negligibly small. A key role for electron tunneling[2] in the Ru(II) → Fe(III) electron transfer is indicated, and we intend to explore appropriate theoretical descriptions of this process in subsequent work.

Acknowledgment. We thank Bob Austin, Dick Dickerson, John Hopfield, Stephan Isied, Bo Malmström, Rudy Marcus, George McLendon, Tom Meyer, Norman Sutin, and Henry Taube for their encouragement and for several helpful discussions. This research was supported by National Science Foundation Grant CHE80-24863.

Registry No. Ru(bpy)$_3^{2+}$, 15158-62-0.

New Approach to Pseudoguaianolide Sesquiterpene Lactone Construction. Total Synthesis of *dl*-Confertin†

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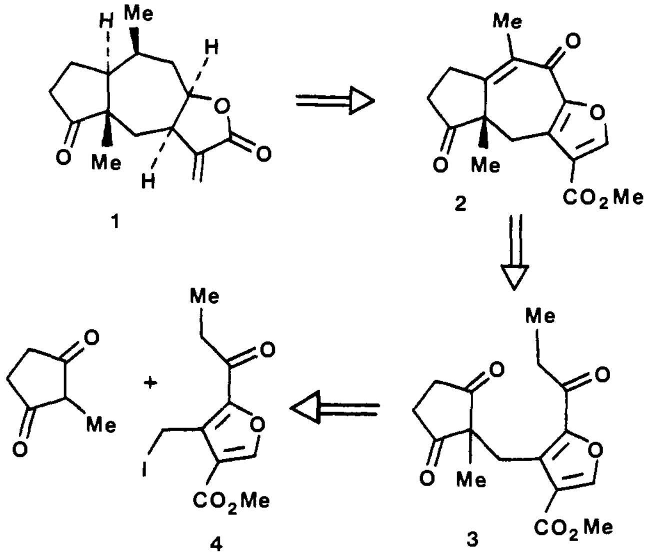
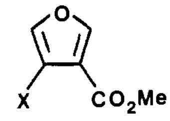
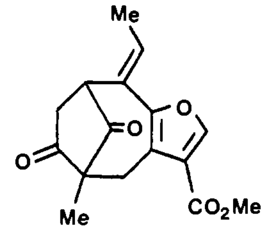
The prodigious effort directed at synthesis of the pseudoguaianolide sesquiterpene lactones[1] has been stimulated in part by reports of cytotoxic and antitumor activity for several of these compounds.[2] Our interest in pseudoguaiane synthesis has evolved from a desire to develop annelation reagents for highly convergent sesquiterpene lactone construction.[3] A total synthesis of *dl*-confertin (**1**), reported herein, demonstrates new seven-membered-ring annelation chemistry (e.g., **4** → **3** → **2**). It is noteworthy that the annelation reagent **4** and 2-methyl-1,3-cyclopentanedione provide all the carbon atoms required for a ten-step synthesis of tricyclic lactone **12**, an advanced intermediate in both the Schlessinger[4] and Heathcock[1] syntheses of confertin. This work should provide an efficient, new strategy for total synthesis of highly complex pseudoguaianes such as the fastigilins (**13**).[5]



Furan **4** is prepared from methyl 4-(hydroxymethyl)furan-3-carboxylate (**5a**)[6] by reaction with phosphorous triiodide in ether to give **5b** (64% yield), followed by acylation with propionic anhydride and boron trifluoride etherate (93%). The ester function in **5** not only provides a directing influence during preparation of **4** but also engenders stability to the furan ring during elaboration of **4** to the perhydroazulene **10** (vide infra); after this service, the ester function is discarded.



5a, X = CH$_2$OH
b, X = CH$_2$I



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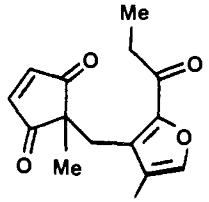

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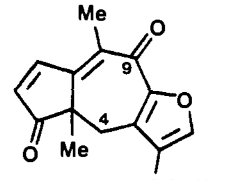

8

Alkylation of 2-methyl-1,3-cyclopentanedione with **4** (1 equiv) in refluxing *tert*-butyl alcohol with potassium *tert*-butoxide gives furan trione **3** (54%; mp 121–122 °C).[7] We note that with these reaction conditions only a trace of O-alkylated product is formed and very little alkoxide-induced cleavage of the nonenolizable β-dicarbonyl functionality in **3** occurs.[8]

We have not been able to directly convert **3** to **2** by base- or acid-catalyzed cyclodehydration. Nucleophilic bases result in β-dicarbonyl cleavage and acidic conditions promote bicyclization to give **6** (88% from *p*-toluenesulfonic acid in refluxing benzene solution; mp 158–159 °C). Apparently, enolization in **3** occurs preferentially within the cyclopentanedione ring. In accord with this supposition, **3** is converted to the yellow enetrione **7** (100%, mp 131–132 °C) on treatment with phenyltrimethylammonium tribromide in dry THF solution.[9] Cyclodehydration of **7** is catalyzed by *p*-toluenesulfonic acid in refluxing benzene solution to give the pale yellow dienedione **8** in 60% isolated yield (mp 186–187 °C).

Selective hydrogenation of **8** with 5% Pt on carbon in ethyl acetate at atmospheric pressure gives **2** (mp 176–177 °C). This can be converted to the bright yellow diene alcohol **9** (mp 125–126 °C) by treatment with sodium borohydride in methanol at room temperature followed by 1 N hydrochloric acid. Control experiments demonstrate that dehydration of an intermediate enediol occurs after addition of the hydrochloric acid.

The hydroxyl and angular methyl substituents in **9** would be expected to direct reagents to the α face of the diene system; in fact, hydrogenation of **9** with 5% Pd on carbon in absolute ethanol at atmospheric pressure gives only the furan alcohol **10a** (mp 112–113 °C) in ~60% overall yield from **8**.

---

† Dedicated to Professor Gilbert Stork on the occasion of his 60th birthday.

(1) For recent pseudoguaianolide synthetic work, see: Heathcock, C. H.; DelMar, E. G.; Graham, S. L. *J. Am. Chem. Soc.* **1982**, *104*, 1907 and references cited therein.

(2) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *101*, 1147.

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(5) Herz, W.; Rajappa, S.; Roy, S. K.; Schmid, J. J.; Mirrington, R. N. *Tetrahedron* **1966**, *22*, 1907. The fastigilins have not as yet yielded to synthesis.

(6) Commerically available furan-3,4-dicarboxylic acid esters are converted to **5a** by monosaponification in methanolic solution and BH$_3$ reduction of the resulting carboxylic acid; see: Corey, E. J.; Crouse, D. N.; Anderson, J. E. *J. Org. Chem.* **1975**, *40*, 2140.

(7) Compounds **2**, **3**, **6**–**9**, **10a**, and **10b** gave satisfactory combustion analyses.

(8) Furan **4** is reminiscent of the 3,4-disubstituted 4-(halomethyl)isoxazole annelation reagents developed by Stork and co-workers for the construction of cyclohexenone rings; e.g.: Stork, G.; Danishefsky, S.; Ohashi, M. *J. Am. Chem. Soc.* **1967**, *89*, 5459. It is noteworthy that C-alkylation of β-dicarbonyl systems with **4** is possible despite the potential for electronic and steric deactivation of **4** by the C(3) and C(5) acyl substituents.

(9) The conversion of **3** into **7** is thought to occur by cyclopentanedione ring bromination followed by in situ dehydrobomination.

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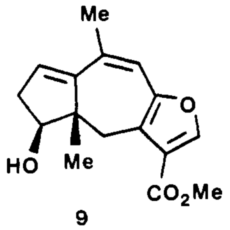

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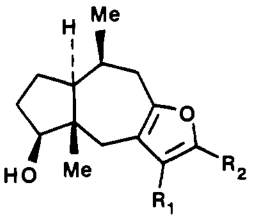
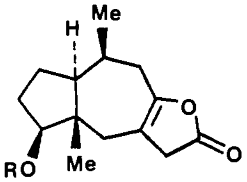
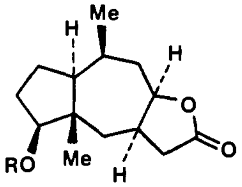


10a, R_1 = COOMe; R_2 = H
b, R_1 = COOH; R_2 = H
c, R_1 = R_2 = H
d, R_1 = H; R_2 = $SiMe_3$

Saponification of **10a** produces the carboxylic acid **10b** (mp 152–153 °C), and this is decarboxylated with copper in refluxing quinoline to give **10c**. Treatment of a THF solution of **10c** with *n*-butyllithium (2 equiv) and excess trimethylsilyl chloride followed by aqueous acid workup gives the (trimethylsilyl)furan **10d** in 82% overall yield from **10a**. The conversion of **10d** to enol lactone **11a** is accomplished by the peracetic acid oxidation method of Kuwajima and Urabe.[10] Acetylation of **11a** with acetic anhydride/pyridine/4-(dimethylamino)pyridine gives **11b**, identical with previously reported **11b**[1,4] in all respects. It is important to note that in contrast to other syntheses that involve **11b**, this oxidative method of enol lactone elaboration gives pure **11a** (and, therefore, pure **11b**) uncontaminated by the isomeric α,β butenolide.



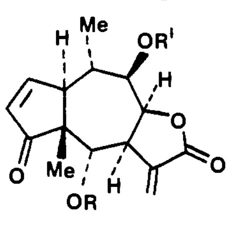
11a, R = H
b, R = Ac



12a, R = H
b, R = Ac

Hydrogenation of **11b** with rhodium on alumina in ethyl acetate at 60 psi[4] gives crystalline **12b** (mp 109–110 °C, lit. mp 110–111 °C).[4] In a more direct formal total synthesis of confertin, enol lactone **11a** is hydrogenated ($Rh{\cdot}Al_2O_3$ in ethyl acetate) to give lactone alcohol **12a** (white foam) in 89% isolated yield, identical with previously reported **12a**[1,4] in all respects.

As a result of this work, we have established the furan **4** based annelation approach to the pseudoguaianolide sesquiterpene lactones. We intend to apply this chemistry to the synthesis of other pseudoguaianes, with the fastigilins (**13**) representing our ultimate goal. The correct placement of the C(9) oxygen atom and the potentially reactive methylene group at C(4) in the key tricyclic dienedione **8** should provide adequate functionality for synthesis of **13**.



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Acknowledgment. This work was supported by the National Cancer Institute (CA 25787). We thank Professor R. H. Schlessinger for providing us with 100- and 400-MHz ^1H NMR spectra of our synthetic **12b**.

Registry No. 1, 60426-81-5; **2**, 83096-96-2; **3**, 83096-97-3; **4**, 83096-98-4; **5a**, 56522-18-0; **5b**, 83096-99-5; **6**, 83097-00-1; **7**, 83097-01-2; **8**, 83097-02-3; **9**, 83097-03-4; **10a**, 83097-04-5; **10b**, 83097-05-6; **10c**, 83097-06-7; **10d**, 83097-07-8; **11a**, 83097-08-9; **11b**, 72341-84-5; **12a**, 72341-86-7; **12b**, 72341-85-6; 2-methyl-1,3-cyclopentanedione, 765-69-5.

Supplementary Material Available: Listing of spectra data for all new compounds prepared in this work (4 pages). Ordering information is given on any current masthead page.

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Convergence, Molecular Complexity, and Synthetic Analysis

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Consideration of molecular complexity[1] results in a clearer understanding of convergence and leads to the more general principle of minimization of molecular complexity for synthetic planning. Convergence is one of the most valuable heuristics organic chemists have to aid in planning the sophisticated syntheses that are the hallmark of modern organic chemistry. In the 2 decades since Velluz introduced the "convergent" synthesis,[2] "doubly convergent"[3] and "triply convergent"[4] syntheses have been devised. If Fuchs' definition of triple convergence is adopted for a process in which three components are brought together in one step, then an ordinary convergent synthesis in which two components are brought together at some stage would be termed "doubly convergent". But then the "doubly convergent" synthesis of Carrupt and Vogel[3] should be called "doubly, doubly convergent", as two components are joined in two different steps. Add to these the definitions[5] of "partially convergent", "fully convergent", and "perfect convergency", and one sees that a simple, universal measure of the degree of probable efficiency in a synthetic plan is needed in order to provide an operational definition of this important concept as well as a numerical basis for the comparison of alternative synthetic routes, a plethora of which can be generated by computer.[6-11]

As summarized by Hendrickson,[5] the *qualitative* basis for the economy of a convergent synthesis is "the idea that when a reaction is carried out on an intermediate, it usually involves only one or two of the synthons that make up the intermediate so that the other, uninvolved synthons comprising the intermediate are subjected to needless waste from yield loss in the reaction." Most treatments of convergence assume equal yields for all reactions, which leads to the conclusion that the convergent synthesis is *always* more efficient than the corresponding linear one. Similarly, Hendrickson's proposed index of convergency, L_k, the sum of all the path lengths (number of steps) from all the starting materials

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