An Annulation Approach to the Synthesis of Pseudoguaianolide Sesquiterpene Lactones. Total Syntheses of *dl*-Confertin and *dl*-Aromatin

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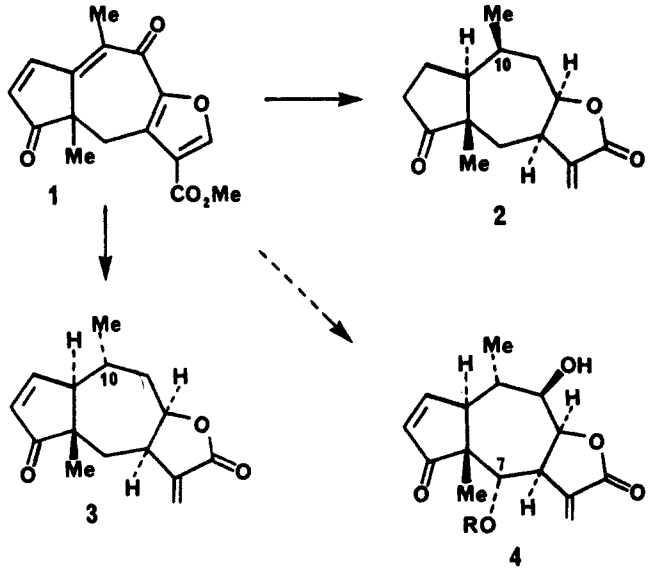
Abstract: Annulation of 2-methyl-1,3-cyclopentanedione with 4-(halomethyl)-5-(1-oxopropyl)-3-furancarboxylic esters **6a** or **6b** provides the fully assembled tricyclic framework, **1**, of the cytotoxic pseudoguaianolide sequiterpene lactones. Dienedione **1** has been used to construct (±)-confertin (**2**) and (±)-aromatin (**3**). Experiments relevant to a total synthesis of the more complex helenanolides (e.g., the fastigilins, **4**) also are discussed.

Much of the interest in the pseudoguaianolide group of sesquiterpenes has been stimulated by reports of cytotoxic and antitumor activity within the series.[1] Several total syntheses of the pseudoguaianolides have been developed[2] since Marshall and Snyder's pioneering synthesis of (±)-4-deoxydamsin[3] and Kretchmer and Thompson's total synthesis of the first naturally occurring pseudoguaianolide, (±)-damsin, reported in 1976.[4]

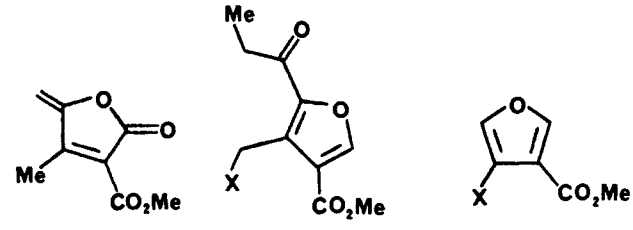
Recently, we communicated a new, potentially general approach to the construction of pseudoguaianolides[5] and demonstrated the efficiency of the method by total synthesis of (±)-confertin (**2**).



Confertin is a member of the more abundant subgroup of the pseudoguaianolides (the ambrosanolides), in which the C(10) methyl group (pseudoguaiane nomenclature) is in the β-configuration. In this paper, we present full details of this work, as well as a new synthesis of (±)-aromatin (**3**), a member of the less-abundant helenanolide subgroup, in which the C(10) methyl group is in the α-configuration. Both syntheses proceed from the readily available, fully assembled tricyclic framework **1**. Total synthesis of **3** is of special importance, because it suggests that the more complex fastigilins (**4**),[5] multiradiatin, and multistatin should be available by appropriate functionalization of **1**.

Results and Discussion

Our approach to sequiterpene lactone construction is based on an annulation strategy that attempts to incorporate the essential features of the α-methylene-γ-butyrolactone ring within the annulation reagent. An earlier example of this strategy, in the context of eudesmanolide sesquiterpene synthesis, made use of the novel butenolide **5**.[7] This substance was used to build six-membered rings via annulation of ketone-derived silyl enol ethers with **5**, employing a 1,6-Michael addition followed by a vinylogous aldol condensation.



At the outset of the present work, the 4-(halomethyl)-5-(1-oxopropyl)-3-furancarboxylic esters **6** were expected to provide an efficient annulation route to tricyclic intermediate **1** by alkylation of 2-methyl-1,3-cyclopentanedione and aldol condensation to close the seven-membered ring. All the carbon atoms required for synthesis of the pseudoguaianolide ring system are present in **1**, leaving only adjustments in functional group oxidation states to be made. In practice, we have found it expedient to remove the carboxylic acid group in **1**.

Preparation of the Annulation Reagent. Commercially available furan-3,4-dicarboxylic esters are converted to **7b**[8] by monosaponification in methanolic solution to give **7a** and BH_3 reduction of **7a**. In our early studies, furan **6b** was prepared by reaction of **7b** with phosphorous triiodide in ether to give **7d** (65–70% yield), followed by acylation of **7d** with propionic anhydride and boron trifluoride etherate. High yields for the acylation step were obtained for small scale reactions,[5] but only ~50% yields could be obtained for a 10-g reaction scale.[9]

(1) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *101*, 1147.
(2) For an excellent presentation of the strategies utilized in pseudoguaianolide sesquiterpene construction, see: Heathoock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In "The Total Synthesis of Natural Products"; ApSimon, J. W. Ed., Wiley: New York, 1982; Vol. 5.
(3) Marshall, J. A.; Snyder, W. R. *J. Org. Chem.* **1975**, *40*, 1656.
(4) Kretchmer, R. A.; Thompson, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 3379.
(5) Schultz, A. G.; Motyka, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 5800.
(6) Herz, W.; Rajappa, S.; Roy, S. K.; Schmid, J. J.; Mirrington, R. N. *Tetrahedron* **1966**, *22*, 1907. These pseudoguaianolides have not as yet been obtained by total synthesis.
(7) Schultz, A. G.; Godfrey, J. D. *J. Am. Chem. Soc.* **1980**, *102*, 2414.
(8) Procedure of: Corey, E. J.; Crouse, D. N.; Anderson, J. E. *J. Org. Chem.* **1975**, *40*, 2140.

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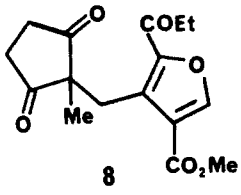
A more efficient and reliable synthesis was developed for bromomethylfuran **6a**. Thus, treatment of **7b** with PBr_3 gives **7c** in 82% yield after distillation. Acylation of **7c** with propionic acid in methanesulfonic acid and phosphorus pentoxide gives the crystalline annulation reagent **6a** in 74% isolated yield (22-g scale).

Annulation of 2-Methyl-1,3-cyclopentanedione. Alkylation of 2-methyl-1,3-cyclopentanedione with **6b** (1 equiv) in refluxing *tert*-butyl alcohol with potassium *tert*-butoxide gives furantrione **8** in ~50% yield. While this procedure provided sufficient **8** for our early synthetic studies,[5] the moderate yield obtained for this key alkylation prompted a search for improved reaction conditions. We soon found that alkylation of 2-methyl-1,3-cyclopentanedione with the more readily available bromomethylfuran **6a**, in the presence of potassium iodide (1 equiv), gives **8** in a reproducible 75% yield. Also isolated from alkylations with **6a** are the product of O-alkylation, **9** (~10%), and lesser quantities of cyclization products **10** and **11**. Significantly (vide infra), very little alkoxide-induced cleavage of the non-enolizable β-dicarbonyl functionality in **8** occurs under these reaction conditions.



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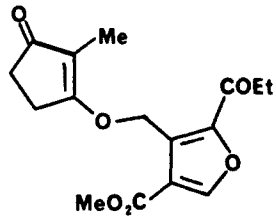

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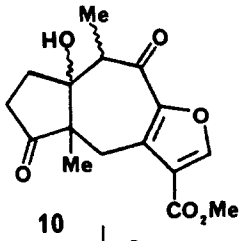

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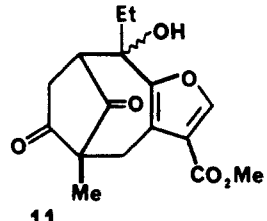

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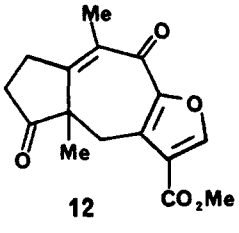

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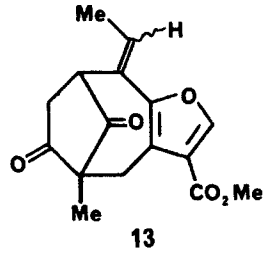
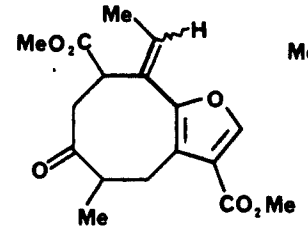


13

It is instructive to compare the reactivity of bromomethylfuran **6b** with the 3,5-disubstituted 4-(halomethyl)isoxazole annulation reagents developed by Stork and co-workers for construction of cyclohexenone rings.[10] In both cases, steric crowding around the alkylation center is present, and yet both systems provide synthetically useful yields of C-alkylation products. The 4-(halomethyl)isoxazoles also C-alkylate β-dicarbonyl enolates,[11] despite the fact that such enolates are notorious for O-alkylation with hindered alkylation reagents.[12] Presumably allylic stabilization of the transition state[13] for enolate alkylation by a relatively "soft"[14] heteroaromatic ring is responsible for predominant C-alkylation with the (halomethyl)isoxazoles as well as the (halomethyl)furans used in our study.

Both β-hydroxy ketones **10** and **11** undergo dehydration on treatment with *p*-toluenesulfonic acid in refluxing benzene solution to give enones **12** and **13**, respectively. However, we were not able to convert **8** directly to **12** by base- or acid-catalyzed cyclodehydration. Nucleophilic bases cause β-dicarbonyl cleavage,[15] and acidic conditions promote cyclization to give **13**; for example, **8** is converted to **13** in 88% yield by treatment with *p*-toluenesulfonic acid in refluxing benzene solution. The use of potassium fluoride[16] with 18-crown-6 in refluxing xylene solution also did not provide **10** or **12**.

The novel cyclization product **13** contains a cycloheptanone ring and a cyclooctanone ring. Both ring systems are found in terpenoids and, for this reason, we explored the possibility of nucleophile-induced β-dicarbonyl cleavage[15] to give either **14** or **15**.



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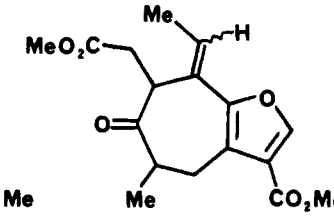

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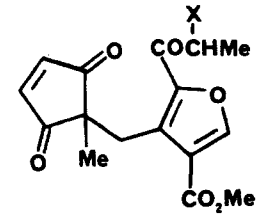
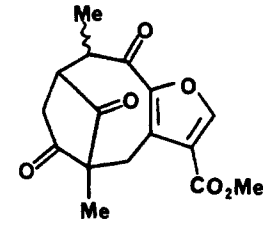
Treatment of **13** with sodium methoxide in methanol gives only **15** in 75% isolated yield. The structure of **15** is supported by mass spectral fragmentation, for which the base peak is *m/e* 247 (M^+ − 73). This fragment corresponds to loss of CH_2CO_2Me, the formation of which can be easily rationalized by structure **15**, but not by the eight-membered ring isomer **14**.

The acid-catalyzed conversion of **8** into **13** suggests that enolization of **8** occurs preferentially within the cyclopentanedione ring. We, therefore, considered the conversion of **8** to dienedione **1** via 4-cyclopentene-1,3-dione **16a**. Dienedione **1** is uniquely attractive because it already contains the fully developed cyclopentenone unit[17a] found in the majority of pseudoguaianolides; e.g., **3** and **4**.

Reaction of **8** with phenyltrimethylammonium tribromide (1 equiv) in THF gives the yellow enetrione **16a** in approximately quantitative yield. This conversion presumably occurs by cyclopentanedione ring bromination followed by in situ dehydrobromination.[17b] In contrast to the reactivity of **8**, cyclodehydration



16 a, X = H
b, X = Br
c, X = PPh_3Br
d, X = $PO(OMe)_2$



17

of **16a** is catalyzed by *p*-toluenesulfonic acid in refluxing benzene

(9) Motyka, L. A. Ph.D. Thesis, Rensselaer Polytechnic Institute, 1983.
(10) Stork, G.; Danishefsky, S.; Ohashi, M. *J. Am. Chem. Soc.* **1967**, *89*, 5459.
(11) Ohashi, M.; Kamachi, H.; Kakisawa, H.; Stork, G. *J. Am. Chem. Soc.* **1967**, *89*, 5460.
(12) For C- vs. O-alkylation studies with 2-methyl-1,3-cyclopentanedione, see: (a) Rosenthal, D.; Davis, K. H., Jr. *J. Chem. Soc. C* **1966**, 1973. (b) Schick, H.; Schwarz, H.; Finger, A. *Tetrahedron* **1982**, *38*, 1279.
(13) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361 and the series of papers immediately following this study.
(14) Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827.
(15) (a) Trost, B. M.; Vladuchick, W. C. *J. Org. Chem.* **1979**, *44*, 148. (b) Muskopf, J. W.; Coates, R. M. *J. Org. Chem.* **1985**, *50*, 69 and references cited within those papers.
(16) Dauben, W. G.; Hart, D. J. *J. Org. Chem.* **1977**, *42*, 3787.
(17) (a) However, in this paper, we do not consider this particular aspect of the annulation strategy. (b) For a related conversion of 2,2-dimethylpentane-1,3-dione to 2,2-dimethyl-4-cyclopentene-1,3-dione, see: Agosta, W. C.; Smith, A. B., III. *J. Org. Chem.* **1970**, *35*, 3856.

solution to give the pale-yellow dienedione **1** in 60% yield,[5] together with a small amount of the intramolecular Michael addition product **17** and resinous material. The same reaction conducted at room temperature in a rapidly stirred two-phase system containing concentrated sulfuric acid and benzene provides **1** in nearly quantitative yield. Thus, at the present stage of development, tricycle **1** is available in ~40% overall yield from commercially available 3,4-furandicarboxylic esters; on several occasions, 20–30-g quantities of **1** have been prepared by this procedure.

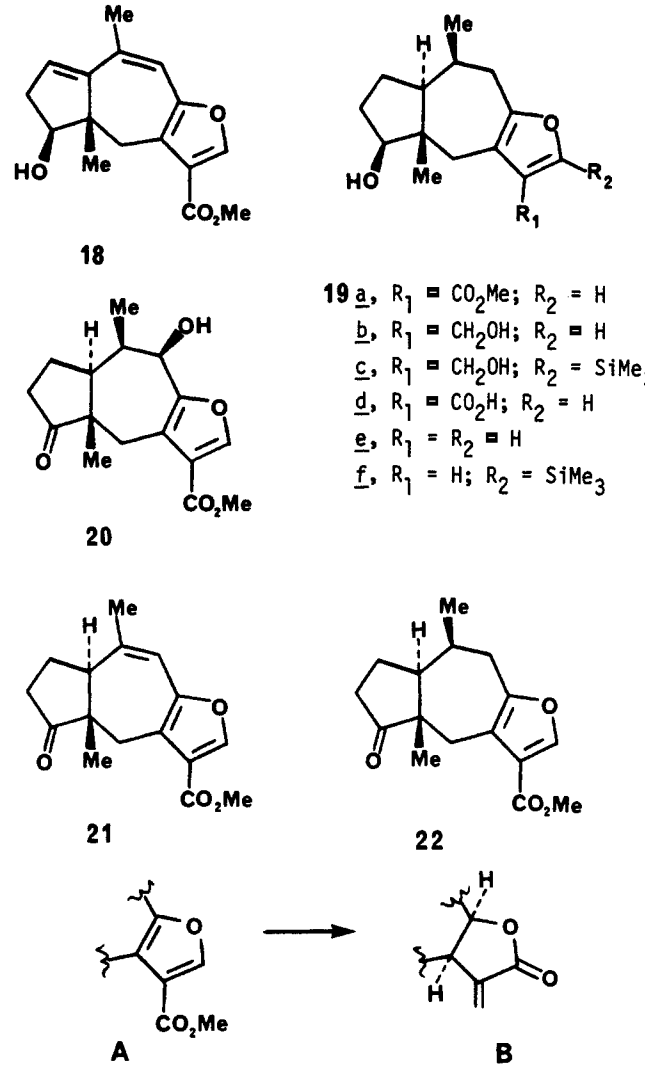
The prochiral nature of synthetic intermediates **8** and **16a** presented the opportunity for asymmetric cyclodehydration to **12** and **1**, respectively. There have been several reports of asymmetric induction in cyclizations of 1,5-dicarbonyl derivatives of 2-methyl-1,3-cyclopentanedione by the use of optically active amino acids.[18] These reactions are thought to proceed by formation of an intermediate enamine, from which stereodirected cyclization occurs. Hydrolysis generally provides the cyclized β-hydroxy ketone or enone in high yield and, in certain cases, near 100% ee. We are not aware of any application of this process to the cyclization of 1,6-diketones and, therefore, the enantioselective synthesis of seven-membered rings. In any event, the use of L-phenylalanine and perchloric acid in refluxing acetonitrile did not result in cyclization of **8** or **16a** nor did the use of L-proline or L-histidine.

The intramolecular Wittig cyclization with an optically active phosphine acting as a chiral auxiliary has produced moderate stereoselection in derivatives of 2-methyl-1,3-cyclopentanedione.[19] With this goal in mind, trione **8** was treated with 2 equiv of phenyltrimethylammonium trobromide in THF. Using these modified bromination conditions, bromoenetrione **16b** was obtained in 73% yield. Unfortunately, reaction of **16b** with an achiral phosphine model (triphenylphosphine) produced none of the desired phosphonium salt **16c** but rather promoted reductive debromination to give enetrione **16a**. Related experiments directed at an enantioselective synthesis of **1** also were unsuccessful.[20]

Total Synthesis of (±)-Confertin (2). We expected that the angular methyl substituent in **1** would function as an efficient stereocontrol element, through which the other stereocenters in confertin (**2**) and aromatin (**3**) would be developed.[2] Selective hydrogenation (1 equiv of H_2) of **1** with 5% Pt on carbon in ethyl acetate at atmospheric pressure gives **12**. Enedione **12** is converted to the bright-yellow diene alcohol **18** by stereoselective reduction with sodium borohydride in methanol, followed by treatment with 1 N hydrochloric acid. Control experiments demonstrate that dehydration of an intermediate enediol occurs after addition of the hydrochloric acid.[9] Hydrogenation of **18** with 5% Pd on carbon gives the furan alcohol **19a** in only moderate overall yield from **1**.[5]

A more efficient conversion of **1** to **19a** begins by hydrogenation (3 equiv of H_2) of **1** with 5% Pt on carbon in 95% ethanol to give keto alcohol **20**. Dehydration of **20** occurs in dilute hydrochloric acid–ethanol solvent at room temperature. Hydrogenation of the resulting keto olefin **21** with 5% Pt on carbon in glacial acetic acid provides ketone **22** in ~75% overall yield from **1**. This substance, **22**, might be suitable for direct conversion to confertin (after carbonyl group protection); however, we elected to merge with our earlier synthesis of **2**[5] by reduction of **22** with sodium borohydride to give **19a** (approximately quantitative yield).

With the key stereoelements in place, attention was focused on conversion of the 3-carbomethoxyfuran unit to a cis-fused α-methylene-γ-butyrolactone ring (e.g., A → B). Several examples of the oxidation of furans to butyrolactones have been reported,[21] but the most general method seems to be the peracid oxidation of 2-(trimethylsilyl)furans, first reported by Kuwajima and Urabe.[22]



Reduction of **19a** with lithium aluminum hydride provides the furan–methanol derivative **19b**. Oxidation of **19b** with *m*-chloroperbenzoic acid in the absence or presence of buffers[21] results in a complex mixture of products. Thus, the presence of the allylic hydroxyl group in **19b** does not impart sufficient activation for regioselective oxidation (epoxidation) of the furan ring. The

(18) (a) Cohen, N. *Acc. Chem. Res.* **1976**, *9*, 412. (b) Danishefsky, S.; Cain, P. *J. Am. Chem. Soc.* **1976**, *98*, 4975. (c) Mander, L. N.; Turner, J. V. *Tetrahedron Lett.* **1981**, *22*, 3683. (d) Takano, S.; Kasahara, C.; Ogasawara, K. *Heterocycles* **1981**, *16*, 1669.

(19) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699.

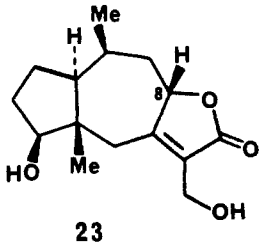
(20) The less-sterically congested *des*-methyl analogue of **16b** was prepared, but attempts to convert this material to the phosphonium salt corresponding to **16c** also resulted in reductive debromination. The *des*-methyl analogue of β-ketophosphonate **16d** could be prepared from the bromide, but base-induced cyclizations of this material only resulted in decomposition. For details of this study, see ref 9.

(21) (a) Hikino, H.; Hikino, Y.; Yosioka, I. *Chem. Pharm. Bull.* **1962**, *10*, 641. (b) Hikino, H.; Hikino, Y.; Yosioka, I. *Chem. Pharm. Bull.* **1964**, *12*, 755. (c) Takeda, K.; Minato, H.; Ishikawa, M.; Miyawaki, M. *Tetrahedron* **1964**, *20*, 2655. (d) Takeda, K.; Minato, H.; Horibe, I.; Miyawaki, M. *J. Chem. Soc. C* **1967**, 631. (e) Wiesner, K.; Ferland, J. M.; Lefebvre, Y.; Deghenghi, R. *Tetrahedron Lett.* **1966**, *30*, 3617. (f) Tsai, T. Y. R.; Minta, A.; Wiesner, K. *Heterocycles* **1979**, *12*, 1397. (g) Schulte, G.; Scheuer, P. J. *Helv. Chim. Acta* **1980**, *63*, 2159. (h) Satoh, D.; Aoyama, K. *Chem. Pharm. Bull.* **1970**, *18*, 1239. (i) Raldugin, V. A.; Lisina, A. I.; Kashtanova, N. K.; Pentegova, V. A. *Khim. Prir. Soedin* **1970**, *5*, 541. (j) Takeda, K.; Horibe, I.; Minato, H. *J. Chem. Soc. C* **1968**, 569. (k) Tada, H., Minato, H.; Takeda, K. *J. Chem. Soc. C* **1971**, 1070. (l) Tada, M. *Chem. Lett.* **1982**, 441. (m) Takeda, K.; Ikuta, M.; Miyawaki, M.; Tori, K. *Tetrahedron* **1966**, *22*, 1159. (n) Rucker, G.; Schikarski, M. *Arch. Pharm.* **1978**, *311*, 754. (o) Hikino, H.; Agatsuma, K.; Takemoto, T. *Tetrahedron Lett.* **1968**, *24*, 2855. (p) Moriyama, Y.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3196. (q) Ley, S. V.; Mahon, M. *Tetrahedron Lett.* **1981**, *22*, 4747. (r) Shono, T.; Matsumura, Y.; Yamane, S. *Tetrahedron Lett.* **1981**, *22*, 3269. (s) Froborg, J.; Magnusson, G.; Thoren, S. *J. Org. Chem.* **1975**, *40*, 1595. This paper describes an electrochemical oxidation of a furan ring in a total synthesis of pyrovellerolactone.

(22) (a) Kuwajima, I.; Urabe, H. *Tetrahedron Lett.* **1981**, *22*, 5191. (b) Goldsmith, D.; Liotta, D.; Saindane, M.; Waykole, L.; Bowen, P. *Tetrahedron Lett.* **1983**, *24*, 5835. (c) Tanis, S. P.; Head, D. B. *Tetrahedron Lett.* **1984**, *25*, 4451.

2-(trimethylsilyl)furan derivative **19c** (furan nomenclature) was expected to undergo a more selective peracid oxidation.

Treatment of **19b** with at least 3 equiv of *n*-butyllithium, followed by trimethylsilyl chloride and an aqueous acid workup gives the (trimethylsilyl)furan **19c** in 85% yield. Oxidation of **19c** with peracetic acid and sodium acetate in methylene chloride gives a mixture of lactones as revealed by absorptions at 1780 and 1740 cm^{-1} in IR spectra of crude reaction mixtures. These absorptions were assumed to be a result of both the β,γ- and α,β-unsaturated lactones, respectively. Only the α,β-unsaturated lactone **23** was obtained after preparative chromatography on silica gel.



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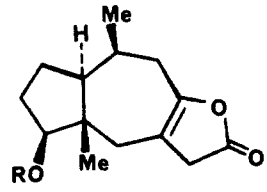
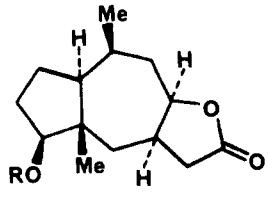
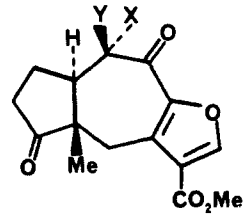


24 a, R = H
b, R = Ac



25 a, R = H
b, R = Ac



26 a, X = H; Y = Me
b, X = Me; Y = H

Inasmuch as **23** is formed under equilibrating conditions, the hydrogen atom at C(8) is tentatively assigned the apparently more stable β-configuration. Attempted hydrogenation of **23** with Pd on carbon resulted in hydrogenolysis of the allylic hydroxyl group, while 5% rhodium on alumina in ethyl acetate at pressures up to 800 psi gave only recovered starting material.[23c]

A solution[24] to the problems associated with generation and isolation of a β,γ-unsaturated butyrolactone from **19a** began by saponification and decarboxylation of the resulting acid **19d** with copper in refluxing quinoline to give **19e**. Treatment of a THF solution of **19e** with *n*-butyllithium (2 equiv) and excess trimethylsilyl chloride followed by aqueous acid workup gives the (trimethylsilyl)furan **19f** in 82% overall yield from **19a**.

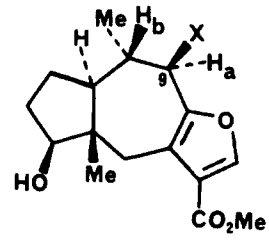
Peracetic acid oxidation of **19f** affords the β,γ-unsaturated lactone **24a**, uncontaminated by the isomeric α,β-butenolide. This compound was converted to **24b**, an intermediate in both the Schlessinger[23a] and Heathcock[23b] total syntheses of (±)-confertin, by acetylation with acetic anhydride/pyridine/4-(dimethylamino)pyridine. Direct comparison of our **24b** with the literature material was carried out at the University of Rochester (100- and 400-MHz ^1H NMR spectroscopy). Hydrogenation of **24b** with rhodium on alumina in ethyl acetate at 60 psi[23a] gives crystalline **25b** (mp 109–110 °C [lit. mp 110–111 °C]).[23a] Alternatively, **24a** is hydrogenated to give the previously reported[23] lactone alcohol **25a** (white foam) in 89% isolated yield.

Thus, a highly stereoselective (and regioselective, with regard to β,γ-unsaturated lactone generation) formal total synthesis of (±)-confertin (**2**) has been accomplished in ~22% overall yield from **1**. Conversion of **25a** to (±)-confertin has been reported to occur in ~64% yield.[25]

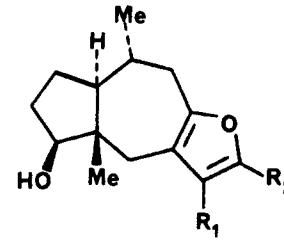
Total Synthesis of (±)-Aromatin (3). Hydroxy lactone **30** is an advanced intermediate in the toal synthesis of (±)-aromatin reported by Ziegler and Fang.[26] We now report the conversion of keto alcohol **20** to **30**. Oxidation of **20** with pyridinium dichromate in methylene chloride gives the diketone **26a**, and this is converted to diketone **26b**, in which the C(10) methyl group is in the considerably more stable α-configuration, by epimerization with anhydrous sodium carbonate in methanol–benzene in ~80% yield from **20**.

Treatment of diketone **26b** with sodium borohydride in methanol gives diol **27a** in approximately quantitative yield. Configuration at C(9) was assigned after consideration of ^1H NMR spectral information. The hydrogen atom at C(9), H_a, appears at δ 4.28 as a doublet with $J_{a,b}$ = 9.4 Hz. This large coupling constant suggests that a diaxial relationship exists between H_a and H_b. With the seven-membered ring in a favorable chairlike conformation, Dreiding stereomodels of **27a** clearly show an ~180° dihedral angle between H_a and H_b when H_a is in the α-configuration. This stereochemical result is of great significance in the context of proposed total syntheses of the fastigilins (**4**); for a synthesis of aromatin, the C(9) hydroxyl group is now superfluous.

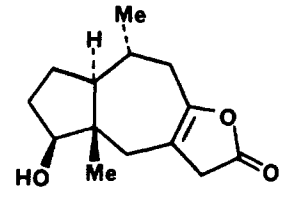
Hydrogenolysis of **27a** using 5% Pd on carbon in acetic acid at 57 psi gives **27b**. Conversion of **27b** to **30** followed the method developed for the analogous transformation in the confertin synthesis. Thus, saponification of **27b** gives the carboxylic acid



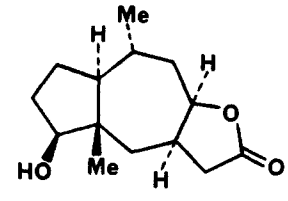
27 a, X = OH
b, X = H



28 a, R_1 = CO_2H; R_2 = H
b, R_1 = R_2 = H
c, R_1 = H; R_2 = $SiMe_3$



29



30

28a, and this substance undergoes decarboxylation by the action of copper in quinoline to give furan **28b** in ~55% overall yield from diketone **26b**. Reaction of **28b** with *n*-butyllithium (>2 equiv) followed by addition of trimethylsilyl chloride and an aqueous workup gives **28c**. Peracid oxidation provides **29**, and **29** is converted to the Ziegler–Fang hydroxy lactone **30** by hydrogenation with 5% rhodium on alumina. Spectral data for our material compared favorably to those reported in the literature.[26] The conversion of **30** to (±)-aromatin (**3**) has been performed in ~50% yield.[26]

Conclusion. Seven-membered ring annulation strategy, involving alkylation reagent **6**, has been used in the development of efficient

(23) (a) Quallich, G. J.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 7627. (b) Heathcock, C. H.; DelMar, E. G.; Graham, S. L. *J. Am. Chem. Soc.* **1982**, *104*, 1907. (c) In confertin syntheses appearing in both of these papers, α,β-unsaturated lactones similar in structure to that of **23** could not be reduced to cis-fused butyrolactones.

(24) For additional experiments toward the conversion A → B, see ref 9.

(25) Quallich, G. J. Ph.D. Thesis, University of Rochester, 1980.

(26) (a) Ziegler, F. E.; Fang, J.-M. *J. Org. Chem.* **1981**, *46*, 825. (b) Ziegler, F. E.; Fang, J.-M.; Tam, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 7174. (c) An alcohol-protected *tert*-butyl derivative of **30** was encountered in the first total synthesis of **3**, reported by: Lansbury, P. T.; Hangauer, Jr., D. G.; Vacca, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 3964. Five steps were required to convert this derivative to (±)-**3** in ~35% yield. (d) Lansbury, P. T.; Vacca, J. P. *Tetrahedron* **1982**, *38*, 2797.

synthetic routes to the ambrosanolides and the helenanolides. Current efforts are directed at the introduction of the C(7) oxygen substituent necessary for helenalin and fastigilin constructions. We expect to be able to demonstrate that all the pseudoguaianolides containing a cis lactone fusion may be assembled from the readily available tricycle **1**.

Experimental Section

Instrumentation. ^{1}H NMR spectra were obtained on a Hitachi–Perkin-Elmer R-600 (60 MHz), Varian T-60 (60 MHz), or Varian XL-200 (200 MHz) NMR spectrometer using tetramethylsilane as an internal standard. Nuclear Overhauser enhancement (NOE) experiments and ^{13}C NMR spectra were obtained on the Varian XL-200 NMR spectrometer. Mass spectra were obtained on a Hitachi–Perkin-Elmer RMU-6E mass spectrometer or a Finnigan 1020 quadrupole gas chromatograph–mass spectrometer. Infrared spectra were recorded on a Perkin-Elmer 298 or Perkin-Elmer 137 infrared spectrometer as a thin film (film) or in chloroform solution ($CHCl_3$). Ultraviolet spectra were obtained on a Perkin-Elmer UV–vis 552 spectrophotometer.

Melting point determinations were performed by using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were carried out by Spang Microanalytical Laboratory, Eagle Harbor, MI, or Galbraith Laboratories, Inc., Knoxville, TN.

Solvents. Tetrahydrofuran (THF) was predried over 4-Å molecular sieves before distillation from sodium metal under a nitrogen atmosphere using benzophenone ketyl as indicator. Hexamethylphosphoramide (HMPA) and dimethylformamide (DMF) were distilled from calcium hydride under reduced pressure and stored over 4-Å molecular sieves under a nitrogen atmosphere. Diisopropylamine, *tert*-butyl alcohol, 2,4,6-collidine, and triethylamine were disilled from calcium hydride under a nitrogen atmosphere. Methanol was distilled from magnesium turnings under a nitrogen atmosphere. Pyridine was distilled from barium hydroxide and stored over 4-Å molecular sieves. Acetone was distilled from anhydrous potassium carbonate and stored over 4-Å sieves.

Commercially available "absolute" ether was used without further purification.

Procedures. Solvents were removed under reduced pressure by placing the appropriate solution on a Buchi Rotovapor-R rotary evaporator. The last traces of solvent were removed by evacuation at room temperature using a Welch Duo-Seal floor pump (ca. 0.10 mmHg). Whatman 1PS silicone treated phase separting paper was used for drying organic solutions by gravity filtration.

A Waters Prep-500 liquid chromatograph with prepacked silica gel cartridges was used for high-pressure liquid chromatography (HPLC) separations. Flash chromatography was performed with Baker silica gel (40-μm average particle size) or Kieselgel 60 silica gel (40–60-μm particle size). Thin-layer chromatography (TLC) was carried out with E. Merck Silica gel 60 F (0.2-mm thickness) or E. Merck Aluminum Oxide F-254 (0.2-mm thickness) precoated TLC sheets. Preparative thick-layer (1.25 mm) plates (silica gel) were made from E. Merck 60 PF-254 or 60 GF-254. Preparative thick-layer (1.50 mm) plates (alumina) were made from E. Merck Aluminum Oxide 60 PF-254. A solution of 15% methanol in dichloromethane was used for extraction.

Nomenclature. In contrast to the previous sections, systematic nomenclature is used in the following section.

4-(Bromomethyl)-3-furancarboxylic Acid Methyl Ester (7c). A solution of **7b**[8] (41.37 g, 0.265 mole in anhydrous diethyl ether (400 mL) under nitrogen was cooled to 0 °C. Phosphorus tribromide (12.45 mL, 0.133 mol) was added, and the resulting solution was stirred for 1 h at 0 °C and at room temperature for 3 h. The reaction was poured onto crushed ice, after which the separated organic layer was washed with water, saturated sodium bicarbonate, and brine. After drying over magnesium sulfate, the solvent was removed under reduced pressure; distillation in a Kugelrohr apparatus (95–100 °C, 0.3 mmHg) afforded **7c** (52.19 g, 82%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.99 (d, 1 H, J = 1.2 Hz), 7.53 (br s, 1 H), 4.60 (s, 2 H), 3.87 (s, 3 H); IR ($CHCl_3$) 1721, 1591, 1541 cm^{-1}; mass spectrum, m/e (rel intensity) 220 (M^+, 23.43), 218 (M^+, 22.24), 189 (28.15), 187 (27.04), 139 (69.47), 108 (100.00).

4-(Bromomethyl)-5-(1-oxopropyl)-3-furancarboxylic Acid Methyl Ester (6a). To a saturated solution of methanesulfonic acid and phosphorus pentoxide (200 mL) was added propionic acid (12.0 mL, 0.161 mol). The resulting solution was heated to 75–80 °C with stirring until yellow in color and then was allowed to cool to room temperature. To this was added **7c** (23.48 g, 0.107 mol), and after 40 min, the stirred solution was poured onto crushed ice. The mixture was extracted with diethyl ether and then dichloromethane. The combined organic layers were washed with water, saturated sodium bicarbonate, and dried over magnesium sulfate. The solvent was removed under reduced pressure; distillation in a Kugelrohr apparatus (105–110 °C at 0.2 mmHg) gave **6a**: 21.86 g, 74%, mp 76–78 °C; ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1 H), 5.02 (s, 2 H), 3.91 (s, 3 H), 2.92 (q, 2 H, J = 7 Hz), 1.20 (t, 3 H, J = 7 Hz); IR ($CHCl_3$) 1720, 1675, 1572, 1505 cm^{-1}; mass spectrum, m/e (rel intensity) 276 (M^+, 7.26), 274 (M^+, 7.20), 195 (100.00).

Anal. Calcd for $C_{10}H_{11}O_4Br$: C, 43.66; H, 4.03. Found: C, 43.84; H, 4.22.

4-(Iodomethyl)-3-furancarboxylic Acid Methyl Ester (7d). A solution of **7b**[8] (16.91 g, 110.1 mmol) in anhydrous diethyl ether (200 mL) was cooled to −15 °C by using an ice–salt bath. To this solution, stirred under nitrogen, was added phosphorus triiodide (25.00 g, 60.7 mmol). After stirring for 1.5 h, the excess phosphorus triiodide was hydrolyzed with crushed ice. The separated organic layer was washed twice with water, once with saturated sodium bicarbonate, and once with 10% sodium thiosulfate. After drying over anhydrous magnesium sulfate, the solvent was removed under reduced pressure to give **7d** as a colorless liquid (18.47 g, 64%, unstable at room temperature over time): bp 112–115 °C (1.4 mmHg); ^{1}H NMR ($CDCl_3$) δ 8.00 (d, 1 H, J = 1.2 Hz), 7.58 (brs, 1 H), 4.53 (s, 2 H), 3.90 (s, 3 H); IR ($CHCl_3$) 1720, 1540 cm^{-1}; mass spectrum, m/e (rel intensity) 139 (M^+ − 1, 0.70), 80 (12.33), 51 (100.00).

4-(Iodomethyl)-5-(1-oxopropyl)-3-furancarboxylic Acid Methyl Ester (6b). To a stirred solution of **7d** (21.43 g, 80.5 mmol) in propionic anhydride (30 mL) was added a solution of boron trifluoride etherate (1.5 mL, 12.0 mmol) in propionic anhydride (21 mL). The solution was stirred at room temperature for 20 min and then refluxed for 2 h. After cooling to room temperature, water was added, and most of the propionic anhydride and acid was removed under reduced pressure. Dichloromethane was added, and the resulting solution was *carefully* neutralized with saturated sodium bicarbonate. The separated organic layer was washed with 10% sodium thiosulfate and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give **6b** as a yellow oil (11.6 g, 45%, unstable at room temperature over time): bp 105–115 °C (0.15 mmHg); ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1 H), 5.00 (s, 2 H), 3.95 (s, 3 H), 2.95 (q, 2 H, J = 7 Hz), 1.23 (t, 3 H, J = 7 Hz); IR ($CHCl_3$) 1725, 1679, 1582 cm^{-1}.

4-[(1-Methyl-2,5-dioxocyclopentyl)methyl]-5-(1-oxopropyl)-3-furancarboxylic Acid Methyl Ester (8). A stirred soltuion of 2-methyl-1,3-cyclopentanedione (2.24 g, 20 mmole in 60 mL of dry *tert*-butyl alcohol and potassium *tert*-butoxide (2.25 g, 20 mmol) was refluxed for 30 min. To this solution was added **6a** (5.5 g, 20 mmol) and potassium iodide (3.32 g, 20 mmol), and the resulting mixture was heated at reflux at 14 h. The solvent was removed under reduced pressure, saturated ammonium chloride was added, and the mixture was extracted with dichloromethane. The separated organic layer was dried over magnesium sulfate, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (1:9 ethyl acetate–dichloromethane) gave a colorless crystalline solid (4.62 g, 75.5%). Recrystallization from ethanol provided an analytical sample of **8** (mp 121–26 °C); ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1 H), 3.84 (s, 3 H), 343 (s, 2 H), 3.35–2.50 (m, 6 H), 1.14 (t, 3 H, J = 7 Hz), 1.03 (s, 3 H); IR ($CHCl_3$) 1721, 1680, 1581 cm^{-1}; mass spectrum, m/e (rel intensity) 306 (M^+, 17.68), 250 (29.24), 57 (100.00).

Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.70; H, 5.84. Also isolated from the chromatography were **9**: 670 mg, 11%, needles, 95% ethanol, mp 122 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (s, 1 H), 5.68 (s, 2 H), 3.84 (s, 3 H), 2.94 (q, 2 H, J = 7 Hz), 2.76 (m, 2 H), 2.46 (m, 2 H), 1.54 (s, 3 H), 1.16 (t, 3 H, J = 7 Hz); IR (KBr) 1725, 1685, 1620, 1340, 1110, 975 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.61; H, 5.90.

4,4a,5,6,7,7aα,8,9-Octahydro-4aα,8α-dimethyl-7a-hydroxy-5,9-dioxoazuleno[6,5-*b*]furan-3-carboxylic Acid Methyl Ester (10): 460 mg, 7.5%, mp 221–222 °C; ^{1}H NMR ($CDCl_3$) δ 8.13 (s, 1 H), 3.87 (s, 3 H), 3.66 (d, 1 H, J = 16 Hz), 3.08 (q, 1 H, J = 8 Hz), 2.75–2.0 (m, 5 H), 1.32 (d, 3 H, J = 7 Hz), .85 (s, 3 H); IR (KBr) 3450, 3120, 1720, 1660, 1580, 1520, 955 cm^{-1};

Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.87; H, 5.93.

4,5,7,8-Tetrahydro-9-hydroxy-6,10-dioxo-5-methyl-9-ethylbicyclo[4.2.1]nonano[3,4-*b*]furan-3-carboxylic Acid Methyl Ester (11): 250 mg, 4%, mp 181 °C; ^{1}H NMR ($CDCl_3$) δ 7.96 (s, 1 H), 3.80 (s, 3 H), 3.43 (d, 1 H, J = 16.5 Hz), 3.35 (dd, 1 H, J = 9.5, J = 2.2 Hz), 3.00 (dd, 1 H, J = 10.3, J = 2.2 Hz), 2.72 (dd, 1 H, J = 10.3, J = 9.5 Hz), 2.70 (s, 1 H exchangeable with D_2O), 2.54 (d, 1 H, J = 16.5 Hz), 1.84 (8 line multiplet, 2 H, J = 3 Hz), 1.26 (s, 3 H), 1.05 (t, 3 H, J = 3 Hz); IR (KBr) 3460, 3140, br 1740–1680, 1595, 1545, 1445, 980 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.84; H, 5.93.

4,4a,5,6,7,9-Hexahydro-4a,8-dimethyl-5,9-dioxoazuleno[6,5-*b*]furan-3-carboxylic Acid Methyl Ester (12). Aldol **10** (50 mg, 0.16 mmol) was

added to benzene (5 mL) and *p*-toluenesulfonic acid (6 mg). The solution was refluxed for 4.5 h using a Dean-Stark apparatus. After cooling to room temperature, dichloromethane was added, and the resulting solution was washed with sodium bicarbonate and brine. After drying over magnesium sulfate, the solvent was removed under reduced pressure to give a colorless solid (31 mg). Flash chromatography on silica gel (1:1 hexane–ethyl acetate) afforded recovered **10** (4 mg) and **12**: 27 mg, 59%, mp 175–176 °C; ^{1}H NMR ($CDCl_3$) δ 8.21 (s, 1 H), 4.00–3.60 (m, 4 H) with resonance centered at 3.89 (s, 3 H), 3.20–2.50 (m, 5 H), 2.02 (s, 3 H), 1.21 (s, 3 H); IR ($CHCl_3$) 1730, 1679, 1620, 1585 cm^{-1}; mass spectrum, *m/e* (rel intensity) 288 (M$^+$, 37.54), 286 (40.37), 271 (93.17), 257 (15.65), 227 (14.06).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.74; H, 5.69.

4,5,7,8-Tetrahydro-6,10-dioxo-5-methyl-9-ethylidenebicyclo[4.2.1]nonano[3,4-*b*]furan-3-carboxylic Acid Methyl Ester (13). A soltuion of **8** (92.0 mg, 0.30 mmol), *p*-toluenesulfonic acid (58.8 mg, 0.31 mmol), and benzene (5 mL) was heated to reflux in a Dean-Stark apparatus for 16 h. After cooling to room temperature, the solution was washed with saturated sodium bicarbonate. The separated aqueous layer was extracted with dichloromethane, the combined organic layers were dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane–ethyl acetate, 1:1) gave crystalline **13** (76.3 mg, 88%); recrystallization from methanol gave an analytical sample: mp 157–159 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1 H), 6.31 (q, 1 H, J = 7.0 Hz), 4.16 (dd, 1 H, J_1 = 9, J_2 = 3 Hz), 3.76 (s, 3 H), 3.68–2.52 (m, 4 H), 1.89 (d, 3 H, J = 7.0 Hz), 1.23 (s, 3 H); IR ($CHCl_3$) 1768, 1725, 1585, 1532 cm^{-1}; mass spectrum, *m/e* (rel intensity) 288 (M$^+$, 100.00), 273 (10.09), 257 (21.94), 245 (40.34).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.54; H, 5.46. Bicycle **13** also was obtained from **11** on treatment with *p*-toluenesulfonic acid in refluxing benzene solution for 5 h (98%).

4,5,7,8-Tetrahydro-6-oxo-7-[methyl(methoxycarbonyl)]-5-methyl-8-ethylidenecyclohepta[*b*]furan-3-carboxylic Acid Methyl Ester (15). To a stirred solution of **13** (103.1 mg, 0.358 mmol) in dry methanol (3 mL) was added sodium methoxide (27.0 mg, 0.50 mmol). After stirring at room temperature for 12 h, the mixture was acidified with 1 M hydrochloric acid and extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. Flash chromatography (hexane–ethyl acetate, 1:1) gave **15** as a pale-yellow oil: 86.7 mg, 76%; ^{1}H NMR ($CDCl_3$) δ 7.88 (s, 1 H), 6.18 (q, 1 H, J = 7 Hz), 4.20 (m, 1 H), 3.80 (s, 3 H), 3.67 (s, 3 H), 3.40–2.10 (m, 5 H), 1.89 (d, 3 H, J = 7 Hz), 1.19 (d, 3 H, J = 7 Hz); IR ($CHCl_3$) 1715 (br), 1590, 1538 cm^{-1}; mass spectrum, *m/e* (rel intensity) 320 (M$^+$, 57), 247 (100).

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.58; H, 6.21.

4-[(1-Methyl-2,5-dioxo-3-cyclopenten-1-yl)methyl]-5-(1-oxopropyl)-3-furancarboxylic Acid Methyl Ester (16a). To a stirred solution of furan **8** (0.8297 g, 2.71 mmol) in dry THF (20 mL) under nitrogen at 0 °C was added phenyltrimethylammonium tribromide (1.027 g, 2.73 mmol) in dry THF (10 mL). The resulting solution was stirred at 0 °C for 20 min and then warmed to room temperature over 10 min. Formation of a precipitate occurs immediately after addition of the tribromide. Dichloromethane was added and the resulting solution was washed with saturated sodium bicarbonate. After drying with phase-separating paper, the solvent was removed under reduced pressure to give **16a** as a yellow crystalline solid (0.824 g, 100%); recrystallization from ethanol gave an analytical sample: mp 134–135 °C; ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 1 H), 7.20 (s, 2 H), 3.84 (s, 3 H), 3.44 (s, 2 H), 2.90 (q, 2 H, J = 8 Hz), 1.16 (t, 3 H, J = 8 Hz), 1.10 (s, 3 H); IR ($CHCl_3$) 1725, 1705, 1675, 1580 cm^{-1}; mass spectrum, *m/e* (rel intensity) 304 (M$^+$, 14.96), 243 (42.09), 57 (100.00).

Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 62.93; H, 5.35.

4,4a,5,9-Tetrahydro-4a,8-dimethyl-5,9-dioxoazuleno[6,5-*b*]furan-3-carboxylic Acid Methyl Ester (1). To a solution of **16a** (8.47 g, 27.84 mmol) in benzene (190 mL) was added 7.7 mL of concentrated sulfuric acid. The resulting mixture was stirred at room temperature for 1 h. The benzene layer was decanted from the sulfuric acid. The sulfuric acid layer was washed with dichloromethane (50 mL) and also decanted. Crushed ice was added to the acid and the resulting yellow solid was dissolved in dichloromethane. The aqueous layer was separated and extracted with dichloromethane. The combined organic layers were washed with water, saturated sodium bicarbonate, and brine. After drying over magnesium sulfate, the dichloromethane was filtered through a thin pad of Florisil and flushed with additional solvent. The dichloromethane was removed under pressure to give **1** as a pale-yellow solid (7.77 g, 97.5%). Recrystallization from acetone gave the analytical sample: mp 186.5–187 °C; ^{1}H NMR ($CDCl_3$) δ 8.26 (d, 1 H, J = 6 Hz), 8.22 (s, 1 H), 6.52 (d, 1 H, J = 6 Hz), 3.88 (s, 3 H), 3.80 (d, 1 H, J = 18 Hz), 2.65 (d, 1 H, J = 18 Hz) 2.23 (s, 3 H), 1.20 (s, 3 H); IR ($CHCl_3$) 3140, 1730, 1710, 1620, 1580 cm^{-1}; mass spectrum, *m/e* (rel intensity) 286 (M$^+$, 53.63), 271 (100.00), 255 (12.33).

Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 66.97; H, 5.01.

Tricycle **1** also was obtained from **16a** on treatment with *p*-toluenesulfonic acid in refluxing benzene solution for 16 h (60%), together with 4,7,8,9-tetrahydro-6-10,11-trioxo-5,9-dimethylbicyclo[5.2.1]decano[3,4-*b*]furan-3-carboxylic acid methyl ester (**17**): 8%, mp 205–206 °C; ^{1}H NMR ($CDCl_3$) δ 8.15 (s, 1 H)8, 3.96 (d, 1 H, J = 15.2 Hz), 3.87 (s, 3 H), 3.16–2.94 (m, 4 H), 2.66 (m, 1 H), 1.41 (d, 3 H, J = 6.4 Hz), 1.20 (s, 3 H); IR (KBr) 3125, 3105, 1755, 1710, 1670, 1565, 1410, 1265, 1245 cm^{-1}.

Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.21; H, 5.38

4-[(1-Methyl-2,5-dioxo-3-cyclopenten-1-yl)methyl]-5-(1-oxo-2-bromopropyl)-3-furancarboxylic Acid Methyl Ester (16b). To a stirred solution of **8** (66.0 mg, 0.216 mmol) in dry THF (1.5 mL) under nitrogen at 0 °C was added phenyltrimethylammonium tribromide (172.5 mg, 0.459 mmol) in dry THF (2 mL). The resulting solution was stirred at 0 °C for 10 min and at room temperature for 2 h. Formation of a precipitate occurs immediately after addition of the tribromide. Dichloromethane was added, and the resulting solution was washed with saturated sodium bicarbonate. After drying over anhydrous magnesium sulfate, the solvent was removed under reduced pressure. Flash chromatography (hexane–ethyl acetate, 1:1) gave **16b** as a yellow solid (R_f = 0.48, 60.0 mg, 73%); recrystallization from ethanol gave an analtyical sample: light-yellow crystals, mp 130–131 °C; ^{1}H NMR ($CDCl_3$) δ 8.08 (s, 1 H), 7.20 (s, 2 H), 5.20 (q, 1 H, J = 7 Hz), 3.84 (s, 3 H), 3.47 (s, 2 H), 1.82 (d, 3 H, J = 7 Hz), 1.13 (s, 3 H); IR ($CHCl_3$) 1725, 1703, 1680, 1580 cm^{-1}; mass spectrum, *m/e* (rel intensity) 384 (M$^+$, 3.27), 382 (M$^+$, 2.64), 303 (20.51), 271 (44.85), 54 (100.00).

Anal. Calcd for $C_{16}H_{15}O_6Br$: C, 50.15; H, 3.95; Br, 20.85. Found: C, 49.74; H, 3.88; Br, 20.69.

Also obtained from the chromatography was **4-[(3-bromo-1-methyl-2,5-dioxo-3-cyclopenten-1-yl)methyl]-5-(1-oxo-2-bromopropyl)-3-furancarboxylic acid methyl ester**: yellow oil; R_f = 0.62, 21.3 mg, 21%; ^{1}H NMR (CDCl δ 8.09 (s, 1 H), 7.43 (s, 1 H), 5.22 (q, 1 H, J = 7 Hz), 3.87 (s, 3 H), 3.42 (s, 2 H), 1.85 (d, 3 H, J = 7 Hz), 1.20 (s, 3 H); IR ($CHCl_3$) 1750, 1710, 1625, 1580, 1560 cm^{-1}; mass spectrum, *m/e* (rel intensity) 463 (M$^+$, 3.77), 461 (M$^+$, 5.72), 383 (14.90), 382 (5.44), 380 (13.02), 53 (100.00).

Reaction of 16b with Triphenylphosphine: Attempted Preparation of 16c. A solution of trione **16b** (12.1 mg, 0.032 mmol) and triphenylphosphine (8.3 mg, 0.032 mmol) in benzene (2 mL) was heated to reflux temperature for 18 h. After cooling to room temperature, dichloromethane was added and the resulting solution was washed with saturated potassium carbonate. After drying over anhydrous magnesium sulfate, the solvent was removed under reduced pressure to give a yellow oil. ^{1}H NMR analysis showed that only **16a** was present. Variations of this procedure using trimethylphosphite in place of the triphenylphosphine gave only recovered starting material even when toluene was used as refluxing solvent. With trimethylphosphite in refluxing xylene, the reaction gave a mixture of **16b** and **16a**.

4,4a,5,6,7,9-Hexahydro-4a,8-dimethyl-5,9-dioxoazuleno[6,5-*b*]furan-3-carboxylic Acid Methyl Ester (12). To **1** (0.7525 g, 2.63 mmol) in ethyl acetate (58 ml) was added 5% platinum on carbon (0.0337 g). The mixture was hydrogenated at atmospheric pressure until 1 equiv of hydrogen was consumed. The catalyst was removed by filtration, and the solvent was removed under reduced pressure to give crystalline **12**. Recrystallization from ethanol gave pale-yellow crystals (mp 176–177 °C). For prior characterization of **12**, see the experimental procedure for preparation from **10**.

4,4a,5,6-Tetrahydro-5β-hydroxy-4aβ,8-dimethylazuleno[6,5-*b*]furan-3-carboxylic Acid Methyl Ester (18). To a soltuion of **12** (0.7665 g, 2.66 mmol) in anhydrous methanol (18 mL) was added sodium borohydride (1.089 g, 26.4 mmol) in small portions at room temperature over a 15-min period. The soltuion was stirred under nitrogen for 2 h, after which 1 M hydrochloric acid was added until the solution turned bright yellow. After the solution was extracted with dichloromethane, the combined extracts were dried with phase-separation paper and the solvent was removed under reduced pressure. Flash chromatography (hexane–ethyl acetate, 1:1) gave crystalline **18** (0.3625 g, 50%); recrystallization from hexane–ethyl acetate gave bright-yellow crystals: mp 125–126 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.84 (s, 1 H), 6.20 (s, 1 H), 5.78 (t, 1 H, J = 2.8 Hz), 4.17 (t, 1 H, J = 7.8 Hz), 3.82 (s, 3 H), 3.70 (dd, 1 H, J_1 = 16, J_2 = 12 Hz), 3.50 (d, 1 H, J = 16 Hz), 2.76 (dd, 1 H, J_1 = 7.4, J_2 = 3.2 Hz), 2.46–2.26 (m, 2 H), 2.04 (s, 3 H), 0.85 (s, 3 H); IR ($CHCl_3$) 3600, 3580–3380 (br), 3150, 1715, 1600, 1572, 1533 cm^{-1}; mass

spectrum, *m/e* (rel intensity) 274 (M^+, 100.00), 259 (53.08), 241 (34.78), 227 (56.70); UV (95% EtOH) 206, 313 nm.

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.17; H, 6.57.

4,4a,5,6,7,7aα,8,9-Octahydro-5β-hydroxy-4aβ,8β-dimethylazuleno-[6,5-*b*]furan-3-carboxylic Acid Methyl Ester (19a). To a solution of **18** (0.3625 g, 1.32 mmole in absolute ethanol (20 mL) was added 5% palladium on carbon (70.0 mg). The mixture was hydrogenated at atmospheric pressure for 14 h, the catalyst was removed by filtration, and the solvent was removed under reduced pressure to give crystalline **19a**; recrystallization from hexane gave colorless crystals: 0.3671 g, 100%, mp 112–113 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.82 (s, 1 H), 3.80 (s, 3 H), 3.77–3.68 (m, 1 H), 3.49 (d, 1 H, J = 14.6 Hz), 2.79 (m, 2 H), 2.12–1.24 (m, 8 H), 0.82 (d, 3 H, J = 7.4 Hz), 0.65 (s, 3 H); IR ($CHCl_3$) 3600, 3660–3200 (br), 1712, 1534 cm^{-1}; mass spectrum, *m/e* (rel intensity) 278 (M^+, 19.21), 260 (14.11), 245 (18.92), 152 (73.24), 125 (84.05), 41 (100.00).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.36; H, 7.99.

4,4a,5,6,7,7aα,8,9-Octahydro-4aβ,8β-dimethyl-3-(hydroxymethyl)azuleno[6,5-*b*]furan-5β-ol (19b). To a stirred solution of furan **19a** (0.2236 g, 0.804 mmol) in dry THF (13 mL) under nitrogen at 0 °C was added a 1 M solution of lithium aluminum hydride in THF (1.6 mL). The resulting solution was stirred at room temeprature for 2.5 h. Several drops of saturated sodium sulfate were added followed by dichloromethane. The resulting mixture was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give diol **19b** as a colorless solid (0.1657 g, 82%): ^1H NMR ($CDCl_3$) δ 7.22 (s, 1 H), 4.47 (s, 2 H), 3.72 (m, 2 H), 3.00–1.26 (m, 11 H), 0.83 (d, 3 H, J = 7 Hz), 0.67 (s, 3 H).

4,4a,5,6,7,7aα,8,9-Octahydro-4aβ,8β-dimethyl-3-(hydroxymethyl)-2-(trimethylsilyl)azuleno[6,5-*b*]furan-5β-ol (19c). To a solution of **19b** (62.3 mg, 0.249 mmol) in dry THF at 0 °C (2 mL) was added a 1.3 M solution of *n*-butyllithium in hexane (1.65 mL, 1.27 mmol). After stirring at 0 °C for 40 min, trimethylsilyl chloride (252 μL, 1.98 mmol) was added, and the resulting solution was stirred at room temperature for 2.5 h. After hydrolysis with 1 M hydrochloric acid, the mixture was extracted with dichloromethane. The combined organic extracts were washed with 10% sodium hydroxide, dried over anhydrous magnesium sulfate, and concentrated to give **19c** (68.0 mg, 85%); ^1H NMR ($CDCl_3$) δ 4.56 (s, 2 H), 3.80 (m, 1 H), 3.00–0.78 (m, 15 H), 0.70 (s, 3 H), 0.34 (s, 9 H).

Peracid Oxidation of 19c. To a mixture of 40% peracetic acid[27] (0.197 g) and anhydrous powdered sodium acetate (30.0 mg, 0.366 mmol) in dichloromethane (1 mL) at 0 °C was added a solution of **19c** (68.0 mg, 0.211 mmol) in dichloromethane (3 mL). The mixture was stirred for 1 h at 0 °C and subsequently washed with saturated sodium bicarbonate and 10% sodium thiosulfate. The separated organic layer was dried over anhydrous magnesium sulfate and concentrated to give a mixture of β,γ- and α,β-unsaturated lactones: IR 1780, 1740 cm^{-1}. Chromatography on silica gel (ethyl acetate) gave lactone **23**: 31.4 mg, 56%; ^1H NMR ($CDCl_3$) δ 5.00 (m, 1 H), 4.40 (s, 2 H), 3.25 (m, 2 H), 3.50–0.70 (m, 17 H) with resonance centered at 0.85 (s, 3 H); IR ($CHCl_3$) 3600, 1740 cm^{-1}.

4,4a,5,6,7,7aα,8,9-Octahydro-5β-hydroxy-4aβ,8β-dimethylazuleno-[6,5-*b*]furan-3-carboxylic Acid (19d). To a solution of **19a** (0.3501 g, 1.24 mmol) in methanol (24 mL) was added 25% sodium hydroxide (4.9 mL). After stirring at room temperature for 18 h, the reaction mixture was acidified by the addition of 1 M hydrochloric acid. The resulting solution was extracted with dichloromethane. The combined organic extracts were dried with phase-separating paper, and the solvent was removed under reduced pressure to give **19d** as a colorless solid (0.3078 g, 93%); recrystallization from hexane–ethyl acetate gave colorless crystals: mp 152–153 °C; ^1H NMR ($CDCl_3$) δ 7.94 (s, 1 H), 6.60 (br s, 2 H, exchangeable with D_2O), 3.76 (t, 1 H, J = 8 Hz), 3.50 (d, 1 H, J = 14 Hz), 2.80 (m, 2 H), 2.14–1.32 (m, 7 H), 0.80 (d, 3 H, J = 8 Hz), 0.64 (s, 3 H); IR ($CHCl_3$) 3620, 3540–2320 (very br), 1698, 1550 cm^{-1}; mass spectrum, *m/e* (rel intensity) 264 (M^+, 57), 246 (60), 231 (33), 217 (30), 125 (100).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found C, 67.68; H, 7.72.

4,4a,5,6,7,7aα,8,9-Octahydro-4aβ,8β-dimethylazuleno[6,5-*b*]furan-5β-ol (19e). To a solution of **19d** (0.3078 g, 1.16 mmol) in freshly distilled quinoline (14.5 mL) was added copper powder (0.7013 g, 11.0 mmol). The mixture was heated to reflux for 2 h. After cooling to room temperature, the mixture was filtered. Diethyl ether was added to the filtrate, and the resulting solution was washed with water, dried over anhydrous magnesium sulfate, and concentrated. Most of the quinoline was removed by distillation in a Kugelrohr apparatus. Flash chromatography (hexane–ethyl acetate, 1:1) gave **19e**: 0.2188 g, 86%; ^1H NMR ($CDCl_3$) δ 7.22 (d, 1 H, J = 2 Hz), 6.22 (d, 1 H, J = 2 Hz), 3.70 (t, 1 H, J = 8 Hz), 2.78 (m, 2 H), 2.60 (d, 1 H, J = 14 Hz), 2.20 (d, 1 H, J = 14 Hz) 2.10–1.20 (m, 7 H), 0.82 (d, 3 H, J = 8 Hz), 0.64 (s, 3 H); IR ($CHCl_3$) 3600, 1500 cm^{-1}; mass spectrum, *m/e* (rel intensity) 220 (M^+, 31.38), 202 (2.44), 187 (3.57), 161 (6.09), 125, (43.26), 95 (79.34), 94 (100.00).

4,4a,5,6,7,7aα,8,9-Octahydro-4aβ,8β-dimethyl-2-(trimethylsilyl)azuleno[6,5-*b*]furan-5β-ol (19f). To a stirred solution of **19e** (0.1373 g, 0.62 mmol) in dry THF (9 mL) under nitrogen at 0 °C was added 1.3 M *n*-butyllithium in hexane (4.1 mL). The reaction mixture was stirred for 30 min. Trimethylsilyl chloride (0.65 mL, 5.1 mmol) was added, and the resulting solution was stirred at room temperature for 1.5 h. After 1 M hydrochloric acid (ca. 10 mL) was added, the reaction mixture was extracted with dichloromethane. The combined organic extracts were washed with 10% sodium hydroxide. After drying over anhydrous magnesium sulfate, the solvent was removed under reduced pressure to give **19f** as a yellow oil (0.1832 g, 100%): ^1H NMR ($CDCl_3$) δ 6.44 (s, 1 H), 3.70 (m, 1 H), 2.91–1.10 (m, 11 H), 0.82 (d, 3 H, J = 7 Hz), 0.67 (s, 3 H), 0.42 (s, 9 H).

4,4a,5,6,7,7aα,8,9-Octahydro-5β-hydroxy-4aβ,8β-dimethylazuleno-[6,5-*b*]furan-2(3*H*)-one (24a). A solution of 40% peracetic acid[27] (58.0 mg, 0.305 mmol) and anhydrous powdered sodium acetate (10.3 mg, 0.265 mmol) in dichloromethane (0.5 mL) was cooled to near 0 °C under nitrogen. To this stirred solution was added **19f** (17.8 mg, 0.061 mmol) in dichloromethane (2.5 mL). The resulting solution was stirred at 0 °C for 3.5 h, after which saturated sodium bicarbonate and sodium thiosulfate were added. The separated aqueous layer was extracted with dichloromethane. The combined organic layers were dried with phase-separating paper, and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane–ethyl acetate, 1:1) gave **24a**: 7.1 mg, 50%; ^1H NMR ($CDCl_3$) δ 3.70 (m, 1 H), 3.20 (m, 2 H), 2.95–1.20 (m, 11 H), 0.97 (d, 3 H, J = 8 Hz), 0.78 (s, 3 H); IR ($CHCl_3$) 3600, 1785 cm^{-1}.

4,4a,5,6,7,7aα,8,9-Octahydro-5β-(acetyloxy)-4aβ,8β-dimethylazuleno[6,5-*b*]furan-2(3*H*)-one (24b). To a solution of **24a** (7.1 mg, 0.030 mmol) in dichloromethane (0.5 mL) was added dry pyridine (2.8 μL, 0.035 mmol), followed by acetic anhydride (4.3 μL, 0.045 mmol. After the solution was stirred at room temperature for 5 min, 4-(dimethylamino)pyridine (catalytic amount) was added, and the soltuion was stirred for 1 h. After washing with 1 M hydrochloric acid and then saturated sodium bicarbonate, the separated organic layer was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to give **24b** as a colorless oil: 8.3 mg, 100%; ^1H NMR ($CDCl_3$) δ 4.70 (m, 1 H), 3.18 (m, 2 H), 2.90–1.15 (m, 13 H) with a resonance centered at 2.07, (s, 3 H), 0.98 (d, 3 H, J = 7 Hz), 0.88 (s, 3 H); IR ($CHCl_3$) 1788, 1725, 1250 cm^{-1}. Spectral data for this material compared favorably with the literature data.[23]

3aα,4,4a,5,6,7,7aα,8,9,9aα-Decahydro-5β-hydroxy-4aβ,8β-dimethylazuleno[6,5-*b*]furan-2(3*H*)-one (25a). To a solution of **24a** (28.7 mg, 0.0122 mmol) in ethyl acetate (5 mL) was added 5% rhodium on alumina (3.6 mg). The mixture was hydrogenated at 50 psi by using a Parr hydrogenation apparatus for 4.5 h. The catalyst was removed by filtration, and the solvent was evaporated under reduced pressure to give **25a** (29.0 mg, 100%). Chromatography on silica gel (hexane–ether, 1:1) gave a colorless foam: ^1H NMR $CDCl_3$) δ 4.72 (7 line m, 1 H), 3.65 (t, 1 H, J = 8.5 Hz), 2.98–2.52 (m, 2 H), 2.24–1.20 (m, 12 H), 1.02 (d, 3 H, J = 6.8 Hz), 0.91 (s, 3 H); IR ($CHCl_3$) 3600, 3560–3360 (br), 1760 cm^{-1}; mass spectrum, *m/e* (rel intensity) 220 (M^+ – 18, 5.95), 208 (3.34), 195 (16.47). Spectral data for this material compared favorably with the literature data.[23]

3aα,4,4a,5,6,7,7aα,8,9,9aα-Decahydro-5β-(acetyloxy)-4aβ,8β-dimethylazuleno[6,5-*b*]furan-2(3*H*)-one (25b). To a stirred solution of **25a** (12.1 mg, 0.051 mmol) in dichloromethane (1 mL) was added dry pyridine (4.1 μL, 0.051 mmol), followed by acetic anhydride (9.5 μL, 0.100 mmol). A catalytic amount of 4-(dimethylamino)pyridine was added, and the mixture was stirred at room temperature for 35 min. After washing with 1 M hydrochloric acid and saturated sodium bicarbonate, the separated organic layer was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give **25b** as a colorless oil (14.2 mg, 100%). Crystallization from ether–hexane gave colorless crystals: mp 109–110 °C [lit.[23] mp 110–111 °C]; ^1H NMR ($CDCl_3$) δ 4.72 (m, 1 H) superimposed on resonance at 4.63, (t, 1 H, J = 8 Hz), 2.98–260 (m, 2 H), 2.14–1.30 (m, 14 H) with resonance centered at 2.07, (s, 3 H), 1.02 (d, 3 H, J = 6.8 Hz), 1.00 (s, 3 H); IR ($CHCl_3$) 1764, 1725, 1250 cm^{-1}; mass spectrum, *m/e* (rel intensity) 238 (M^+ – 43, 0.22), 220 (21.08), 205 (8.61), 178 (15.48), 43 (100.00).

(27) Prepared by the method of: Harpp, D. N.; Mathiaparanam, P. *J. Org. Chem.* **1972**, *37*, 1367.

Spectral data for this material compared favorably with the literature data.[23] Method B. A mixture of **24b** (59.2 mg, 0.213 mmol) and 5% rhodium on alumina (71.5 mg) in ethyl acetate (11 mL) was hydrogenated by using a Parr hydrogenation apparatus at 50 psi for 4.5 h. The catalyst was removed by filtration, the solvent was removed under reduced pressure, and chromatography on silica gel (ether–hexane, 1:1) gave **25b** (45.0 mg, 89%).

4,4a,5,6,7,7aα,8,9-Octahydro-4aβ,8β-dimethyl-9β-hydroxy-5-oxoazuleno[6,5-*b*]furan-3-carboxylic Acid Methyl Ester (20). To a solution of **1** (2.86 g, 10 mmol) in 95% ethanol (250 mL) was added 5% platinum on carbon (0.57 g). The mixture was hydrogenated at 1 atm for 24 h and then filtered and concentrated to give a white foam (2.90 g, 99%), which was crystallized from methanol: mp 179–181 °C; ^{1}H NMR ($CDCl_3$) δ 7.97 (s, 1 H), 4.94 (t, 1 H, J = 4.2 Hz), 3.84 (s, 3 H), 3.68 (d, 1 H, J = 15.2 Hz), 2.65 (m, 1 H), 2.60–1.80 (m, 6 H), 1.67 (s, 1 H), 0.88 (d, 3 H, J = 7.5 Hz), 0.79 (s, 3 H); IR ($CHCl_3$) 3600, 1730, 1540 cm^{-1}; mass spectrum, m/e (rel intensity) 292 (M^+, 11.91), 274 (13.04), 259 (36.46), 125 (78.76), 41 (100.00).

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.89. Found: C, 65.59; H, 6.80.

4,4a,5,6,7,7aα-Hexahydro-4aα,8-dimethyl-5-oxoazuleno[6,5-*b*]furan-3-carboxylic Acid Methyl Ester (21). To a solution of **20** (100 mg, 0.34 mmole in 5 mL of 95% ethanol was added 10% HCl (0.5 mL). After 14 h at room tempreature, dichloromethane was added, and the resulting solution was washed with water, saturated sodium bicarbonate, and brine. After drying over magnesium sulfate, the solvent was removed under reduced pressure to give a colorless solid: 70.8 mg, 76%, mp 127–128 °C; ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1 H), 6.25 (s, 1 H), 3.77 (s, 3 H), 3.16 (d, 1 H, J = 18.5 Hz), 2.80 (M, 1 H), 2.63 (d, 1 H, J = 18.5 Hz), 2.52–1.65 (m, 4 H), superimposed on 1.94 (s, 3 H), 0.84 (s, 3 H); IR (KBr) 2950, 1715, 1537, 1425, 1275, 805, 755 cm^{-1}; mass spectrum, m/e (rel intensity) 274 (M^+, 100.00), 259 (27.20), 216 (42.54), 203 (41.50).

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.02; H, 6.57.

4,4a,5,6,7,7aα,8,9-Octahydro-4aβ,8β-dimethyl-5-oxoazuleno[6,5-*b*]-furan-3-carboxylic Acid Methyl Ester (22). To a solution of **21** (0.137 g, 0.5 mmol) in glacial acetic acid (10 mL) was added 5% platinum on carbon (0.030 g). The resulting mixture was hydrogenated at 1 atm for 4.5 h, the catalyst was removed by filtration, and water was added to the filtrate. The filtrate was extracted with dichloromethane, washed with water, and then saturated sodium bicarbonate. After drying over magnesium sulfate, the solvent was removed under reduced pressure to give a colorless oil that slowly solidified (0.129 g, 99%). Flash chromatograph on silica gel (3:1 hexane–ethyl acetate) provided an analytical sample: mp 95–97 °C; ^{1}H NMR ($CDCl_3$) δ 7.80 (s, 1 H), 3.75 (s, 3 H) 3.55 (d, 1 H, J = 15.24 Hz), 2.77 (br s, 2 H), 2.24–1.60 (m, 7 H), 0.84 (d, 3 H, J = 7.37 Hz), 0.72 (s, 3 H); IR (film) 2950, 1715, 1530, 1435, 1278, 1105 cm^{-1}; chemical ionization mass spectrum, m/e (rel intensity) 277 (M + 1, 96.55), 259 (35.17), 245 (100.00).

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.29. Found: C, 69.51; H, 7.28.

4,4a,5,6,7,7aα,8,9-Octahydro-4aβ,8β-dimethyl-5,9-dioxoazuleno[6,5-*b*]furan-3-carboxylic Acid Methyl Ester (26a). To a solution of **20** (2.92 g, 10 mmol) in dichloromethane (150 mL) was added pyridinium dichromate (2.94 g, 0.75 equiv). The resulting mixture was stirred at room temperature for 12 h and filtered through a pad of Florisil (1:9 ethyl acetate–dichloromethane). Solvent was removed under reduced pressure to give a colorless solid (2.48 g, 85.4%), which was used without further purification. An analytical sample was prepared by recrystallization from ethanol: mp 138–139 °C; ^{1}H NMR ($CDCl_3$) δ 8.20 (s, 1 H), 3.86 (s, 3 H), 3.56 (d, 1 H, J = 17 Hz), 2.76–1.90 (m, 7 H), 1.41 (d, 3 H, J = 7.9 Hz), 1.08 (s, 3 H); mass spectrum, m/e (rel intensity) 290 (M^+, 3.48), 275 (67.65), 259 (20.43), 232 (51.77), 219 (64.18), 139 (100.00).

Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25. Found: C, 66.09; H, 6.15.

4,4a,5,6,7,7aα,8,9-Octahydro-4aβ,8α-dimethyl-5,9-dioxoazuleno[6,5-*b*]furan-3-carboxylic Acid Methyl Ester (26b). To a solution of **26a** in methanol–benzene (1:1, 150 mL) was added anhydrous sodium carbonate (100 mg). The mixture was stirred at room temperature for 8 h, and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane and filtered through magnesium sulfate; removal of solvent gave a colorless solid (2.34 g, 94%). Recrystallization from ethanol provided an analytical sample: mp 152–153 °C; ^{1}H NMR ($CDCl_3$) δ 8.19 (s, 1 H), 3.86 (s, 3 H), 3.52 (d, 1 H, J = 19.3 Hz), 2.68 (d, 1 H, J = 19.3 Hz), 2.60–2.15 (m, 6 H), 1.39 (d, 3 H, J = 6.8 Hz), 1.01 (s, 3 H); IR ($CHCl_3$) 1735 with shoulder at 720, 1652, 1581 cm^{-1}; mass spectrum, m/e (rel intensity) 290 (M^+, 10.84), 275 (61.74), 259 (14.76), 232 (50.90), 219 (60.48), 139 (100.00). A solution of **26b** 2($CDCl_3$ was subjected to an NOE experiment; pulse width = 4 μs, delay time = 10 s, acquisition time = 3 s, decoupler mode = YYY; irradiation centered at δ 1.01 (angular methyl group) resulted in a 10% integration enhancement of the resonance at δ 3.52. No other resonances in the spectrum showed significant enhancement.

4,4a,5,6,7,7aα,8,9-Octahydro-5β,9β-dihydroxy-4aβ,8α-dimethylazuleno[6,5-*b*]furan-3-carboxylic Acid Methyl Ester (27a). To a stirred solution of **26b** (17.2 mg, 0.059 mmol) in dry methanol (1 mL) under nitrogen was added an excess of sodium borohydride. After stirring at room temperature for 50 min, the reaction was quenched with several drops of saturated ammonium chloride. The resulting solution was extracted with dichloromethane and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give crystalline **27a** (18.2 mg, 100%). Recrystallization from benzene gave colorless crystals: mp 146–148 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.87 (s, 1 H), 4.28 (d, 1 H, J = 9.4 Hz), 3.90–3.64 (m, 4 H) with resonance centered at 3.81, (s, 3 H), 3.52 (d, 1 H, J = 15 Hz), 2.62 (brs, 1 H), 2.18–1.18 (m, 8 H), 1.11 (d, 3 H, J = 6.3 Hz), 0.67 (s, 3 H); IR ($CHCl_3$) 3600, 1710, 1539 cm^{-1}; mass spectrum, m/e (rel intensity) 294 (M^+, 34), 277 (20), 258 (14), 107 (100.00).

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.05; H, 7.46.

4,4a,5,6,7,7aα,8,9-Octahydro-5β-hydroxy-4aβ,8α-dimethylazuleno-[6,5-*b*]furan-3-carboxylic Acid Methyl Ester (27b). A mixture of **27a** (28.2 mg, 0.096 mmol) and 5% palladium on carbon (10.0 mg) in glacial acetic acid (2 mL) was hydrogenolyzed by using a Parr hydrogenation apparatus at 57 psi for 7 h. The catalyst was removed by filtration, the filtrate was neutralized with saturated sodium bicarbonate, and the resulting mixture was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. Flash chromatography (hexane–ethyl acetate, 1:1) gave **27b** as a colorless oil (14.2 mg, 91% yield based on recovered starting material). Crystallization from hexane gave an analytical sample: mp 107–108 °C; ^{1}H NMR ($CDCl_3$, 200 Mz) δ 7.78 (s, 1 H), 3.88–3.66 (m, 4 H) with resonance centered at 3.80, (s, 3 H), 3.48 (d, 1 H, J = 15 Hz), 2.78 (m, 1 H), 2.40–1.20 (m, 9 H), 0.94 (d, 3 H, J = 6 Hz), 0.58 (s, 3 H); IR ($CHCl_3$) 3600, 1715, 1538 cm^{-1}; mass spectrum, m/e (rel intensity) 278 (M^+, 100), 260 (33), 245 (32).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.75; H, 8.02.

4,4a,5,6,7,7aα,8,9-Octahydro-5β-hydroxy-4aβ,8α-dimethylazuleno-[6,5-*b*]furan-3-carboxylic Acid (28a). To a solution of **27b** (25.0 mg, 0.090 mmol) in methanol (2 mL) was added 25% sodium hydroxide (0.5 mL). The reaction mixture was stirred at room temperature for 12 h. After acidifying with 1 M hydrochloric acid, the resulting solution was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, and the solent was removed under reduced pressure to give **28a** as a colorless solid (quantitative). Recrystallization from hexane–ethyl acetate gave colorless crystals: mp 192–193 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.90 (s, 1 H), 6.932 (brs, 2 H, exchangeable with D_2O), 3.80 (t, 1 H, J = 8.5 Hz), 3.49 (d, 1 H, J = 15.2 Hz), 2.79 (dd, 1 H, J_1 = 15.2, J_2 = 3.0 Hz), 2.36 (m, 1 H), 2.14–1.26 (m, 7 H), 0.95 (d, 3 H, J = 6.3 Hz), 0.61 (s, 3 H); IR ($CHCl_3$) 3600, 3300–2440 (br), 1688, 1540 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.86; H, 7.64.

4,4a,5,6,7,7aα,8,9-Octahydro-4aβ,8α-dimethylazuleno[6,5-*a*]furan-5β-ol (28b). To a stirred solution of **28a** (46.9 mg, 0.178 mmol) in quinoline (2 mL) was added copper powder (89.3 mg, 1.4 mmol). The mixture was heated to reflux temperature for 1.5 h. After cooling to room temperature, the mixture was filtered. Most of the quinoline was removed by distillation in a Kugelrohr apparatus. Flash chromatography (hexane–ethyl acetate, 1:1) gave **28b** oil: 23.4 mg, 60%; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.12 (d, 1 H, J = 1.6 Hz), 6.13 (d, 1 H, J = 1.6 Hz), 3.68 (m, 1 H), 3.00–1.30 (m, 10 H), 0.88 (d, 3 H, J = 6 Hz), 0.57 (s, 3 H); IR ($CHCl_3$) 3600, 1500 cm^{-1}.

4,4a,5,6,7,7aα,8,9-Octahydro-4aβ,8α-dimethyl-2-(trimethylsilyl)azuleno[6,5-*b*]furan-5β-ol (28c). To a stirred solution of **28b** (23.4 mg, 0.106 mmol) in dry THF (2 mL) under nitrogen at 0 °C was added 1.55 M *n*-butyllithium in hexane (0.60 mL). The mixture was stirred for 25 min. Trimethylsilyl chloride (0.15 mL, 1.2 mmol) was added, and the resulting solution was stirred at room temperature for 1.5 h. After 1 M hydrochloric acid (ca. 5 mL) was added to the reaction mixture, the organic material was extracted with dichloromethane. The combined organic extracts were washed with 10% sodium hydroxide and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give **28c**: oil, 28.0 mg, 90%; ^{1}H NMR ($CDCl_3$, 200 Mz) δ 6.37 (s, 1 H), 3.70 (m, 1 H), 2.90–1.08 (m, 10 H), 0.93 (d, 3 H, J = 6.5 Hz), 0.61 (s, 3 H), 0.22 (s, 9 H); IR ($CHCl_3$) 3600, 1455, 1248 cm^{-1}.

4,4a,5,6,7,7aα,8,9-Octahydro-5β-hydroxy-4aβ,8α-dimethylazuleno-[6,5-*b*]furan-2(3*H*)-one (29). A stirred solution of 40% peracetic acid (97.0 mg, 0.510 mmol)[27] and anhydrous powdered sodium acetate (17.5

mg, 0.214 mmol) in dichloromethane (1 mL) was cooled to 0 °C. To this mixture was added a solution of **28c** (16.8 mg, 0.058 mmol) in dichloromethane (1.5 mL). After stirring at 0 °C for 3.5 h, the solution was washed with saturated sodium bicarbonate and sodium thiosulfate. The separated organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography (hexane–ethyl acetate, 1:1) gave **29** as a colorless oil: 6.5 mg, 49%; ^{1}H NMR ($CDCl_3$) δ 3.70 (m, 1 H), 3.13 (m, 2 H), 3.00–1.20 (m, 11 H), 0.91 (d, 3 H, J = 6 Hz), 0.76 (s, 3 H); IR ($CHCl_3$) 3605, 1790, 1012 cm^{-1}.

3aα,4,4a,5,6,7,7aα,8,9,9aα-Decahydro-5β-hydroxy-4aβ,8α-dimethylazuleno[6,5-*b*]furan-2(3*H*)-one (30). To a solution of **29** (6.5 mg, 0.027 mmol) in ethyl acetate (3 mL) was added 5% rhodium on alumina (7.9 mg). The mixture was hydrogenated at 58 psi by using a Parr hydrogenation apparatus for 4.5 h. The catalyst was removed by filtration, and the solvent was removed under reduced pressure. Flash chromatography (ethyl acetate) gave **30** as a colorless oil (3.8 mg, 58%): ^{1}H NMR ($CDCl_3$, 200 mHz) δ 4.78 (7 line m, 1 H), 3.67 (t, 1 H, J = 8.5 Hz), 2.89 (dd, 1 H, J_1 = 18.2, J_2 = 10.5 Hz), 2.74–2.50 (m, 1 H), 2.17 (dd, 1 H, J_1 = 18.2, J_2 = 2.7Hz), 2.10–1.10 (m, 10 H) 0.98 (d, 3 H, J = 6.9 Hz), 0.84 (s, 3 H); IR ($CHCl_3$) 3605, 3010–2830, 1762 cm^{-1}. Spectral data for this material compared favorably with those data reported in the literature.[26]

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Registry No. (±)-**1**, 83097-02-3; (±)-**2**, 60426-81-5; **6a**, 99783-47-8; **6b**, 83096-98-4; **7b**, 56522-18-0; **7c**, 92243-46-4; **7d**, 83096-99-5; **8**, 83096-97-3; **9**, 99783-48-9; (±)-**10**, 99783-49-0; **11**, 99783-50-3; (±)-**12**, 83096-96-2; (±)-**13**, 99783-51-4; **15**, 99783-52-5; **16a**, 83097-01-2; (±)-**16b**, 99783-54-7; **16b** (3-bromo deriv active), 99783-55-8; **17**, 99783-53-6; (±)-**18**, 83097-03-4; (±)-**19a**, 83097-04-5; (±)-**19b**, 99783-56-9; (±)-**19c**, 99783-57-0; (±)-**19d**, 83097-05-6; (±)-**19e**, 83097-06-7; (±)-**19f**, 83097-07-8; (±)-**20**, 99783-59-2; (±)-**21**, 99783-60-5; (±)-**22**, 99783-61-6; (±)-**23**, 99783-58-1; (±)-**24a**, 83097-08-9; (±)-**24b**, 72341-84-5; (±)-**25a**, 72341-86-7; (±)-**25b**, 72341-85-6; (±)-**26a**, 99783-62-7; (±)-**26b**, 99783-63-8; (±)-**27a**, 99783-64-9; (±)-**27b**, 99783-65-0; (±)-**28a**, 99783-66-1; (±)-**28b**, 99783-67-2; (±)-**28c**, 99783-68-3; (±)-**29**, 99783-69-4; (±)-**30**, 76156-91-7; 2-methyl-1,3-cyclopentanedione, 765-69-5.

Hemoglobin as a Receptor of Drugs and Peptides: X-ray Studies of the Stereochemistry of Binding

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Abstract: In an attempt to establish a stereochemical rationale for the development of drugs against sickle cell anemia, we have crystallized human deoxyhemoglobin with the antihyperlipoproteinemia drug bezafibrate (I), with the diuretic drug ethacrynic acid (III), with succinyl-L-tryptophan-L-tryptophan (IV), and with *p*-bromobenzyloxyacetic acid (V) and have determined the structures of the complexes by X-ray analysis. Our results show that these compounds seek out niches in the protein where their stereochemistry of binding is determined by the available van der Waals space and, within that space, by a tendency to maximize electrostatic interactions. These range from strong hydrogen bonds to weakly polar interactions between halogens and aromatic quadrupoles. Another large part of the binding energy is due to hydrophobic effects. The binding site of *p*-bromobenzyloxyacetic acid lies in the interior of the α-chain, in a position hitherto believed to be filled by close-packed side chains of the globin. The binding of these varied compounds induces small distortions in the hemoglobin molecule which affect the solubility of deoxyhemoglobin S. Ethacrynic acid, *p*-bromobenzyloxyacetic acid, and succinyl-L-tryptophan-L-tryptophan increase and bezafibrate reduces the solubility of deoxyhemoglobin S. Ethacrynic acid increases while bezafibrate and succinyl-L-tryptophan-L-tryptophan lower the oxygen affinity of hemoglobin A. *p*-Bromobenzyloxyacetic acid does not affect it.

The stereochemistry of drug binding to proteins is an almost virgin field, because most receptors are probably membrane proteins of unknown structure. The only crystallographically analyzed complexes are those of myoglobin and hemoglobin with the anaesthetic gas CH_2Cl_2,[2,3] of carbonic anhydrase with sulfanilamide,[4] and of dihydrofolate reductase with methotrexate.[5] CH_2Cl_2 occupies crevices in the globin, while the two drugs are analogues to the enzymes' natural substrates and act as inhibitors at their active sites. In a search for agents that would alleviate sickle cell anemia, we have made X-ray studies of complexes of hemoglobin with several compounds, three of them commonly used drugs. Their binding sites are diverse and coincide neither with the active site at the heme nor with the site of the natural allosteric effector 2,3-diphosphoglycerate (DPG). The compounds either inhibit or promote the polymerization of deoxyhemoglobin S in ways not yet fully understood.

Hemoglobin is a tetramer made up of two α-chains, each containing 141, and two β-chains, each containing 146 amino acid residues. Each chain carries one heme. The α-chains contain 7 and the β-chains 8 helical segments, interrupted by nonhelical ones. Each chain also carries short nonhelical segments at the N- and C-termini. Starting from the N-terminus the helical segments are denoted A to H and the nonhelical ones NA, AB, BC, etc., to HC, which denotes a segment of three nonhelical segments at the C-terminus. Residues within each segment are numbered from the amino end A1 to A16 etc. We label each residue by its structural position followed by its position in the sequence, e.g.,

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