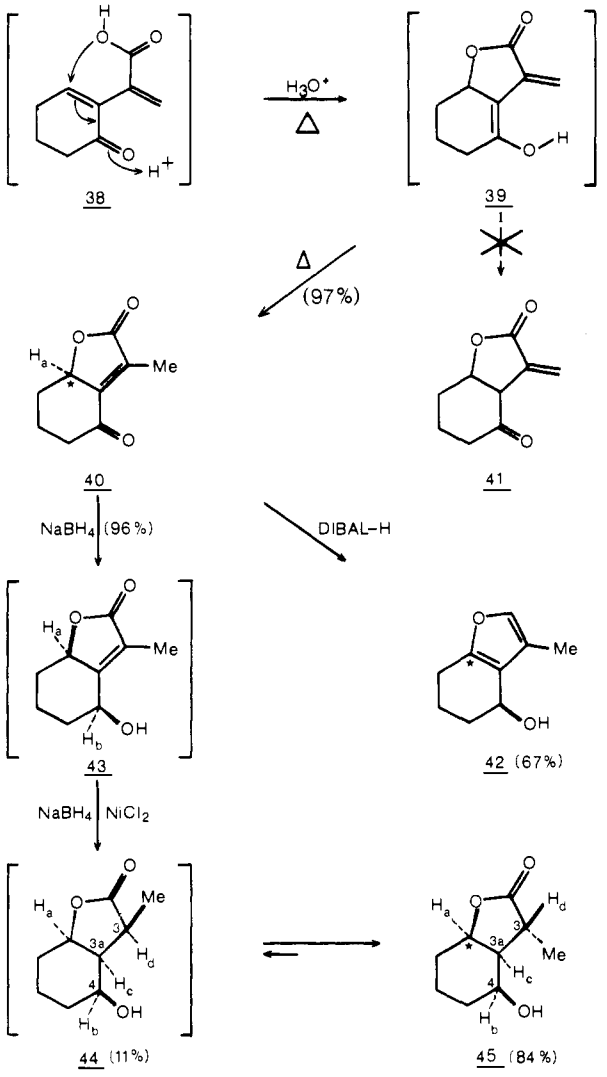
(15) (a) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1982**, *104*, 7591. (b) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *Ibid.* **1979**, *101*, 6996. (c) see also ref 1a.

(16) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(17) In the absence of $PrCl_3$ conjugate addition occurred to give iv and v (4:1) in a combined yield of 50%:

iv v

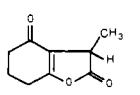
Scheme VI



butenolide **40**, in turn, could be smoothly reduced to either of three related products. With DIBAL-H, for example, **40** gave a 67% yield of the β-methylfuran **42**,[19] while $NaBH_4$ effected clean reduction of **40** to hydroxybutenolide **43** (96%). In addition, both **40** and **43** gave an 84% yield of the methyl lactone **45**, accompanied by **44** (11%), with the reagent system $NaBH_4/NiCl_2$.[7]

Stereochemical assignments for **43**, **44**, and **45** were made on the basis of literature precedence as well as the following observations. The diequatorial configuration of **43** was evident from that fact that both H_a and H_b exhibited long-range coupling with the 3-methyl substituent (J = 2.5 Hz).[20] Since **43**, in turn, was converted to **44** and **45** under conditions which did not epimerize H_a, it follows that the relative configuration of H_a and H_b in both **44** and **45** must be cis. Next, the cis configuration for lactones **44** and **45** was assigned on the basis of an exhaustive comparison with published NMR spectra of similar compounds.[3] In particular,

(18) In no case could we detect measurable quantities of methylene lactone **41**, a product which could conceivably arise by kinetic protonation of intermediate **39**. Also, all attempts at effecting the direct conversion of **40** to **41** via a kinetic deprotonation–protonation sequence gave the isomeric lactone vi as the only observed product:

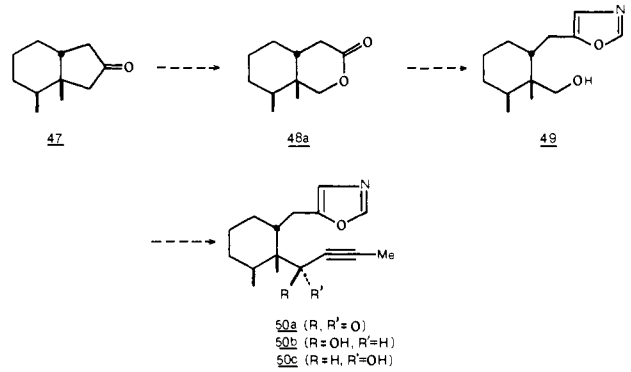


vi

(19) Grieco, P. A.; Pogonowski, C. S.; Burke, S. *J. Org. Chem.* **1975**, *40*, 543.

(20) Pavia, D. L.; Lampman, G. M.; Kris, G. S. "Introduction to Spectroscopy"; W. B. Saunders: London, 1979.

Scheme VII



we and others have noted that methine protons of type H_a invariably absorb in the region 4.4–5.0 ppm for the *cis*-lactone series and in the 3.8–4.2-ppm region for the trans series.[21] These general assignments appear to be valid regardless of the substitution patterns at C-3 and C-4. For **44** and **45**, H_a absorbed as a multiplet centered at δ 4.4 and 4.5, respectively, thereby establishing the configuration at C-3a as indicated. The remaining issue relating to stereochemistry at C-3 was easily resolved as follows. The epimeric nature of **44** and **45** was confirmed by the fact that pure **44** or **45** could be equilibrated to the same 84:11 mixture upon brief exposure to potassium *tert*-butoxide. Also, **44** was slowly converted to **45** upon standing in $CDCl_3$ solution, a result, undoubtedly, of servere steric repulsion between the C-3 β-methyl group and the cis fused six-membered ring. Models clearly indicate that this interaction should be highly unfavorable. Regarding the mechanism for this process, we consider it likely that initial reduction takes place in a cis fashion to give **44**, followed by rapid equilibrium under the reaction conditions to give the observed product ratio. It is noteworthy, we feel, that methyl lactone **45** was prepared in only three steps from acetylenic oxazole **29** with virtually complete stereo- and regiochemical control, and we might also emphasize the close structural resemblance between model systems **33**–**45** and a variety of naturally occurring materials (cf. Chart I).

Ligularone (1b) and Petasalbine (1). Having thus established the viability of the bis heteroannulation process for the preparation of highly substituted furans of type **23**, it was of interest to see if similar procedures might be employed for the synthesis of β-methylfurans. Members of this class are widely distributed in nature and as our initial targets we chose the furanoeremophilanes ligularone (**1b**) and petasalbine (**1**).[25,26] In part, at least, this choice was based on the inherent challenge offered by the eremophilane skeleton.

In a retrosynthetic sense it was readily apparent that acetylenic oxazole **50a** contained all of the stereo- and regiochemical features requisite for a completely unambiguous synthesis of **1b**, and we considered it likely, in turn, that **50a** should be routinely available from the oxazole alcohol **49** (Scheme VII).[27] Furthermore, there

(21) (a) Brocksom, T. J.; Ferreira, J. T. B. *Synth. Commun.* **1981**, *11*, 105. (b) Lansbury, P. T.; Vacca, J. P. *Tetrahedron* **1982**, *38*, 2797.

(22) Taylor, E. C.; McKillop, A. *J. Am. Chem. Soc.* **1965**, *87*, 1984.

(23) Parikh, J. R.; Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

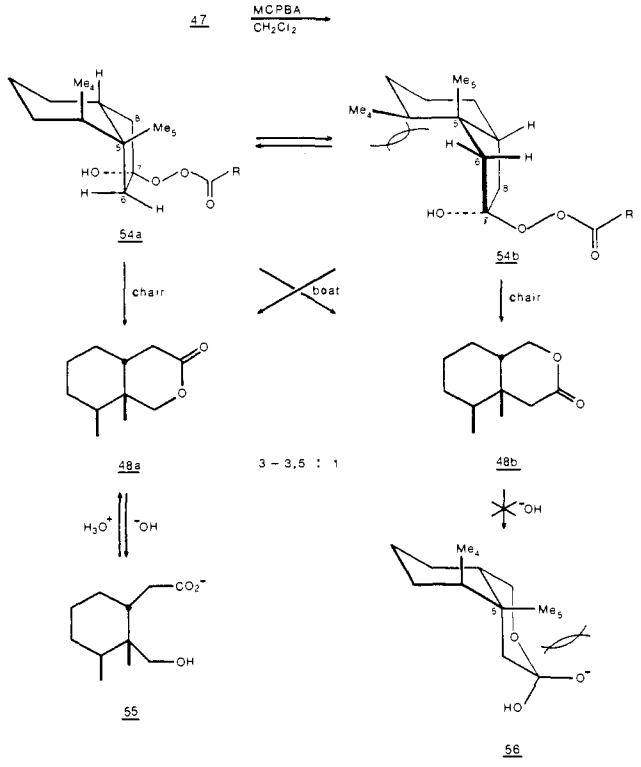
(24) An alternative synthesis of the methyl ester corresponding to **33** and the butenolide **40** has recently appeared: Hudrlik, P. F.; Chou, D. T.-W.; Stephenson, M. A. *J. Org. Chem.* **1982**, *47*, 2987.

(25) Isolation of ligularone (**1b**) and petasalbine (**1**): (a) Novotný, L.; Herout, V.; Sǒrm, F. *Tetrahedron Lett.* **1961**, 697. (b) Naya, K.; Nakagawa, M.; Hayashi, M.; Tsuji, K.; Naito, M. *Ibid.* **1971**, 2961. (c) Reference 6b.

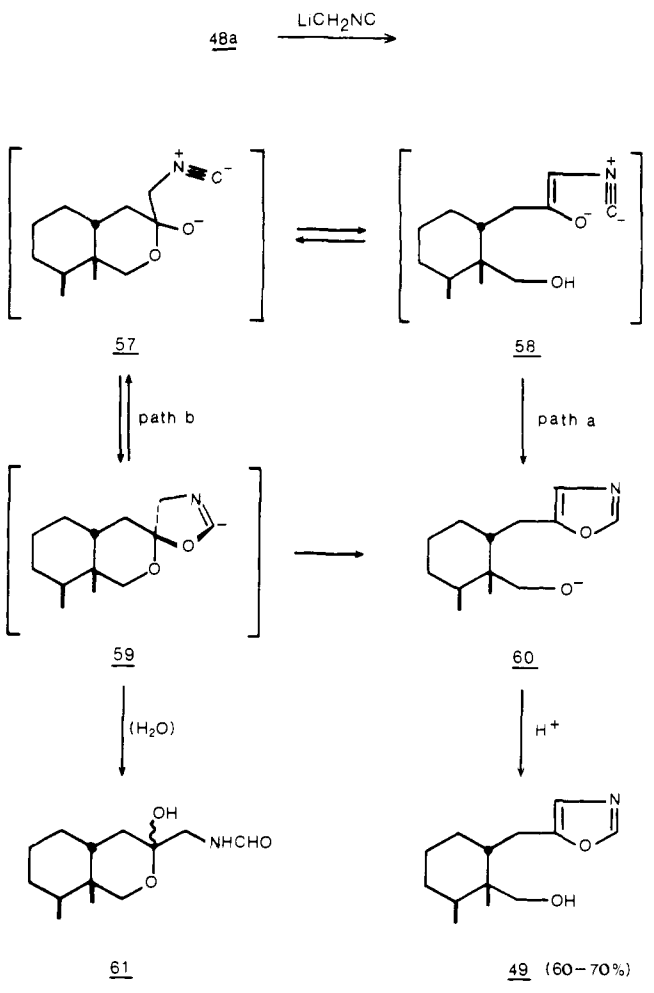
(26) Previous syntheses of ligularone (**1b**): (a) Bohlmann, F.; Förster, H.-J.; Fischer, C.-H. *Liebigs Ann. Chem.* **1976**, 1487. (b) Yamakawa, K.; Satoh, T. *Chem. Pharm. Bull.* **1977**, *25*, 2535. (c) *Ibid.* **1978**, *26*, 3704. (d) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *Chem. Lett.* **1979**, 163. Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Org. Chem.* **1980**, *45*, 2945. (e) Tada, M.; Sugimoto, T.; Takahashi, T. *Chem. Lett.* **1979**, 1441. (f) Conversion of ligularone to petasalbine: Yamakawa, K.; Satoh, T. *Chem. Pharm. Bull.* **1979**, *27*, 1747.

(27) Brandsma, L. "Preparative Acetylenic Chemistry"; Elsevier: New York, 1971.

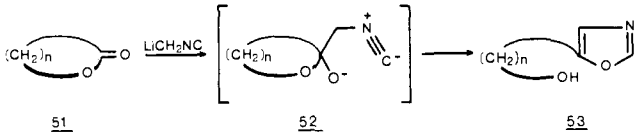
Scheme VIII



Scheme IX



was reason to believe that this latter material might be prepared from the dimethyl lactone **48a**. Thus, in related studies in this area we have demonstrated that lactones of general structure **51** are readily converted to oxazole alcohols **53** through the use of



lithiomethyl isocyanide under carefully defined conditions.[2b,28] Finally, it was of particular interest that **48a** might be derived via a selective Baeyer–Villiger oxidation[29] of the readily available perhydroindanone **47**.[30] If such were the case then the relative configurations at positions 4, 5, and 10 would be firmly established at the earliest stage of the synthesis.

In the event, this last supposition was easily tested by experiment, and we were pleased to find that **47** was smoothly converted to a 3–3.5:1 mixture of the lactones **48a** and **48b** with *m*-chloroperbenzoic acid in methylene chloride (Scheme VIII; combined yield 85–95%). This isomer ratio was remarkably insensitive to changes in both solvent and oxidant, although the rate of reaction was dramatically accelerated under both acid and base catalysis.

It is interesting to speculate on the reasons for selectivity in the conversion of **47** to **48a**. It is likely, we believe, that initial attack by peracid takes place from the less hindered β-face of **47** to give equilibrium mixtures of the tetrahedral intermediates **54a** and **54b**. Each of these conformers might then rearrange to either **48a** or **48b** depending upon whether a chair or boat transition state if followed. If one assumes, however, that both **54a** and **54b** rearrange mainly through the normally more favorable chair transition state,[29b] with comparable $E_{act's}$, then the ratio of **48a** and **48b** obtained should closely parallel the relative stabilities of **54a** and **54b**.[29c] In support of this hypothesis, careful examination of molecular models suggests that **54b** should be ~0.8 kcal/mol less stable than **54a** as a result of one extra gauche interaction involving C-6 and Me-4,[31] and when this value is used, the calculated isomer ratio of ~3.8:1 is in excellent agreement with experimental observation.

Finally, we note in passing that lactones **48a** and **48b** exhibited remarkably different reactivity under alkaline hydrolysis conditions. At pH 10, in particular, **48a** was rapidly opened to the carboxylate anion **55** while **48b** was totally inert to these conditions even after extended reaction periods (≥24 h). The most likely reason for this difference resides in the fact that there are no conformations available in which tetrahedral intermediates of type **56** can avoid severe 1,3-diaxial interactions. In contrast, however, **48a** can proceed through a relatively strain-free conformation to give **55** by virtue of the fact that its lactone carbonyl is three bonds removed from the C-5 quaternary center. Since **55**, in turn, cleanly reverted to **48a** upon acidification to pH 2, these observations provided a convenient basis for the separation of **48a** and **48b** (cf. Experimental Section).

We next turned our attention to the preparation of the oxazole alcohol **49** and were gratified to find that this material was readily derived through a modified Schöllkopf reaction on the dimethyl lactone **48a** (Scheme IX, 60–70%).[28] As in our previous studies, however,[2b] this conversion required considerable experimentation before optimal conditions were found, and it is worth noting that

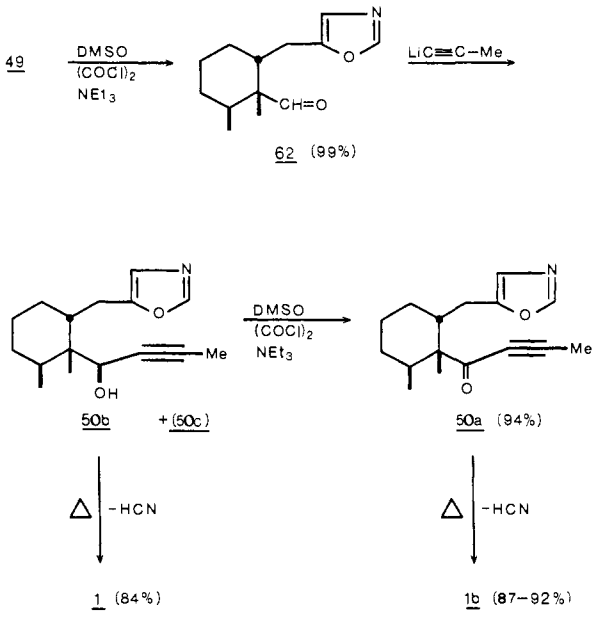
(28) See also: (a) Schöllkopf, U.; Schröder, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 333. (b) Hoppe, D. *Ibid.* **1974**, *13*, 789. (c) Schöllkopf, U. *Pure Appl. Chem.* **1979**, *51*, 1347. (d) Walborsky, H. M.; Pereasamy, M. P. *Org. Prep. Proceed. Int.* **1979**, *11*, 293. (e) Kozikowski, A. P.; Ames, A. *J. Am. Chem. Soc.* **1980**, *102*, 860. (f) Hall, R. H.; Bischofberger, K.; Eitelman, S. J.; Jordaan, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 743; **1977**, 2236.

(29) (a) "Organic Reactions"; Adams, R., Ed.; Wiley: New York, 1957; Vol. 9. (b) Grant, R. K. *Tetrahedron* **1981**, *37*, 2697. (c) This analysis also assumes, of course, that the transformation of **54a,b** to **48a,b** is the rate-determining step in the sequence. Such is normally the case (ref 29b).

(30) Evans, D.; Sims, C.; Andrews, G. *J. Am. Chem. Soc.* **1977**, *99*, 5453.

(31) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis"; Interscience: New York, 1967.

Scheme X



at least two pathways are functioning in the overall transformation of **57** to **49**. One of these, path a, is quite rapid and probably involves the direct cyclization of **58** through an aromatic transition state to give **60**. This process corresponds to the normal mechanism of the Schöllkopf reaction as carried out with simple ester derivatives.[28] In addition, however, we have also isolated the unstable oxazoline derivative **59** which *must* arise by direct cyclization of intermediate **57** (path b). Compound **59**, in turn, is slowly converted to a mixture of the desired oxazole **49** and the amide derivative **61** upon standing in basic solution (proton transfers have been omitted for the sake of clarity). Each of these processes, of course, finds excellent precedence in the literature,[28,32] but it is important to note that the rate of conversion of **59** to **49** is *much* slower than the rate of formation of **49** in the early stages of the reaction. Therefore, we believe, the rate of equilibration between **57** and **58** plays an important role in determining the reaction path of choice.

Once in hand, the desired conversion of **49** to (±)-ligularone (**1b**) followed in a straightforward fashion as illustrated in Scheme X. Thus **49** was cleanly oxidized[33] to the unstable aldehyde **62** which was directly condensed with lithiopropyne to give a 55:45 mixture of the diastereomeric alcohols **50b** and **50c** (80–85% overall yield). Oxidation of this mixture then gave a virtually quantitative yield of the single acetylenic ketone **50a**,[33] which was smoothly converted to (±)-**1b** in refluxing ethylbenzene (24 h, 87–92% yield). The material thus obtained had identical NMR, IR, and UV spectral data as that reported for the naturally occurring substance[25c,34] and was readily converted to (±)-epipetasalbine (**1c**) following the published procedure.[25c,26f]

Since ligularone (**1b**) has previously been converted to petasalbine (**1**) by dissolving metal reduction,[26f] this work constitutes a formal total synthesis of (±)-**1**. In addition, however, we were pleased to find that (±)-**1** could also be readily derived by thermolysis of acetylenic alcohol **50b** in identical fashion as described above (80–85% yield). The synthetic (±)-**1** thus obtained had identical ^{1}H NMR, ^{13}C NMR, and other spectral data as that reported for the naturally occurring substance,[25c,26f,35] and was easily converted to both (±)-**1b** and petasalbine acetate (**1d**) following the published procedures.[25c,34]

In closing, we might only add that this latter conversion, in particular, further illustrates the extraordinary reactivity of the oxazoles in Diels–Alder reactions,[13] and we feel confident that similar procedures will find widespread applicability in the synthesis of furanosesquiterpenes.

(32) Gigg, R.; Warren, C. D. *J. Chem. Soc. C* **1968**, 1903. See also ref 28f.
(33) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(34) Tada, M.; Takahashi, T. *Tetrahedron Lett.* **1973**, 5169.
(35) Sato, T.; Tada, M.; Takahashi, T.; Horibe, I.; Ishii, H.; Tori, K. *Tetrahedron Lett.* **1977**, 3895.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6E spectrometer. A Varian XL-200 spectrometer was used for the NMR spectra, and IR spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer.

Ethyl *N*-(4-(Carbomethoxy)butyryl)alaninate (25). A solution of 25.60 g (167 mmol) of ethyl alaninate hydrochloride in 65 mL of dry pyridine was cooled with stirring in a flame-dried 250-mL round-bottom flask to 0 °C (ice bath). While this temperature was maintained, 28.00 g (170 mmol, 1.02 equiv) of methyl 4-(chloroformyl)butyrate[22] was added, with vigorous stirring, in a dropwise fashion over a period of ~1 h. Following addition, the cooling bath was removed, and the reaction mixture was allowed to stir overnight at 25 °C. Most of the pyridine was then removed under reduced pressure, and the remaining slurry was dissolved in 65 mL of H_2O and extracted with 5 × 30 mL portions of CH_2Cl_2. The combined extracts were washed twice with 30 mL of cold 5% $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated to give a yellow oil. Crystallization of this material from 50 mL of 4:1 Et_2O/petroleum ether gave 36.00 g (88%) of **25** as a colorless solid: mp 42–43 °C; mass spectrum, *m/e* 245 (M^+); IR (KBr) 3280, 2920, 1725, 1640, 1515, 1430, 1200, 1050, 1015 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (t, *J* = 7.5 Hz, 3 H), 1.40 (d, *J* = 8 Hz, 3 H), 1.8–2.7 (m, 6 H), 3.72 (s, 3 H), 4.25 (q, *J* = 7.5 Hz, 2 H), 4.58 (q, *J* = 8 Hz, 1 H), 6.6 (br d, 1 H).

Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.88; H, 7.76; N, 5.71. Found: C, 53.62; H, 7.58; N, 5.44.

2-(3-Carbomethoxypropyl)-4-methyl-5-ethoxyoxazole (26). To a 500-mL 3-necked round-bottom flask equipped with a Hershberg stirrer and reflux condenser was added 21.5 g (88.0 mmol) of diester **25**, 50.0 g (355 mmol) of powdered P_2O_5, and 200 mL of ethanol-free $CHCl_3$. The resulting suspension was heated at reflux, with exclusion of moisture, for a period of 12 h (*vigorous stirring*) and then allowed to cool to room temperature. A total of 100 mL of ice-cold 5% $NaHCO_3$ solution was then added to decompose unreacted P_2O_5, and the pH of the aqueous phase was adjusted to neutrality with 6 N NaOH. After separation of layers, the aqueous phase was extracted with an additional 2 × 50 mL of $CHCl_3$, and the combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give 18.2 g of **26** as a dark yellow oil. Vacuum distillation (101–104 °C, 0.3 mm) then afforded 17.5 g (88%) of pure **26** as a very pale yellow oil: mass spectrum, *m/e* 227 (M^+); IR (film) 2910, 1725, 1660, 1570, 1430, 1315, 1220, 1085, 1021 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (t, *J* = 7 Hz, 3 H), 1.99 (s, 3 H), 2.06 (m, 2 H), 2.40 (m, 2 H), 2.66 (t, *J* = 7 Hz, 2 H), 3.66 (s, 3 H), 4.10 (q, *J* = 7 Hz, 2 H).

Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.15; H, 7.49; N, 6.17. Found: C, 57.79; H, 7.43; N, 6.33.

2-(4-Oxobutyl)-4-methyl-5-ethoxyoxazole (27). A solution of 10.0 g (44 mmol) of oxazole ester **26** in 120 mL of dry toluene was cooled to −78 °C under nitrogen and treated in a dropwise fashion, with vigorous stirring, with a total of 65 mL (2.1 equiv) of 25% DIBAL-H in toluene over a period of 3.5 h. After stirring at −78 °C for an additional hour, 40 mL of absolute EtOH was added followed by 60 mL of 10% KH_2PO_4. The bath was then removed, and the reaction mixture was allowed to warm to room temperature. The resulting emulsion was extracted with 10 × 100 mL portions of $CHCl_3$, and the combined extracts were dried over $MgSO_4$. Concentration under reduced pressure then gave 9.71 g of a mixture of the desired aldehyde **27** together with the corresponding alcohol **27b** derived from overreduction. The mixture was separated by chromatography on 600 g of SiO_2 using 40% EtOAc/benzene as eluent to give 3.8 g (43%) of alcohol **27b** and 4.4 g (51%) of aldehyde **27**. If desired, alcohol **27b** could be oxidized to **27** in 56% yield with the reagent system pyr·SO_3[23] (overall yield ~75%): mass spectrum, *m/e* 197 (M^+); IR (film) 3470, 2920, 1720, 1660, 1560, 1430, 1380, 1250, 1225, 1085, 1025 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (t, *J* = 7 Hz, 3 H), 1.98 (s, 3 H), 2.2–2.8 (m, 6 H), 4.1 (q, *J* = 7 Hz, 2 H), 9.57 (t, *J* = 1 Hz, 1 H). The analytical sample was prepared by distillation at 100 °C (bath temperature)/0.05 mm.

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.91; H, 7.61; N, 7.11. Found: C, 61.09; H, 7.39; N, 6.69.

2-(4-Hydroxy-7-methoxy-5-heptynyl)-4-methyl-5-ethoxyoxazole (28). A solution of 1.78 g (37 mmol) of methyl propargyl ether in 30 mL of dry THF was cooled to −78 °C under nitrogen and treated, in a dropwise fashion (30 min), with 21 mL (25 mmol) of a 1.20 M *n*-BuLi solution in hexane. After being stirred one additional hour, a solution of 4.30 g (22 mmol) of **27** in 30 mL of dry THF was added over a period of 30 min. The reaction mixture was stirred at −78 °C for 1 h and was then

allowed to warm slowly to room temperature over a period of 1.5 h. The reaction was quenched with 35 mL of ice-cold 10% KH_2PO_4 followed by extraction (CH_2Cl_2) and drying ($MgSO_4$), and concentration under reduced pressure then gave 5.8 g of a dark yellow oil. This material was chromatographed on 200 g of SiO_2 with 60% EtOAc/benzene eluent to give 5.50 g (94%) of **28** as a pale yellow oil. IR (film) 3325, 2940, 1740, 1675, 1575, 1450, 1130, 1095, 1020 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (t, J = 7 Hz, 3 H), 1.75–1.95 (m, 4 H), 1.98 (s, 3 H), 2.5–2.9 (m, 2 H), 3.34 (s, 3 H), 4.18 (q, J = 7 Hz, 2 H), 4.20 (d, J = 2 Hz, 2 H), 4.22 (m, 2 H). The analytical sample was prepared by distillation at 140 °C (bath temperature)/0.05 mm.

Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.92; H, 7.87; N, 5.24. Found: C, 63.05; H, 7.69; N, 5.22.

2-(4,7-Dimethoxy-5-heptynyl)-4-methyl-5-ethoxyoxazole (29). A solution of 2.00 g (7.50 mmol) of alcohol **28** in 35 mL of dry THF was cooled to −20 °C (ice–salt bath) and treated with 0.41 g (8.5 mmol, 1.2 equiv) of a 50% NaH oil dispersion. After the reaction stirred 30 min at −20 °C, 0.49 mL (7.85 mmol) of iodomethane was added, and the reaction was kept at −20 °C for an additional 30 min before removing the bath and allowing it to warm to room temperature. After being stirred an additional hour, the reaction mixture was quenched with 20 mL of 10% KH_2PO_4 and extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give 2.3 g of a yellow oil. This material was chromatographed on 100 g of SiO_2 with 60% EtOAc/benzene as eluent to afford 2.10 g (99%) of pure **29** as a pale yellow oil: IR (film) 2940, 1675, 1580, 1440, 1320, 1220, 1095, 1015 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (t, J = 7 Hz, 3 H), 1.67–1.95 (m, 4 H), 1.98 (s, 3 H), 2.5–2.8 (m, 2 H), 3.38 (s, 6 H), 4.12 (q, J = 7 Hz, 2 H), 4.15 (d, J = 2 Hz, 2 H), 4.20 (m, 1 H). The analytical sample was prepared by distillation at 140 °C (bath temperature)/0.05 mm.

Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.06; H, 8.18; N, 4.98. Found: C, 63.72; H, 7.95; N, 4.73.

2-(4-Oxo-7-methoxy-5-heptynyl)-4-methyl-5-ethoxyoxazole (30). A solution of 100 mg (0.37 mmol) of alcohol **28** in 10 mL of CH_2Cl_2 was treated with 710 mg (8.17 mmol) of active MnO_2, and the resulting suspension was heated at reflux for a period of 12 h. Filtration of the MnO_2 through a Celite pad, followed by several washings with CH_2Cl_2, afforded a filtrate that was concentrated under reduced pressure to give 99 mg of a mixture of starting material **28** and the desired ketone **30**. This mixture was separated by preparative TLC with 50% EtOAc/benzene as eluent to give 63 mg (64%) of ketone **30** as a pale yellow oil. Resubjection of recovered **28** to the above reaction conditions raised the overall yield of **30** to ~85%: IR (film) 2920, 2220, 1680, 1575, 1445, 1370, 1320, 1280, 1230, 1190, 1140, 1105, 1015, 950 cm^{-1}; NMR ($CDCl_3$) δ 1.44 (t, J = 7 Hz, 3 H), 2.08 (s, 3 H), 2.11–3.03 (m, 6 H), 3.58 (s, 3 H), 4.34 (q, J = 7 Hz, 2 H), 4.48 (s, 2 H).

2-Ethoxy-4,5,6,7-tetrahydro-4-methoxy-3-(methoxymethyl)benzofuran (31). A solution of 1.10 g (3.91 mmol) of acetylenic oxazole **29** in 70 mL of dry ethylbenzene was treated with 86 mg (0.78 mmol) of hydroquinone, and the resulting mixture was heated at reflux, with protection from light and moisture, for a period of 72 h. The resulting solution was then concentrated under reduced pressure to a dark viscous oil, which was chromatographed on 100 g of SiO_2 with 20% Et_2O/CH_2Cl_2 as eluent to give 0.89 g (94%) of **31** as a yellow oil: mass spectrum, m/e 240 (M^+); IR (film) 2930, 1765, 1650, 1625, 1445, 1310, 1185, 1080, 1025 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (t, J = 7 Hz, 3 H), 1.70–2.70 (m, 6 H), 3.28 (s, 3 H), 3.42 (s, 3 H), 4.18 (q, J = 7 Hz, 2 H), 4.20 (m, 1 H), 4.24 (d, J = 1 Hz, 2 H). The analytical sample was prepared by distillation at 98 °C (bath temperature)/0.05 mm to give **31** as a colorless oil.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 65.00; H, 8.33. Found: C, 65.00; H, 8.04.

2-Ethoxy-4,5,6,7-tetrahydro-4-oxo-3-(methoxymethyl)benzofuran (32). A solution fo 275 mg (1.04 mmol) of acetylenic ketone **30** in 50 mL of dry benzene was heated at reflux, with protection from light and moisture, for a period of 87 h. The resulting brown solution was evaporated under reduced pressure to afford 260 mg of a dark oil, which was purified by preparative TLC with 50% EtOAc/benzene as eluent. Removal of the band with R_f 0.6–0.8 yielded 194 mg (83%) of pure **32** as a pale yellow oil: mass spectrum, m/e 224 (M^+); IR (film) 2940, 1730, 1675, 1645, 1590, 1445, 1380, 1300, 1250, 1190, 1080, 1050, 1005 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (t, J = 7.5 Hz, 3 H), 2.0–3.0 (m, 6 H), 3.44 (s, 3 H), 4.35 (q, J = 7.5 Hz, 2 H), 4.50 (s, 2 H).

Ethyl α-Methylene-6-oxo-1-cyclohexene-1-acetate (33).[24] A solution of 1.60 g (6.67 mmol) of ethoxyfuran **31** in 9 mL of 1 N H_2SO_4 was stirred at room temperature for a period of 30 min and then was extracted with 3 × 10 mL of CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give 1.43 g of crude **33**. This material was chromatographed on 150 g of SiO_2 with 10% Et_2O/CH_2Cl_2 as eluent to afford 1.11 g (86%) of methylene ester **33** as a pale yellow oil: mass spectrum, m/e 194 (M^+); IR (film) 2960, 1730, 1680, 1340, 1295, 1230, 1180, 1150, 1120, 1085, 1045, 1035, 1020 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3 H), 2.04 (m, 2 H), 2.46 (m, 4 H), 4.18 (q, J = 7 Hz, 2 H), 5.63 (d, J = 1.8 Hz, 1 H), 6.16 (d, J = 1.8 Hz, 1 H), 6.88 (t, J = 4 Hz, 1 H). The analytical sample was prepared by distillation at 80 °C (bath temperature)/0.05 mm.

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22. Found: C, 67.79; H, 7.23.

Ethyl α-Methylene-2,6-dioxocyclohexaneacetate (34). A solution of 110 mg (0.49 mmol) of ethoxyfuran **32** in 4 mL of H_2O was treated with 220 mg of Dowex 50W-X4 acid resin, and the resulting suspension was stirred for 3 h at room temperature. The resin was then filtered and washed with several portions of CH_2Cl_2, and the aqueous phase was extracted with 3 × 10 mL of CH_2Cl_2. The combined washings and extracts were dried over $MgSO_4$ and concentrated under reduced pressure to afford 85 mg (82%) of **34** as a pale yellow oil: mass spectrum, m/e 210 (M^+), IR (film) 2930, 1730, 1675, 1370, 1330, 1280, 1230, 1090, 1050, 1025 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 3 H), 1.83–2.83 (m, 6 H), 4.17 (q, J = 7.5 Hz, 2 H), 5.67 (d, J = 2 Hz, 1 H), 6.42 (d, J = 2 Hz, 1 H), 6.86–7.23 (m, 1 H).

Ethyl α-(Bromomethyl)-6-oxo-1-cyclohexene-1-acetate (35). A solution of 100 mg (0.52 mmol) of methylene ester **33** in 16 mL (0.64 mmol) of 0.04 M ethereal HBr was stirred at room temperature for a period of 24 h. The reaction mixture was then quenched with 5 mL of ice-cold 10% KH_2PO_4, and the resulting layers were separated. The aqueous layer was extracted with 3 × 10 mL portions of CH_2Cl_2, and the combined CH_2Cl_2 and Et_2O extracts were dried over $MgSO_4$. Concentration under reduced pressure then afforded 138 mg of a dark yellow oil which was purified by preparative TLC. Elution with 20% Et_2O/CH_2Cl_2 and removal of the band with R_f 0.9–0.95 gave 128 mg (90%) of **35** as a pale yellow oil. On standing in the presence of base, **35** was rapidly converted back to **33**: IR (film) 2910, 1735, 1680, 1425, 1370, 1285, 1230, 1195, 1150, 1135, 1095, 1020 cm^{-1}; NMR ($CDCl_3$) δ 1.24 (t, J = 7 Hz, 3 H), 1.83–2.68 (m, 6 H), 3.30–3.97 (m, 3 H), 4.16 (q, J = 7 Hz, 2 H), 7.00 (t, J = 4 Hz, 1 H).

Ethyl α-Methylene-1,2-epoxy-6-oxocyclohexaneacetate (36). A solution of 20 mg (0.10 mmol) of methylene ester **33** in 1 mL of toluene was treated with 10 μL (0.26 mmol) of 90% H_2O_2 and 20 μL of triethylamine. The reaction was then stirred at room temperature for a period of 24 h before being quenched with 3 mL of 10% KH_2PO_4. Extraction with CH_2Cl_2 followed by concentration under reduced pressure and preparative TLC then afforded 15 mg (69%) of **36** as an unstable pale yellow oil: mass spectrum, m/e 210 (M^+); IR ($CDCl_3$) 3010, 2930, 1710, 1400, 1315, 1290, 1250, 1170, 1145, 1090, 1045, 1010 cm^{-1}. NMR ($CDCl_3$) δ 1.27 (t, J = 7.5 Hz, 3 H), 1.50–2.53 (m, 6 H), 3.21–3.36 (m, 1 H), 4.16 (q, J = 7.5 Hz, 2 H), 5.87 (d, J = 1.8 Hz, 1 H), 6.31 (d, J = 1.8 Hz, 1 H).

Ethyl α-Methylene-6-hydroxy-1-cyclohexene-1-acetate (37). A solution of 20 mg (0.10 mmol) of methylene ester **33** in 0.25 mL (0.10 mmol) of 0.4 M $PrCl_3 \cdot 6H_2O/CH_3OH$ was stirred for 15 min before adding 5 mg (0.13 mmol) of $NaBH_4$. The resulting suspension was then stirred at room temperature for an additional 10–15 min before quenching with 5 mL of 10% KH_2PO_4 and extracting with 3 × 5 mL portions of CH_2Cl_2. The combined extracts were then dried over $MgSO_4$ and concentrated under reduced pressure, and the residue was purified by preparative TLC to give 18 mg (89%) of **37** as an unstable pale yellow oil: NMR ($CDCl_3$) δ 1.33 (t, J = 7.5 Hz, 3 H), 1.49–2.18 (m, 6 H), 2.58–2.84 (m, 1 H), 4.24 (q, J = 7.5 Hz, 2 H), 4.15–4.43 (m, 1 H), 5.70 (d, J = 1.8 Hz, 1 H), 5.96 (t, J = 4 Hz, 1 H), 6.03 (d, J = 1.8 Hz, 1 H).

α-Methylene-6-oxo-1-cyclohexene-1-acetic Acid (38). A mixture of 300 mg (1.55 mmol) of methylene ester **33** and 20 mL of distilled H_2O was treated with 7 mL of 1 N NaOH. The resulting suspension was then stirred vigorously for a period of 30 in to give a pale yellow solution, which was acidified to pH 3 with 2 N HCl and extracted with 3 × 10 mL portions of CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give 248 mg (97%) of **38** as a colorless crystalline solid, mp 89–93 °C: mass spectrum, m/e 166 (M^+); IR (CCl_4) 2970 (br), 2350, 1690, 1545, 1250, 1080 cm^{-1}; NMR ($CDCl_3$) δ 1.94–2.20 (m, 2 H), 2.32–2.62 (m, 4 H), 5.74 (d, J = 1.8 Hz, 1 H), 6.32 (d, J= 1.8 Hz, 1 H), 6.99 (t, J = 4 Hz, 1 H), 6.78–7.08 (br, 1 H). Upon standing in EtOH in the presence of acid, **38** was slowly converted back to **33**.

5,6,7,7a-Tetrahydro-3-methyl-2,4-benzofurandione (40).[24] **Method A.** A mixture of 94 mg (0.49 mmol) of methylene ester **33** and 5 mL of 1 N H_2SO_4 was heated at reflux, with vigorous stirring, for a period of 15 h, and the resulting solution was extracted with 3 × 10 mL portions of CH_2Cl_2. The combined extracts were then dried over $MgSO_4$ and concentrated under reduced pressure to give 85 mg of a dark yellow residue which was purified by preparative TLC (15% Et_2O/CH_2Cl_2). Removal of the band with R_f 0.6–0.75 then gave 71 mg (88%) of **40** as a colorless

crystalline solid, mp 55–58 °C. Sublimation at 120 °C/0.25 mm increased the melting point to 58–59.5 °C: mass spectrum, *m/e* 166 (M^+); IR ($CHCl_3$) 2970, 1755, 1695, 1655, 1310, 1200, 1135, 1095, 1045, 1020, 947 cm^{-1}; NMR ($CDCl_3$) δ 1.53–2.85 (m, 6 H), 2.04 (d, *J* = 2 Hz, 3 H), 4.98 (m, 1 H).

Anal. Calcd for $C_9H_{10}O_3$: C, 65.06; H, 6.02. Found: C, 64.94; H, 6.25.

Method B. A mixture of 62 mg (0.37 mmol) of methylene acid **38** and 10 mL of 1 N H_2SO_4 was heated at reflux, with vigorous stirring, for a period of 5 h. Isolation and purification as described above then gave 60 mg (97%) of **40**, identical in all respects with the material prepared by method A.

Method C. A mixture of 90 mg (0.38 mmol) of ethoxyfuran **31** and 4.5 mL of 1 N H_2SO_4 was heated at reflux, with vigorous stirring, for a period of 36 h. Isolation and purification as described above then gave 40 mg (64%) of **40**, identical in all respects with the material prepared by methods A and B.

4,5,6,7-Tetrahydro-4-hydroxy-3-methylbenzofuran (42). A solution of 35 mg (0.21 mmol) of **40** in 5 mL of dry THF was cooled to −30 °C under nitrogen and treated, in a dropwise fashion, with 0.55 mL (0.84 mmol) of a 25% DIBAL-H/toluene solution with vigorous stirring. The reaction was kept at −30 °C for 3 h and then quenched with 1.5 mL of 10% H_2SO_4 and allowed to warm to room temperature. The resulting mixture was extracted with 3 × 5 mL portions of CH_2Cl_2, and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give 37 mg of a dark oil which was purified by preparative TLC. Elution with 50% EtOAc/benzene and removal of the band with R_f 0.7–0.8 yielded 21 mg (67%) of **42** as a pale yellow oil: mass spectrum, *m/e* 152 (M^+); IR ($CDCl_3$) 3660, 3500, 3030, 2980, 2880, 1640, 1565, 1435, 1410, 1375, 1305, 1140, 1075, 1055, 940 cm^{-1}; NMR ($CDCl_3$) δ 1.64–1.92 (m, 5 H), 2.02 (d, *J* = 2 Hz, 3 H), 2.30–2.66 (m, 2 H), 4.64–4.76 (m, 1 H), 7.02 (br s, 1 H).

5,6,7,7aα-Tetrahydro-4β-hydroxy-3-methyl-2-benzofuranone (43). A solution of 70 mg (0.42 mmol) of butenolide **40** in 5 mL of absolute EtOH was cooled to 0 °C (ice bath) and treated, portionwise, with 11 mg (0.42 mmol) of $NaBH_4$. After being stirred an additional 15 min at 0 °C, the reaction was quenched with 10 mL of pH 7 buffer and extracted with 3 × 5 mL portions of CH_2Cl_2. The combined extracts were then dried ($MgSO_4$) and concentrated under reduced pressure to give 68 mg (96%) of **43** as a colorless crystalline solid: mp 102–103.5 °C; mass spectrum, *m/e* 168 (M^+); IR (film) 3600, 2990, 2930, 1745, 1685, 1440, 1335, 1080, 1050 1020 cm^{-1}; NMR ($CDCl_3$) δ 1.2–2.6 (m, 6 H), 2.06 (t, *J* = 2.5 Hz, collapsing to a singlet upon irradiation at 4.55 ppm, 3 H), 4.4–4.7 (m, 2 H).

3β,3aα,5,6,7,7aα-Hexahydro-4β-hydroxy-3α-methyl-2-benzofuranone (45) and 3α,3aα,5,6,7,7aα-Hexahydro-4β-hydroxy-3β-methyl-2-benzofuranone (44). Method A. A solution of 250 mg (1.5 mmol) of **40** in 20 mL of absolute MeOH was cooled to 0 °C and treated with 50 mg (1.3 mmol) of $NaBH_4$. The resulting suspension was stirred at 0 °C for 20 min before adding 62 mg (0.26 mmol) of $NiCl_2 \cdot 6H_2O$. After the solution stirred for an additional 20 min, a further 100 mg (2.6 mmol) of $NaBH_4$ was added, and the reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. The resulting suspension was quenched with 10 mL of distilled H_2O, and the aqueous mixture was acidified to pH 4 with 1 N HCl before being continuously extracted with CH_2Cl_2 overnight. The extracts were then dried over $MgSO_4$ and concentrated under reduced pressure to afford a dark yellow viscous oil. The crude product mixture was purified by medium-pressure liquid chromatography (SiO_2) with 60% hexane/EtOAc as eluent to give 29 mg (11%) of lactone **44**, mp 100–105 °C, and 214 mg (84%) of lactone **45**, mp 101–104 °C. Analytical data for **44**: mass spectrum, *m/e* 180 (M^+); IR ($CHCl_3$) 3030, 2950, 1790, 1225, 1190, 1075, 1025 cm^{-1}; NMR ($CDCl_3$) δ 1.16–1.72 (m, 4 H), 1.4 (d, *J* = 6 Hz, collapsing to a singlet upon irradiation at 2.66, 3 H), 1.73–1.98 (m, 2 H), 2.20–2.31 (m, 2 H), 2.56–2.78 (m, 1 H), 4.04–4.20 (m, 1 H), 4.34–4.48 (m, 1 H). Upon standing in solution ($CDCl_3$), **44** was slowly converted to **45**. Analytical data for **45**: mass spectrum, *m/e* 180 (M^+); IR ($CHCl_3$) 3035, 2950, 1795, 1225, 1190, 1075, 1025 cm^{-1}; NMR (CCl_4) δ 1.25–1.82 (m, 3 H), 1.33 (d, *J* = 6.9 Hz, collapsing to a singlet upon irradiation at 2.7, 3 H), 1.92–2.21 (m, 2 H), 2.29–2.52 (m, 1 H), 2.41–2.52 (m, 1 H), 2.61 (br s, −O*H*), 2.66–2.74 (m, collapsing to a doublet, *J* = 9.5 Hz, upon irradiation at 1.33, 1 H), 3.96–4.01 (m, 1 H), 4.47–4.53 (m, 1 H). Upon brief exposure to potassium *tert*-butoxide, **45** was converted to an 84:11 mixture of **45** and **44**. The analytical sample was prepared by sublimation at 60 °C/0.05 mm to afford **45** as a colorless solid, mp 102–103.5 °C.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.53; H, 8.23. Found: C, 63.61; H, 8.11.

Method B. A solution of 168 mg (1.0 mmol) of **43** in 20 mL of absolute MeOH was cooled to 0 °C and treated with 36 mg (0.15 mmol) of $NiCl_2 \cdot 6H_2O$. The resulting suspension was stirred for 15 min before adding 112 mg (2.9 mmol) of $NaBH_4$ in several portions. After the suspension stirred for an additional 1 h at 0 °C, isolation and purification as described above gave an identical 84:11 mixture of **45** and **44**.

(4aβ,8β,8aβ)-1,4,4a,5,6,7,8,8a-Octahydro-8,8a-dimethyl-3*H*-2-benzopyran-3-one (48a) and (4aβ,5β,8aβ)-1,4,4a,5,6,7,8,8a-Octahydro-4a,5-dimethyl-3*H*-2-benzopyran-3-one (48b). A solution of 2.45 g (14.7 mmol) of perhydroindanone **47**[30] in 12 mL of dry (P_2O_5) CH_2Cl_2 was added with efficient stirring to a solution of 6.97 g (2.2 equiv) of 80% *m*-chloroperbenzoic acid in 83 mL of dry CH_2Cl_2 with protection from light and moisture. After stirring a total of 96 h at 23 °C, the resulting suspension was filtered through Celite, and the filtrate was washed with 6 × 40 mL of 10% $NaHSO_4$, 5 × 40 mL of pH 7 phosphate buffer (CRC), and finally 6 × 40 mL of 5% $NaHCO_3$. Each aqueous layer was then back-extracted with 2 × 20 mL of CH_2Cl_2, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 2.67 g (99%) of a crude mixture of lactones **48a** and **48b**. Flash chromatography[36] (9% acetone/hexanes) of this residue then afforded 2.34 g (87%) of **48a** and **48b** as a chromatographically inseparable mixture, R_f 0.32 (10% acetone/hexanes), which by NMR analysis consisted of ~75% **48a**. For the purpose of separation, the material thus obtained was next covered with a buffer solution prepared from 45 mL of pH 10 buffer solution (CRC) and 45 mL of peroxide-free THF, and the resulting solution was stirred vigorously while a pH value of 10 (pH meter) was maintained by the dropwise addition of 5% NaOH. After a period of 2.5 h the pH had stabilized, and the reaction mixture was directly extracted with 6 × 20 mL of CH_2Cl_2, the combined extracts being dried over Na_2SO_4 and concentrated under reduced pressure to afford 0.61 g (22%) of lactone **48b** as a pale yellow oil: bp 90–100 °C (0.001 mm); mass spectrum, *m/e* 182 (M^+); IR (CH_2Cl_2) 1740 cm^{-1}; NMR ($CDCl_3$) δ 0.78 (d, *J* = 7 Hz, 3 H), 0.89 (s, 3 H), 1.19–1.75 (br m, 8 H), 2.06 (d, *J* = 17 Hz, 1 H), 2.60 (d, *J* = 17 Hz, 1 H, collapsing to a singlet upon irradiation at 2.06), 4.22 (d, *J* = 8 Hz, 2 H).

The aqueous phase from above was adjusted to pH 2 with 6 N HCl and immediately extracted with 6 × 20 mL of CH_2Cl_2. The combined extracts were then dried over Na_2SO_4 and concentrated under reduced pressure to afford 1.69 g (63%) of **48a** as a colorless crystalline solid, which after sublimation at 90 °C (0.001 mm) had mp 33–34.5 °C: mass spectrum, *m/e* 182 (M^+); IR (CH_2Cl_2) 1740 cm^{-1}; NMR ($CDCl_3$) δ 0.75 (d, *J* = 7 Hz, 3 H), 0.77 (s, 3 H), 1.19–1.75 (br m, 7 H), 1.83 (m, 1 H, collapsing to a triplet, *J* = 4 Hz, upon irradiation at 2.45), 2.45 (d, *J* = 9 Hz, 2 H, collapsing to a singlet upon irradiation at 1.83), 3.68 (d, *J* = 11 Hz, 1 H), 4.15 (d, *J* = 11 Hz, 1 H, collapsing to a singlet upon irradiation at 3.68).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.20; H, 9.75.

(1′α,2′α,3′β)-5-[[2′,3′-Dimethyl-2′-(hydroxymethyl)cyclohexyl]methyl]oxazole (49). A solution of 227 μL (2 eq, 4 mmol) of methyl isocyanide in 19.6 mL of dry THF was cooled to −78 °C with stirring under nitrogen and treated in a dropwise fashion with 1.6 mL (2 equiv) of 2.50 M *n*-BuLi in hexane. The resulting solution, consisting of lithiomethyl isocyanide, was next treated in a dropwise fashion with a solution of 365 mg (2 mmol) of lactone **48a** in 12 mL of dry THF, and stirring was continued for an additional 10 min at −78 °C before removing the cooling bath and allowing the reaction mixture to slowly warm to ambient temperature (23 °C). The reaction mixture was then diluted with 12 mL of *anhydrous* DMF (Aldrich) and the resulting yellow-orange solution was kept at ambient temperature, under nitrogen, for a period of 72 h. During this time TLC analysis (silica gel, 20% acetone/hexanes) indicated an initially rapid formation of the desired oxazole **49** (R_f 0.29) together with varying amounts of the oxazoline intermediate **59** (R_f 0.10) and the amide byproduct **61** (R_f 0.09). The reaction was then quenched with 230 μL (4 mmol) of glacial acetic acid and concentrated under reduced pressure to give a dark residue which was taken up in 50 mL of 5% $NaHCO_3$ and extracted with 4 × 50 mL of CH_2Cl_2. The combined extracts were then washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography[36] (18% acetone/hexanes) to afford 307 mg (68%) of **49** as a colorless crysalline solid: mp 74–75 °C; mass spectrum, *m/e* 223 (M^+); IR (CH_2Cl_2) 3635, 1510, 1480 cm^{-1}; NMR ($CDCl_3$) δ 0.77 (d, *J* = 7 Hz, 3 H, collapsing to a singlet upon irradiation at 1.62), 0.94 (s, 3 H), 1.02–1.57 (br m, 6 H), 1.62 (m, 1 H, sharpening upon irradiation to 0.77), 1.88 (m, 1 H, sharpening upon irradiation at 2.60), 2.60 (dd, *J* = 12, 15 Hz, 1 H, collapsing to a doublet upon irradiation at 1.88), 2.86 (dd, *J* = 4, 15 Hz, 1 H, collapsing to a doublet upon irradiation at either 1.88 or 2.60), 3.61 (m, 2 H, collapsing to two doublets, *J* = 11 Hz, upon addition of D_2O), 6.76 (s, 1 H), 7.78 (s, 1 H).

(36) Still, W. C. *J. Org. Chem.* **1978**, *43*, 2923.

The analytical sample was prepared by sublimation at 70 °C (0.001 mm).

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: c, 69.87; H, 9.63; N, 6.57.

Intermediates 57 and 58. These materials were isolated as an equilibrium mixture upon quenching an aliquot of the above reaction prior to warming to ambient temperature (preparative TLC, R_f 0.50 in 20% acetone/hexanes, vs. 0.60 for **48a**). In the absence of base this mixture exhibited moderate stability, but in the presence of base or upon heating it was rapidly converted to mixtures of **59**, **61**, and **49**, as well as several other unidentified decomposition products: mass spectrum, *m/e* 223 (M^+); IR (neat) 3375, 2940, 2160 (s), 1670 (m) cm^{-1}; NMR ($CDCl_3$) δ 0.70 (s, 3 H), 0.73 (d, J = 7 Hz, 3 H), 1.10–1.90 (m, 10 H), 2.50 (br s, 1 H), 3.41 (d, J = 12 Hz, 1 H), 3.44 (br s, 2 H), 3.53 (d, J = 12 Hz, 1 H).

Oxazoline Intermediate 59. This material was isolated as an unstable oil, R_f 0.10 (preparative TLC, 20% acetone/hexanes), from the reaction mixture described above for the preparation of oxazole **49**. Upon standing in solution (THF/DMF) in the presence of potassium *tert*-butoxide, **59** was slowly converted to a mixture of the desired oxazole **49** as well as the amide byproduct **61**: mass spectrum, *m/e* 223 (M^+); IR (CCl_4) 2950, 1645, 1575 cm^{-1}; NMR ($CDCl_3$) δ 0.70 (s, 3 H), 0.74 (d, J = 7 Hz, 3 H), 1.10–1.60 (m, 7 H), 1.65–2.00 (m, 2 H) 2.20 (t, J = 13 Hz, 1 H), 3.41 (d, J = 12 Hz, 1 H), 3.44 (dd, J = 16,3 Hz, 1 H, collapsing to a doublet, J = 16 Hz upon irradiation at 6.80), 3.57 (d, J = 12 Hz, 1 H), 3.65 (dd, J = 16,2 Hz, 1 H, collapsing to a doublet, J = 16 Hz, upon irradiation at 6.80), 6.80 (dd, J = 2,3 Hz, 1 H).

Amide Byproduct 61. This material was obtained in trace amounts as a cryalline solid, mp 150–152 °C, from the reaction mixture described above for the preparation of oxazole **49** (preparative TLC, R_f = 0.09, 20% acetone/hexanes): mass spectrum, *m/e* 241 (M^+); IR (CH_2Cl_2) 3559, 3437, 2960, 2929, 2865, 1697 cm^{-1}; NMR (acetone-d_6) δ 0.68 (s, 3 H), 0.72 (d, J = 7 Hz, 3 H), 1.10–2.10 (m, 10 H), 2.76 (s, 1 H, exchanges with D_2O), 2.29 (d, J = 7 Hz, 3 H), 1.10–2.10 (m, 10 H), 2.76 (s, 1 H, exchanges with D_2O), 2.29 (d, J = 7 Hz, 2 H, collapses to a singlet upon addition of D_2O), 3.37 (d, J = 11 Hz, 1 H), 3.47 (d, J = 11 Hz, 1 H, collapsing to a singlet upon irradiation at 3.37), 7.20 (br s, 1 H, exchanges with D_2O), 8.16 (d, J = 0.5 Hz, 1 H, collapsing to a singlet upon addition of D_2O). (Note: In solution this material exists as an ~90:10 mixture of anomers. The data presented are that for the major isomer.)

(1′α,2′α,3′β)-5-[(2′,3′-Dimethyl-2′-formylcyclohexyl)methyl]oxazole (62). A flame-dried flask under a blanket of dry nitrogen was charged with 3.1 mL of dry (P_2O_5) CH_2Cl_2 and 136 μL (1.6 mmol, 1.3 equiv) of freshly distilled oxalyl chloride. The resulting solution was cooled to −60 °C (dry ice/EtOH), and a solution of 222 μL (3.1 mmol, 2.6 equiv) of dry Me_2SO (from NaH) in 1.0 mL of dry CH_2Cl_2 was added dropwise with stirring (concomitant gas evolution). After being stirred an additional 5 min, a solution of 265 mg (1.2 mmol) of alcohol **49** in 1.2 mL of dry CH_2Cl_2 was added dropwise with continued stirring, and the resulting mixture was stirred for an additional 20 min at −60 °C. The reaction was then treated with 830 μL (6.0 mmol, 5.0 equiv) of dry triethylamine (from CaH) in one portion and was allowed to warm slowly to room temperature to afford a heterogeneous mixture. A total of 6 mL of H_2O was added, the organic layer was separated, and the aqueous phase was extracted with 4 × 5 mL of CH_2Cl_2. The combined organic layers were than washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford 260 mg (99%) of aldehyde **62** of high purity. This material decomposed slowly on standing, and rapidly upon attempted distillation or chromatography, and was used as such for all subsequent steps. R_f 0.40 (20% acetone/hexanes); Mass spectrum, *m/e* 221 (M^+), IR (CH_2Cl_2) 2700, 1705, 1600, 1510 cm^{-1}; NMR ($CDCl_3$) δ 0.85 (d, J = 7 Hz, 3 H, collapsing to a singlet upon irradiation at 2.06), 1.05 (s, 3 H), 1.08–1.64 (br m, 6 H), 1.91 (m, 1 H, sharpening upon irradiation at 2.74), 2.06 (m, 1 H, sharpening upon irradiation at 0.85), 2.74 (m, 2 H, collapsing to two doublets, J = 15 Hz, upon irradiation at 1.91), 6.78 (s, 1 H), 7.80 (s, 1 H), 9.61 (s, 1 H).

(1′α,2′α,3′β)-5-[[[2′,3′-Dimethyl-2′-(1″β-hydroxy-2″-butynyl)]cyclohexyl]methyl]oxazole (50b) and [(1′α,2′α,3′β)-5-[[[2′,3′-Dimethyl-2′-(1″α-hydroxy-2″-butynyl)]cyclohexyl]methyl]oxazole (50c). A flame-dried flask under a blanket of dry nitrogen was charged with 392 mg (1.6 mmol, 1.3 equiv) of 97% triphenylmethane and 30 mL of dry THF (from benzophenone ketyl). The resulting solution was cooled to −78 °C and was treated, in dropwise fashion, with 0.66 mL (1.3 equiv) of 2.35 M *n*-BuLi in hexane. After the reaction stirred an additional 5 min, a stream of dry propyne gas was slowly bubbled through the solution until the characteristic red color of triphenylmethyl anion had dissipated. A solution of 260 mg (~1.2 mmol) of crude aldehyde **62** in 6 mL of dry THF was then added dropwise over a period of 5 min and stirring was continued at −78 °C for an additional 45 min. The reaction mixture was then quenched with 5 mL of 2.5% KH_2PO_4, removed from the cooling bath, and allowed to warm slowly to room temperature. A total of 20 mL of saturated brine was added, the organic phase was separated, and the aqueous layer was extracted with an additional 4 × 5 mL of CH_2Cl_2. The combined extracts were then washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford a crude product contaminated with triphenylmethane. Flash chromatography[36] of this residue (18% acetone/hexanes) then gave 262 mg (84%) of a 55:45 mixture of **50b** (R_f 0.30, 20% acetone/hexanes) and **50c** (R_f 0.32, 20% acetone/hexanes). For the purpose of preparing ketone **50a**, and ligularone (**1b**), this mixture was carried on as obtained. For the purpose of characterization, as well as for preparing petasalbine (**1**), **50b** could be separated by careful chromatography (silica gel, 15% acetone/hexanes) to give a colorless, crystalline solid: mp 117–119 °C; mass spectrum, *m/e* 261 (M^+); IR (CH_2Cl_2) 3585, 2230, 1590, 1495 cm^{-1}; NMR ($CDCl_3$) δ 0.78 (d, J = 7 Hz, 3 H, collapsing to a singlet upon irradiation at 1.91), 0.95 (s, 3 H), 1.01–1.73 (br m, 6 H), 1.75 (d, J = 2.5 Hz, 3 H, collapsing to a singlet upon irradiation at 4.38), 1.91 (m, 1 H, sharpening upon irradiation at 0.78), 1.98 (m, 1 H, sharpening upon irradiation at 3.17), 2.71 (dd, J = 12, 15 Hz, 1 H, collapsing to a doublet upon irradiation at 1.98 or 3.17), 3.17 (dd, J = 2, 15 Hz, 1 H, collapsing to a doublet upon irradiation at either 1.98 or 2.71), 4.38 (br s, 1 H, sharpening upon irradiation at 1.75), 6.74 (s, 1 H), 7.77 (s, 1 H). The analytical sample was prepared by sublimation at 115 °C (0.003 mm).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.28; H, 8.71; N, 5.10.

(1′α,2′α,3′β)-5-[[[2′,3′-Dimethyl-2′-(1″-oxo-2″-butynyl)]cyclohexyl]methyl]oxazole (50a). A flame-dried flask under a blanket of dry nitrogen was charged with 3.7 mL of dry (P_2O_5) CH_2Cl_2 and 96 μL (1.1 mmol, 1.1 equiv) of freshly distilled oxalyl chloride. The resulting solution was cooled to −60 °C (dry ice/EtOH) and a solution of 157 μL (2.2 mmol, 2.2 equiv) of dry Me_2SO (from NaH) in 1.3 mL of dry CH_2Cl_2 was added dropwise with stirring (concomitant gas evolution). After being stirred an additional 5 min, a solution of 262 mg (1.0 mmol, 1 equiv) of alcohols **50b** and **50c** (as a 55:45 mixture) in 1.3 mL of CH_2Cl_2 was added with continued stirring, and the resulting mixture was stirred an additional 20 min at −60 °C. The reaction was then treated with 697 μL (5 mmol) of dry triethylamine (from CaH) in one portion and was allowed to warm slowly to room temperature to afford a heterogeneous mixture. A total of 6 mL of H_2O was added, the organic layer was separated, and the aqueous phase was extracted with 4 × 5 mL of CH_2Cl_2. The combined organic layers were than washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford 262 mg of crude **50a**, which after purification by flash chromatography[36] gave 245 mg (94%) of **50a** as a viscous, colorless oil: bp 155 °C (0.002 mm); R_f 0.35 (20% acetone/hexanes); mass spectrum, *m/e* 259 (M^+); IR (CH_2Cl_2) 2200, 1650, 1595, 1500 cm^{-1}; NMR ($CDCl_3$) δ 0.79 (d, J = 7 Hz, 3 H, collapsing to a singlet upon irradiation at 2.22), 1.02–1.60 (br m, 6 H), 1.21 (s, 3 H), 1.98 (s, 3 H), 2.06 (m, 1 H, sharpening upon irradiation at 2.79), 2.22 (m, 1 H, collapsing to a triplet, J = 4 Hz, upon irradiation at 0.79), 2.55 (dd, J = 4, 15 Hz, 1 H, collapsing to a doublet upon irradiation at either 2.06 or 2.79), 2.79 (dd, J = 12, 15 Hz, 1 H, collapsing to a doublet upon irradiation at either 2.06 or 2.55), 6.78 (s, 1 H), 7.78 (s, 1 H).

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.99; H, 7.97; N, 5.20.

(±)-Ligularone (1b). A flame-dried flask under a blanket of dry nitrogen was charged with 245 mg (0.94 mmol) of acetylenic ketone **50a**, 10 mg (0.1 equiv) of hydroquinone and 34 mL of dry, freshly distilled ethylbenzene (from Na). The resulting solution was then heated under reflux, with protection from light, for a period of 24 h, during which period all **50a** was slowly consumed (R_f 0.35, 20% acetone/hexanes) concomitant with the formation of **(±)-1b** (R_f 0.70). The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to afford 239 mg of crude **(±)-1b** as a dark oil. Flash chromatography of this material (5% acetone/hexanes) gave 189 mg (87%) of **(±)-1b** as colorless crystals, which after crystallization from 30–60 °C petroleum ether had mp 70–71 °C (lit.[26d] mp 70.5–71 °C, **(±)-1b**; 64–65 °C, natural[25c]). The IR, NMR, and UV spectra of **(±)-1b** thus obtained were in complete agreement with data reported for the natural material.[25c,34]

(±)-Epipetasalbine (1c). A flame-dried flask under a blanket of dry nitrogen was charged with 10 mg (0.26 mmol, 5.1 equiv) of LAH and 5 mL of dry ethyl ether (from LAH). A solution of 50 mg (0.22 mmol) of **(±)-1b** in 4 mL of ether was added dropwise with efficient stirring at room temperature. After being stirred at total of 45 min, 5 mL of H_2O and 1 mL of 5% aqueous HCl were cautiously added, and the phases were separated. The aqueous phase was then extracted with 2 × 10 mL of ether, and the combined ethereal extracts were washed with 2% $NaHCO_3$ (10 mL), dried over anhydrous $MgSO_4$, and concentrated to afford 47 mg of crude **(±)-1c**, R_f 0.55 (20% acetone/hexanes). Prepa-

rative TLC of this residue followed by crystallization from 30–60 °C petroleum ether then gave 36 mg (71%) of (±)-**1c** as colorless crystals, mp 69–70 °C (lit.[25c] mp 67–68 °C, for material derived from natural **1b**; (±)-**1c** previously reported as an oil[26f]). The IR and NMR spectra of (±)-**1c** thus obtained were in complete agreement with data reported for the naturally derived material.[25c]

(±)-Petasalbine (1). A flame-dried flask under a blanket of dry nitrogen was charged with 26 mg (0.10 mmol) of acetylenic alcohol **50b**, 1 mg (0.1 equiv) of hydroquinone and 5 mL of dry, freshly distilled ethylbenzene (from Na). The resulting solution was then heated under reflux, with protection from light, for a period of 32 h, during which period most of **50b** was slowly consumed (R_f 0.30, 20% acetone/hexanes) concomitant with the formation of (±)-**1** (R_f 0.5). The reaction mixture was then cooled to room temperature and concentrated under reduced pressure (bath temperature 25 °C) to afford 25 mg of a dark residue which was purified by preparative TLC (20% acetone/hexane) to give 5 mg (17%) of starting **50b** and 16 mg (69%, 84% based upon recovered **50b**) of (±)-**1** as a colorless crystalline solid. Recrystallization from 30–60 °C petroleum ether gave (±)-**1** of mp 73–74 °C (lit.[25c] mp 80–81 °C, natural; (±)-**1** previously reported as an oil.[26f] The IR, UV, ^{1}H NMR, and ^{13}C NMR spectra of (±)-**1** thus obtained were in complete agreement with data reported for the naturally occurring substance.[25c,26f,35]

(±)-Petasalbine Acetate (1d). A flame-dried flask under a blanket of dry nitrogen was charged with 24 mg (0.1 mmol) of (±)-**1**, 0.5 mL of dry pyridine (stored over molecular sieves), and 0.4 mL of acetic anhydride. After being stirred at ambient temperatures for 16 h, the resulting solution was concentrated to dryness under reduced pressure (bath temperature 25 °C), and the residue obtained was purified by flash chromatography[36] (5% acetone/hexanes) to afford 21 mg (76%) of **1d** as a colorless oil. Crystallization of this material from 30–60 °C petroleum ether then gave **1d** as a colorless crystalline solid, mp 34–35 °C (lit.[25c] mp 54–55 °C for the naturally derived material). The IR and NMR spectra of (±)-**1d** thus obtained were in complete agreement with data reported for the naturally derived material.[25c,34]

(±)-Ligularone (1b) from (±)-Petasalbine (1). A solution of 16 mg (0.08 mmol, 1.0 equiv) of $(pyr)_2CrO_3$ in 0.6 mL of dry pyridine was added dropwise and with efficient stirring to a solution of 19 mg (0.08 mmol) of (±)-**1** in 0.3 mL of pyridine.[25c] The resulting solution was stirred at ambient temperature for a period of 14 h before being quenched with 4 mL of H_2O and extracted with 5 × 10 mL of ether. The combined ethereal extracts were then washed with 2 × 10 mL of 2% aqueous HCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give, after preparative TLC, 8 mg (42%) of (±)-**1b** which was identical in all respects with the material prepared previously.

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Total Synthesis of (±)-Saxitoxin†

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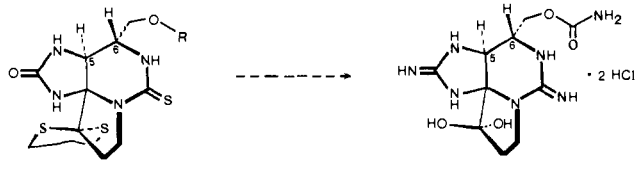
Abstract: (±)-Saxitoxin (**3**), the paralytic agent of the Alaska butter clam *Saxidomas giganteus*, has been synthesized in a totally stereospecific fashion through a sequence involving as the key steps (a) an intramolecular 1,3-dipolar addition of an azomethine imine to a 2-imidazolone, (b) a reductive cleavage of the resulting pyrazolidine ring followed by intramolecular acylation, and (c) final elaboration of a bis(pseudourea) to the requisite guanidine functionality.

Saxitoxin (**3**), the paralytic agent of the Alaska butter clam *Saxidomas giganteus*, is one of the most toxic of the non-protein poisons known and it has also found widespread use in the study of various nerve disorders.[1] Its physiological action arises from



1 (R = CH_2Ph)
2 (R = H)

Saxitoxin (**3**)

a disruption of the propagation of impulses in skeletal muscles and nerves, a result due chiefly to a specific interference with the increase in sodium ion permeability normally associated with excitation. The pharmacology[2] and biochemistry of **3** have been reviewed,[3] as has its isolation and purification[4] and chemical and physical properties.[5] Although initially purified in 1957,[4] however, it remained until 1975 for an X-ray analysis to conclusively reveal the molecular geometry as indicated.[6] This accomplishment was followed shortly thereafter by the elegant total synthesis of Kishi et al.,[7] who utilized the thiourea derivative **1** as a key intermediate for elaboration to **3**. In this paper we report on an alternative synthesis of **3** which proceeds through the closely related species **2**. Compound **2**, in turn, has been prepared by a route which is noteworthy for its efficiency (0.5–1.0-g scale) and the fact that no chromatographic separations are required throughout the entire reaction sequence.

Discussion and Results

The key intermediate for our synthesis of **2** was the hydrazide derivative **4** which was conveniently derived from 2-imidazolone on 5–10-g scales and larger (Scheme I).[8] This material, upon

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