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Investigation of Methods for Seven-Membered Ring Synthesis: A Practical Synthesis of 4-Oxo-5,6,7,8-tetrahydro-4H-cyclohepta[*b*]furan-3-carboxylic Acid

John A. Ragan,*[,1] Jerry A. Murry,[2] Michael J. Castaldi, Alyson K. Conrad, Brian P. Jones, Bryan Li, Teresa W. Makowski, Ruth McDermott, Barb J. Sitter, Timothy D. White, and Gregory R. Young

Chemical Research and Development, Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06340, U.S.A.

Abstract:

Several synthetic routes to 4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[*b*]furan-3-carboxylic acid (1) are described, and the scale-up issues with each route are discussed. Seven-membered ring formation is a key issue with these syntheses, and several strategies are presented, including preparation from cycloheptane-1,3-dione, ring-expansion routes, Dieckmann cyclization, acetylene-furan [4 + 2] cycloaddition, and Friedel−Crafts cyclization. Two of the routes were scaled in the pilot plant to provide kilogram quantities of the title compound. The first scale-up route is outlined in Scheme 2 and utilizes a ring-expansion strategy to prepare cycloheptane-1,3-dione from cyclopentanone, via a [2 + 2] cycloaddition between dichloroketene and the silyl enol ether of cyclopentanone. The diketone is converted to the title compound by condensation with ethyl bromopyruvate and base, followed by acid hydrolysis. This route was efficient on laboratory scale but encountered problems upon scale-up due to a competing fragmentation pathway in the Zn/AcOH-mediated retro-aldol of cyclobutanone 11. The second, more successful scale-up route is described in Scheme 15, and involves Friedel−Crafts acylation of 3-carboethoxyfuran selectively at the 5-position. Reduction, lactonization, and hydrogenolysis provide acid 43, which is cyclized via a second Friedel−Crafts reaction to form the seven-membered ketone.

Introduction

4-Oxo-5,6,7,8-tetrahydro-4H-cyclohepta[*b*]furan-3-carboxylic acid (**1**) is an intermediate in the synthesis of a clinical drug candidate, and we thus required access to multikilogram quantities of this bicyclic keto-furan (Figure 1).

A central issue for all approaches investigated was the strategy for formation of the seven-membered ring (e.g. several approaches struggled with the kinetic preference for formation of five-membered rings). Strategies described herein include furan annulation onto a preexisting seven-membered ring, ring-expansion strategies (both [5 + 2] and [6 + 1]), intramolecular acetylene-furan [4 + 2] cycloaddition, and Friedel−Crafts cyclization onto a furan. The advantages and limitations of each strategy will be discussed, and the two routes which were scaled in the pilot plant will be presented.

Discussion

The first synthesis of **1** is shown in Scheme 1 and proceeds through cycloheptane-1,3-dione (**7**). Several syntheses of this diketone have been reported,[3] but none were deemed suitable for large-scale preparations. For example, the synthesis shown in Scheme 1[3f] involves a stoichiometric oxymercuration of alkene **4**, and issues with organomercurial intermediates (including worker safety, tank contamination, and potential contamination of clinical supplies) discouraged use of this reaction beyond laboratory scale. Consequently, while this route worked well for preparing 10−100 g quantities of **1** to support in vitro studies of the drug candidate derived from this intermediate, a new route was needed for preparation of the kilogram quantities of cGMP (current Good Manufacturing Practice) material that would be needed for further progression of the drug candidate.

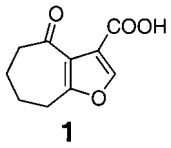

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Figure 1.

The conversion of cyclic 1,3-diketones to 3-carboxyfurans is well-precedented for six-membered rings (e.g., cyclohexane-1,3-dione[4] and 5,5-dimethylcyclohexane-1,3-dione),[5] and this methodology worked well for the seven-membered analogue (**7** to **8** to **1**, Scheme 1). Thus, our initial approach was to identify a practical, scaleable synthesis of cycloheptane-1,3-dione. This led to the development of a three-step synthesis of cycloheptane-1,3-dione from cyclopentanone[6] and thus an overall five-step conversion of cyclopentanone to **1** (Scheme 2). This route was used to provide the first multikilogram, cGMP bulk lots of **1**.

The [2 + 2] route proceeds well on laboratory scale: starting with 19 g of cyclopentanone, 15 g of **1** was obtained (33% yield over five steps, an average of 80% per step).

(1) To whom correspondence should be addressed. Pfizer Global Research & Development, P.O. Box 8156-101, Groton, CT, 06335, USA. Telephone: (860)441-6334. Fax: (860)441-5445. E-mail: john_a_ragan@groton.pfizer.com.
(2) Current address: Chemical Process Development, Merck & Co., Rahway, NJ.

(3) (a) Eistert, B.; Haupter, F.; Schank, K. *Liebigs Ann. Chem.* **1963**, *665*, 55−67. (b) Maclean, I.; Sneeden, R. P. A. *Tetrahedron* **1965**, *21*, 31−34. (c) Hutmacher, H.-M.; Kruger, H.; Musso, H. *Chem. Ber.* **1977**, *110*, 3118−3125. (d) Suzuki, M.; Watanabe, A.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 2095−2096. (e) Nishiguchi, I.; Hirashima, T. *Chem. Lett.* **1981**, 551−554. (f) Bhushan, V.; Chandrasekaran, S. *Synth. Commun.* **1984**, *14*, 339−345.
(4) Kneen, G.; Maddocks, P. J. *Synth. Commun.* **1986**, *16*, 1635−1640.
(5) Nagarajan, K.; Talwalker, P. K.; Goud, A. N.; Shah, R. K.; Shenoy, S. J.; Desai, N. D. *Indian J. Chem., Sect. B* **1988**, *27B*, 1113−1123.
(6) Ragan, J. A.; Makowski, T. W.; am Ende, D. J.; Clifford, P. J.; Young, G. R.; Conrad, A. K.; Eisenbeis, S. A. *Org. Process Res. Dev.* **1998**, *2*, 379−381.

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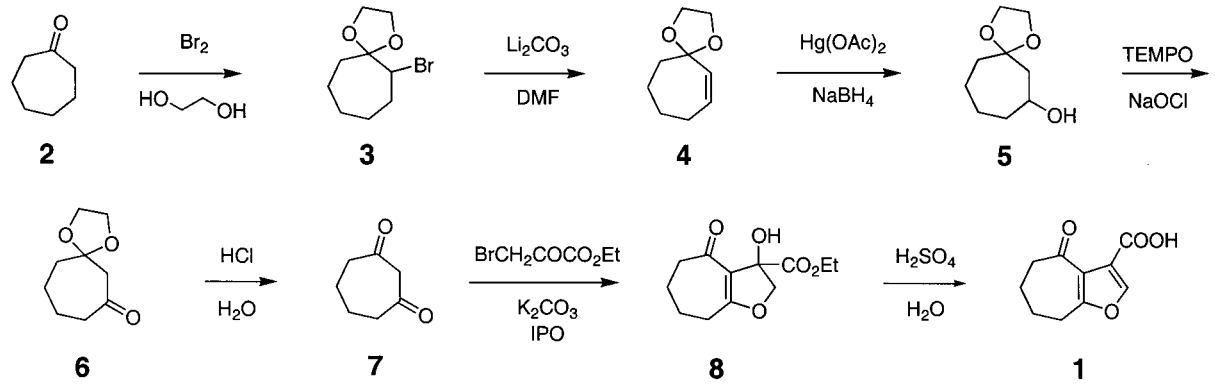
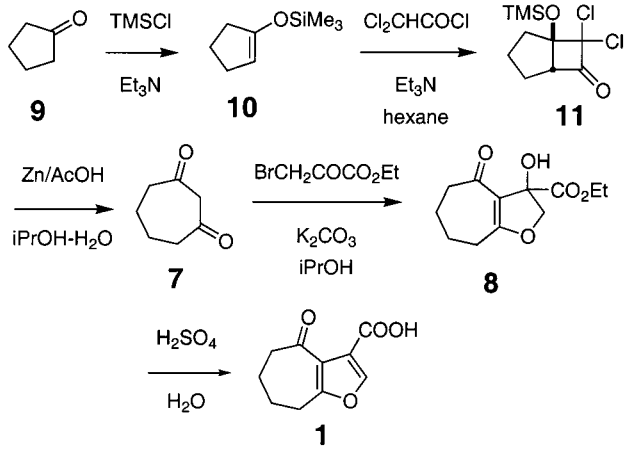
Scheme 1



Scheme 2



The sequence was operated without purification of any intermediates, all of which are oils. **1** was formed as a brown solid, which was purified by trituration with methyl *tert*-butyl ether to provide the product as a tan, free-flowing solid. Upon scale-up, however, the overall yield to **1** dropped significantly: starting from 28.5 kg of cyclopentanone, 3.35 kg of **1** was obtained, representing an overall yield of just 5%. Moreover, isolation of solid **1** required a tedious series of silica gel filtrations, which did not bode well for further scale-up. The major contaminant in the crude product was 6-oxoheptanoic acid (**17**), which was traced back to acetylcyclopentanone (**16**) formed in the Zn/AcOH reduction (Scheme 3). Subjection of acetylcyclopentanone to the final aqueous acid conditions cleanly formed 6-oxoheptanoic acid via a retro-Claisen process. These byproducts had been observed at significantly lower levels on laboratory scale (ca. 10%, vs 40−45% upon scale-up). The lack of crystalline intermediates forced us to carry these byproducts through the sequence, which significantly complicated the purification of **1**, thus lowering the overall yield.

Reexamination of the Zn/AcOH reduction of dichlorocyclobutanone **11** on laboratory scale demonstrated a strong temperature dependence for the amount of acetylcyclopentanone formed. When kept at or below 0 °C, 5−10% of this byproduct was observed. However, when the reaction was run at 40−50 °C, significantly higher levels (40−50%) of the byproduct were formed. Our reasoning for this, as outlined in Scheme 3, is the temperature dependence of two competing processes: hydrolysis of the silyl ether versus chloro reduction. If both chlorines are reduced while the silyl ether is still intact (e.g., **12**), then hydrolysis and retro-aldol are highly selective for the seven-membered diketone (path A). However, if the silyl ether is cleaved while one (or both) chlorines are still intact (e.g., **14**), then hydrolysis and retro-aldol cleavage favors formation of cyclopentanone **15** (path B),[7] presumably due to the increased acidity of the dichloromethyl ketone. We tested this theory by subjecting dichlorocyclobutanone **11** to aqueous acid in the absence of zinc; as expected, clean formation of dichloroacetylcyclopentanone (**15**) was observed by GC/MS and ^{1}H NMR.[7] Subjection of this material to Zn/AcOH reduction generated acetylcyclopentanone as the sole product. Since heat-transfer processes can differ significantly based on reaction volume,[8] we felt that this strong temperature dependence for byproduct formation, coupled with the lack of recrystallization methods for product purification, did not signify a robust process.

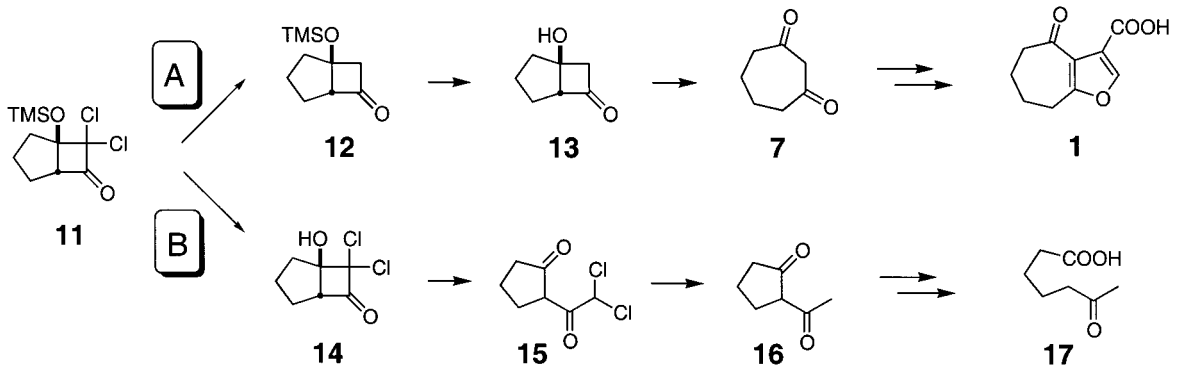
Given the problems with the [2 + 2] route, particularly the lack of crystalline intermediates and the instability of cycloheptane-1,3-dione itself,[9] a route which bypassed this diketone altogether was an attractive goal. Several strategies were investigated, as outlined below.

Dieckmann Cyclization. Scheme 4 shows the retrosynthetic analysis for this approach, in which base-mediated cyclization of tri-ester **21** was envisioned to provide seven-membered keto-ester **18**. Hydrolysis and decarboxylation would then provide **1**.

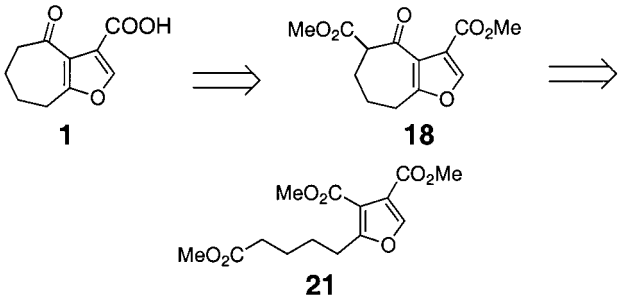
Preparation of known[10] tri-ester **21** was achieved via a furan annulation similar to that used for conversion of cycloheptane-1,3-dione to **1** (Scheme 5). Thus, known keto ester **20**[11] was treated with ethyl bromopyruvate and KOH

(7) Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 3173−3179.
(8) Due to the different scale dependencies of surface area (m^2) and reaction volume (m^3), and since the heat transfer capacity of a given reaction vessel is roughly proportional to its surface area.
(9) Cyclohexane-1,3-dione and cycloheptane-1,3-dione possess remarkably different physical properties: the former is a stable, white, crystalline solid, whereas the seven-membered ring analogue is a colorless oil which decomposes if stored for several weeks at room temperature. Their ^{1}H NMR properties in $CDCl_3$ are also quite different: the six-membered diketone is completely enolized, whereas the seven-membered diketone is in the diketo form. Transannular interactions or some other form of ring strain is presumably responsible for this difference in enolization propensity, and may explain the greater reactivity (and thus instability) of the seven-membered ring diketone. House has reported similar observations with 2-phenylcycloheptane-1,3-dione: House, H. O.; Wasson, R. L. *J. Am. Chem. Soc.* **1956**, *78*, 4394−4400.
(10) Archer, S.; Pratt, M. G. *J. Am. Chem. Soc.* **1944**, *66*, 1656−1659.
(11) Thoma, H.; Spiteller, G. *Liebigs Ann. Chem.* **1983**, *7*, 1237−1248.

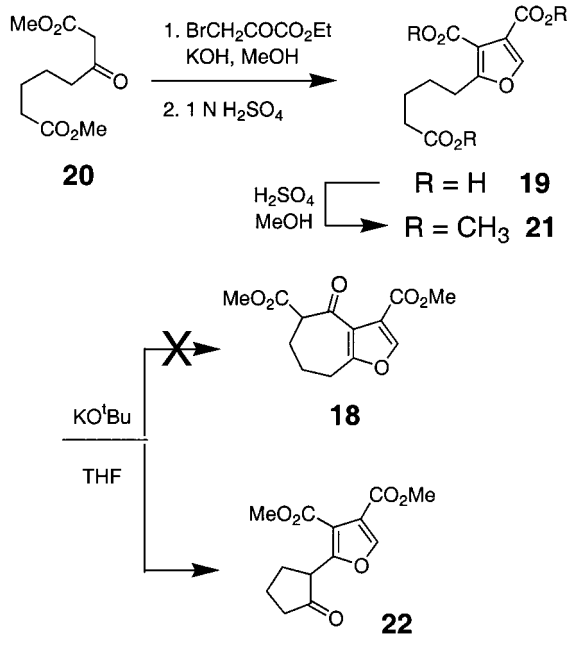
Scheme 3



Scheme 4

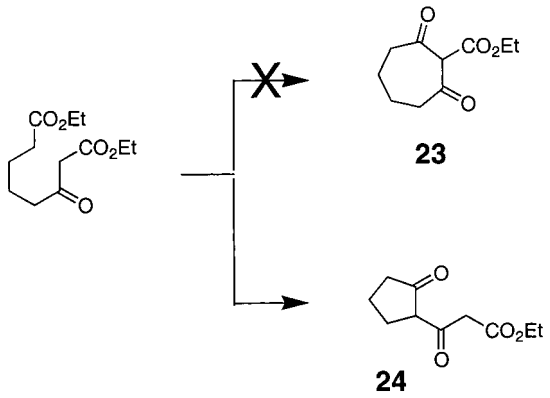


Scheme 5



in MeOH and then hydrolyzed with 1 N H_2SO_4 to provide tri-acid **19**.[12] Fischer esterification (HCl−MeOH) then provided tri-ester **21**. Treatment of this compound with KOtBu in THF led to formation of a new compound corresponding to loss of MeOH by GC/MS, and displaying ^{1}H and ^{13}C NMR data consistent with the desired keto-ester **18**. However, saponification and attempted decarboxylation did not form **1**. The resulting diacid was surprisingly reluctant to decarboxylate, throwing suspicion on our initial structural assignment. Further characterization, particularly the IR carbonyl band at 1745 cm^{-1}, suggested that cyclopentanone **22** had instead been formed (this presumably occurs via deprotonation of the methylene adjacent to the furan and cyclization onto the ester carbonyl five atoms removed).

Scheme 6



This is reminiscent of the reaction shown in Scheme 6,[13] in which base treatment of diethyl-3-oxo-octane-1,8-dioate generates cyclopentanone **24** instead of cycloheptanone **23**. This provides a dramatic example of the Curtin−Hammett principle, in which seven-membered ring formation from a more stable β-keto-ester anion fails to compete with five-membered ring cyclization from a thermodynamically less acidic position.

Ring Expansion. The analogous six-membered keto-furan (**25**) is readily available from cyclohexane-1,3-dione,[4] which, unlike cycloheptane-1,3-dione, is an inexpensive, commercially available, crystalline solid. We had investigated several ring expansion approaches to cycloheptane-1,3-dione, but none were superior to the [2 + 2] method described previously (Scheme 2). However, a ring expansion *subsequent* to the furan annulation (Scheme 7) was viewed as an attractive alternative for several reasons (e.g. keto-furan **25** is a crystalline solid, and it was hoped that intermediates derived from it would also be crystalline).

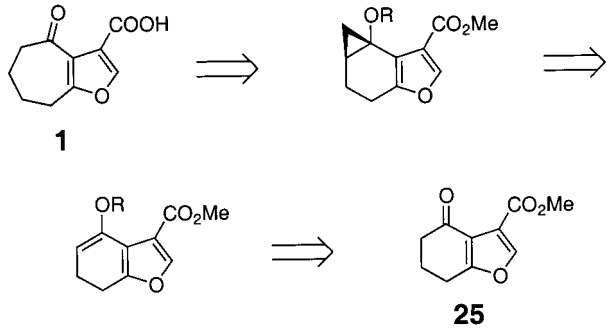
The silyl enol ether **26** could be prepared from ketone **25** by treatment with TMSCl, NaI, and Et_3N in CH_3CN (Scheme 8). This particular reagent and solvent combination[14] was critical for realizing high regioselectivity: for example, use

(12) Hofmann, K. *J. Am. Chem. Soc*. **1944**, *66*, 51−53.

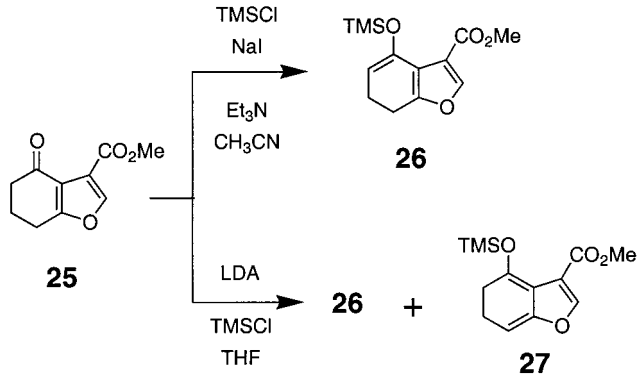
(13) Allan, A. W.; Sneeden, R. P. A. *Tetrahedron* **1962**, *18*, 821−826.

(14) Wenkert, E.; Arrhenius, T. S.; Bookser, B.; Guo, M.; Mancini, P. *J. Org. Chem*. **1990**, *55*, 1185−1193.

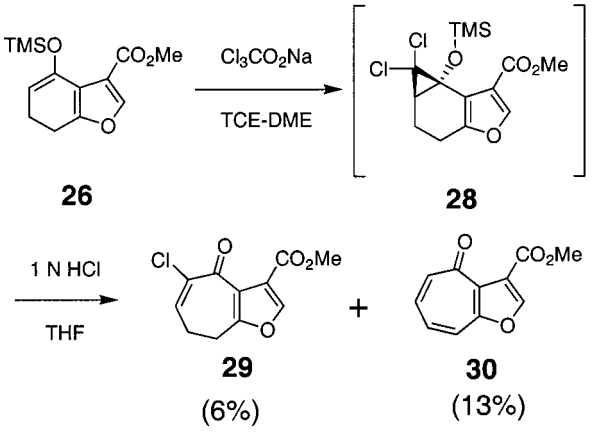
Scheme 7



Scheme 8



Scheme 9

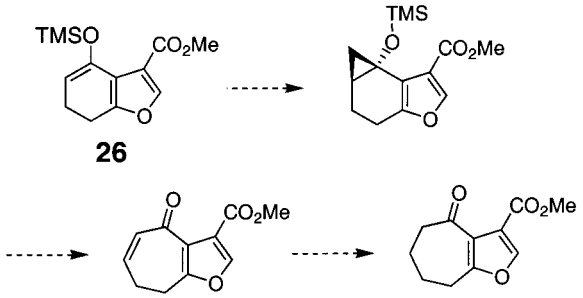


of LDA/TMSCl provided a 1:1 mixture of α- and γ-deprotonation products (**26** and **27**).

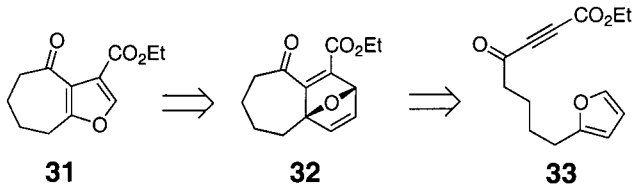
Stork has described the one carbon ring expansion of a silyl enol ether by treatment with dichlorocarbene (generated by thermolysis of trichloroacetic acid) and hydrolysis to form the ring-expanded α-chloro enone.[15] We attempted a similar ring expansion with TMS enol ether **26** but largely without success. The best conditions found were those of Stork: sodium trichloroacetate in refluxing tetrachloroethylene−DME (4:1) followed by hydrolysis with 1 N HCl in THF delivered a mixture of products, from which were isolated α-chloro enone **29** (6%) and tropinone **30** (13%) (Scheme 9). Numerous alternative carbene-forming conditions were less successful (e.g. $CHBr_3$/KOtBu,[16] Cl_3CCO_2Et/NaOEt[17]).

(15) Stork, G.; Macdonald, T. L. *J. Am. Chem. Soc.* **1975**, *97*, 1264−1265.
(16) Last, L. A.; Fretz, E. R.; Coates, R. M. *J. Org. Chem.* **1982**, *47*, 3211−3219.

Scheme 10



Scheme 11

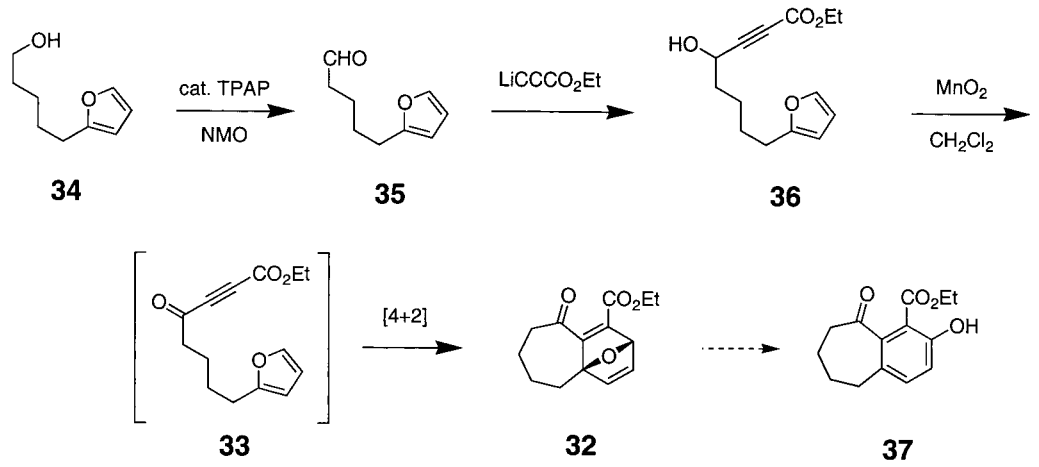


A conceptually similar approach was to cyclopropanate enol ether **26** (Scheme 10); ring expansion under oxidative conditions (e.g., $FeCl_3$)[18] would be expected to provide the ring-expanded β-chlorocycloheptanone, which would eliminate to form the seven-membered enone. Hydrogenation would then provide the target ketone. Unfortunately, all attempts to cyclopropanate enol ether **26** (e.g., CH_2I_2/Zn(Cu), Simmons−Smith, etc.) gave a mixture of products, in which starting material and mono- and bis-cyclopropanation products were all observed by GC/MS. Oxidative cleavage with $FeCl_3$ then resulted in complex mixtures, in which the desired enone or β-chloroketone were at best minor components. Apparently the furan ring is too reactive towards the reagents investigated to allow for regioselective cyclopropanation of the TMS enol ether olefin.

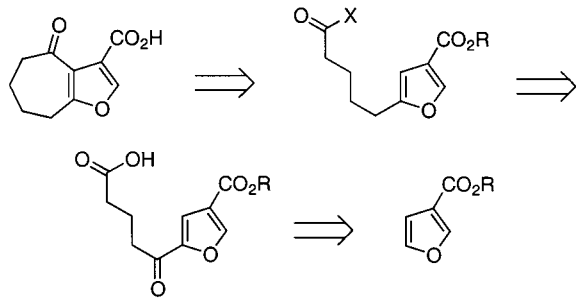
[4 + 2] Cycloaddition. A fundamentally different strategy for formation of the seven-membered ring is an intramolecular furan-acetylene [4 + 2] cycloaddition, outlined retrosynthetically in Scheme 11. Such furan-acetylene [4 + 2] cycloadditions are well precedented in an intermolecular sense,[19] and Keay has reported the $MeAlCl_2$-catalyzed intramolecular cycloaddition of a silyl propynone-furan.[20] Iwasawa has studied a similar intramolecular furan-acetylene cycloaddition with a $Co_2(CO)_8$-complexed acetylene.[21] In addition, Jacobi has utilized intramolecular acetylene-oxazole [4 + 2] cycloadditions in syntheses of norsecurinine[22] and stemoamide.[23] In Jacobi's work, the initial cycloadduct extrudes CH_3CN to form the furan product; application of this strategy to our system appeared tenuous, however, as Jacobi's target is a 2-methoxyfuran (which is ultimately converted to a 2-furanone). Our hope was that extrusion of acetylene from the initial cycloadduct would lead to the target

(17) (a) Parham, W. E.; Schweizer, E. E. *J. Org. Chem.* **1959**, *24*, 1733−1735. (b) Duggan, A. J.; Hall, S. S. *J. Org. Chem.* **1975**, *40*, 2234−2237.
(18) Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* **1976**, *41*, 2073−2074.
(19) Hoffmann, K. *J. Am. Chem. Soc.* **1944**, *66*, 51−53.
(20) Roger, C.; Keay, B. A. *Can. J. Chem.* **1992**, *70*, 2929−2947.
(21) Iwasawa, N.; Sakurada, F.; Iwamoto, M. *Org. Lett.* **2000**, *2*, 871−873.
(22) Jacobi, P. A.; Blum, C. A.; DeSimone, R. W.; Udodong, U. E. S. *J. Am. Chem. Soc.* **1991**, *113*, 5384−5392.
(23) (a) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **1997**, *119*, 3409−3410. (b) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295−4303.

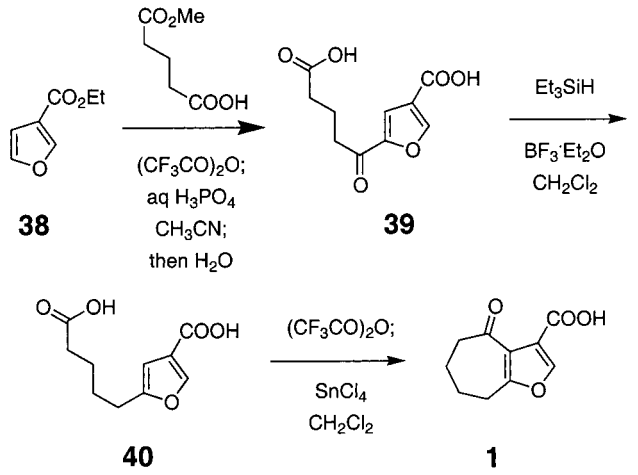
Scheme 12



Scheme 13



Scheme 14



furan, although it was not clear if this would occur at temperatures obtainable in our pilot plant (i.e., <130 °C).

Preparation of the requisite cyclization substrate is shown in Scheme 12. Known alcohol **34**[24] was oxidized with TPAP,[25] and aldehyde **35** was treated with the lithium anion of ethyl propynoate. Oxidation with MnO_2 generated the corresponding ketone by GC/MS, and a second, isomeric product; warming the reaction mixture effected complete conversion to the second product. We initially suspected this product to be keto-phenol **37**, but further characterization indicated that tricyclic diene **32** had been isolated (comparison of ^1H and ^{13}C data from two closely related [4 + 2] cycloadducts was particularly revealing[20,26]). Even following 24 h treatment at 100 °C in DMSO, no evidence of conversion to the desired furan was seen. Evaluation of higher temperatures to effect expulsion of C_2H_2 (or hydrogenation followed by C_2H_4 expulsion) was not pursued, as the practicality of scaling such conditions was of concern.

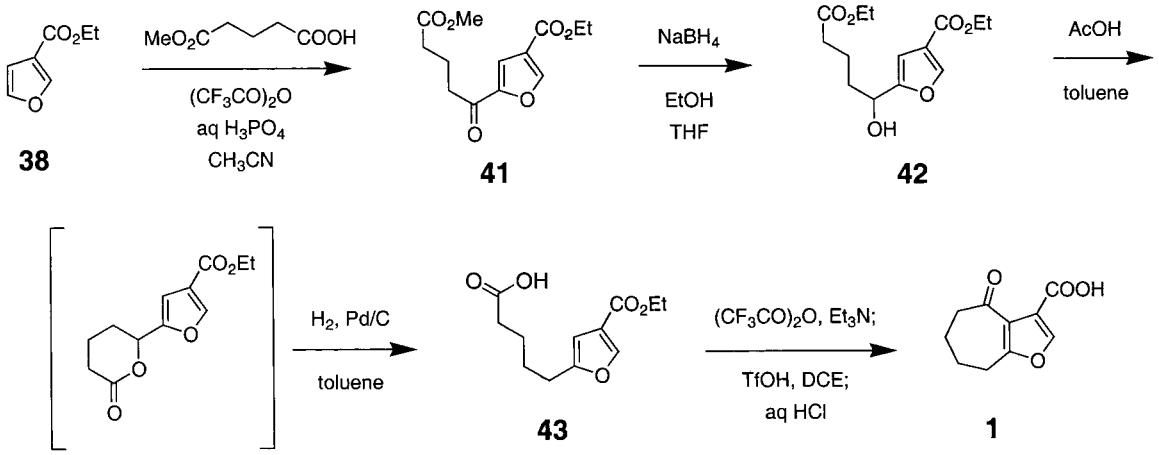
Friedel−Crafts Cyclization. The final and most successful route to **1** was an intramolecular Friedel−Crafts cyclization to form the seven-membered ring (Scheme 13).[27] A key retrosynthetic manipulation was introduction of a ketone adjacent to the furan, which allows introduction of the side chain via an intermolecular Friedel−Crafts addition to the 5-position of a 3-carboxyfuran. The benzylic nature of this position facilitates subsequent reduction of the ketone.

Two variants of this basic strategy were developed; the first route is shown in Scheme 14. Starting with the ethyl ester of 3-carboxyfuran,[28] acylation with monomethylglutarate was effected with trifluoroacetic anhydride (TFAA) and phosphoric acid in acetonitrile to provide keto-furan **39** in 64% yield. Reduction of the ketone to the corresponding methylene can be effected by treatment with Et_3SiH and $BF_3 \cdot Et_2O$ (82% yield on 4.5-g scale). Cyclization of diacid **40** is then effected by treatment with TFAA and $SnCl_4$, but this reaction was capricious and frequently failed to go to completion.

The inefficiency of the final Friedel−Crafts cyclization in Scheme 14 was attributed to the presence of two nonequivalent carboxylic acids; activation of the carboxylate adjacent to the furan might lead to intermolecular oligomerization processes. We reasoned that if only the desired position was available for activation, a more efficient cyclization could be realized. This strategy required a method for differentiation of the two carboxylic acids, which was achieved as outlined in Scheme 15.

(24) Foehlisch, B.; Herter, R. *Chem. Ber*. **1984**, *117*, 2580−2596.
(25) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625−1627.
(26) Aicart, M.; Mavoungou-Gomes, L. *J. Heterocycl. Chem*. **1985**, *22*, 921−925.
(27) Danishefsky recently reported a similar intramolecular furan Friedel−Crafts cyclization in his synthesis of Frondosin B: Inoue, M.; Frontier, A. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 761−764.
(28) Although somewhat expensive on research scale ($2−3/g from Aldrich), 3-furoic acid was available to us as a raw material from an unrelated development candidate, and we felt that the price would likely decrease if larger orders were placed in the future.

Scheme 15



Reduction of ketone **41** with $NaBH_4$ provided alcohol **42**,[29] which cyclized to the corresponding δ-lactone upon treatment with AcOH in toluene. Hydrogenolysis of the pseudobenzylic C−O bond then provided carboxylic acid **43**, in which the desired carboxylate was now differentiated from the ethyl ester.

As predicted, Friedel−Crafts cyclization of this substrate was more efficient, although significant optimization was required. Several combinations of acyl activation (trifluoroacetate mixed anhydride, acid chloride), Lewis acid ($AlCl_3$, BF_3·OEt_2, $SnCl_4$, H_3PO_4, CF_3SO_3H), and solvent (dichloromethane, CH_3CN, nitrobenzene, dichloroethane) were investigated. The major side products appeared to be higher-molecular weight oligomers, from intermolecular Friedel−Crafts processes which competed with the desired cyclization. Minimization of these intermolecular processes was complicated by the fact that the higher oligomers were generally not observable by our HPLC method and evidenced themselves more in the form of tarring, particularly during workup. Thus, an experiment would seem to have proceeded cleanly to the desired product based on its HPLC profile, but upon workup and purification, the isolated yield of **1** would be low. Inverse addition or high dilution conditions were found to help minimize the formation of these oligomers.

Optimal conditions were found to be formation of the mixed anhydride with trifluoroacetic anhydride and Et_3N, followed by slow addition to triflic acid in dichloroethane (DCE) at reflux (83 °C).[30] This addition protocol minimized intermolecular side reactions (running the reaction under high-dilution conditions achieved the same effect), resulting in a 62−68% isolated yield of **1** following aqueous hydrolysis of the ethyl ester.

Conclusions

In summary, a variety of methods for the preparation of **1** have been investigated, all of which struggled with formation of the seven-membered ring. Two of these routes have been utilized to provide multikilogram quantities of material: the ketene [2 + 2] route to cycloheptane-1,3-dione (Scheme 2) and the intramolecular Friedel−Crafts cyclization (Scheme 15). The latter route was particularly efficient, and is viewed as the optimal route to this compound identified to date.

Experimental Section

All chemicals were used as purchased unless otherwise noted. Dimethylformamide (DMF) and tetrahydrofuran (THF) were purchased in anhydrous form from Aldrich in "Sure-Seal" glass bottles; all other solvents were reagent grade. Reactions were run under a positive pressure of nitrogen unless otherwise stated. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were obtained on a Varian Unity+400 spectrometer equipped with two RF channels, indirect detection, and pulsed-field gradients (*z*-axis only). ^1H spectra were acquired using 45° acquisition pulses, 3.0 s recycle delay, and 16 scans at a resolution of 0.2 Hz/point. The acquisition window was typically 6800 Hz, and processing used 0.1 Hz line broadening. ^{13}C spectra were acquired using 45° acquisition pulses, 0.7 s recycle delay, and 512 scans at a resolution of 0.8 Hz/point. Proton decoupling was applied at 3 W of power during acquisition, and 2 Hz line broadening was used during processing. Mass spectral data was collected on either a Hewlett-Packard GC/MS (electron impact ionization), or a Micromass (Fisons) Platform II mass spectrometer (atmospheric pressure chemical ionization). Thin-layer chromatography (TLC) was performed on precoated sheets of 60 F254 (Merck Art. 5719). Visualization was achieved by UV, and by staining with iodine, phosphomolybdic acid, ceric ammonium molybdate, or *p*-anisaldehyde solutions and heating. Combustion analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

4-Oxo-5,6,7,8-tetrahydro-4H-cyclohepta[*b*]furan-3-carboxylic Acid (1). Method A (from Cycloheptane-1,3-dione). To a 0 °C solution of cycloheptane-1,3-dione (18.5 g, 147 mmol, prepared as described previously[6] without distillation) in isopropyl alcohol (148 mL) was added ethyl bromopyruvate (18.5 mL, 147 mmol) and K_2CO_3 (20.3 g, 147 mmol). The resulting slurry was warmed to room temperature and stirred for 16 h. The reaction was quenched

(29) Initial reductions in EtOH provided a mixture of methyl and ethyl esters, which were converted to the bis-ethyl ester **42** to simplify characterization. On scale-up, MeOH was used to avoid this issue.

(30) Similar cyclization conditions were utilized by workers at Sakai Research Laboratories: Chujo, I.; Masuda, Y.; Fujino, K.; Kato, S.; Mohri, S.; Ogasa, T.; Kasai, M. *Abstracts of Papers*, 217th National Meeting of the American Chemical Society, Anaheim, CA.; American Chemical Society: Washington, DC, 1999; ORG 77.

by addition of 185 mL of water, and extracted with two 200-mL portions of dichloromethane. Concentration provided a pale yellow oil (GC/MS and ^{1}H NMR analysis indicated this to be hydroxy-ester **8**), which was treated with 185 mL of 1 N H_2SO_4 and warmed in a 95 °C oil bath for 16 h. After cooling to room temperature, the mixture was extracted with two 300-mL portions of dichloromethane. The organic extracts were washed with brine and concentrated to provide 24.8 g of a brown solid, which was purified by trituration with 124 mL of hot methyl *tert*-butyl ether (with warming on a steam bath). The resulting slurry was allowed to granulate overnight at ambient temperature, and the solids were collected by vacuum filtration to provide 14.9 g of a tan, free-flowing solid (52% yield, 33% overall from cyclopentanone): ^{1}H NMR ($CDCl_3$) δ 8.07 (s, 1H), 3.14−3.11 (m, 2H), 2.90−2.87 (m, 2H), 2.05−1.94 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 202.5, 168.7, 162.3, 150.6, 120.2, 119.9, 43.1, 29.0, 23.5, 21.7. MS (CI): *m*/*z* 195 (M + 1, 100). Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.66; H, 5.17.

4-Oxo-5,6,7,8-tetrahydro-4H-cyclohepta[*b*]furan-3-carboxylic Acid (1). Method B (Friedel−Crafts Cyclization of 43). A 250-mL round-bottom flask was charged with **43** (10.0 g, 41.7 mmol) and 100 mL of dichloroethane. To this solution was added trifluoroacetic anhydride (17.7 mL, 125 mmol), and the resulting solution was stirred at room temperature for 25 min. A separate, 500-mL round-bottom flask was charged with trifluoromethanesulfonic acid (3.7 mL, 42 mmol) and 100 mL of dichloroethane and was warmed to reflux under nitrogen. The solution of mixed anhydride from the first flask was then added to the triflic acid solution via addition funnel over 40 min, and the resulting solution was stirred at reflux for an additional 45 min. HPLC analysis at this point shows complete conversion to the ethyl ester of **1**. The solution was then treated with 100 mL of 1 N HCl, a distillation head was added, and the bulk of the dichloroethane (ca. 200 mL) was removed by distillation (this required ca. 2 h). HPLC analysis showed complete conversion to **1**. After cooling to room temperature, the solution was diluted with brine (100 mL) and extracted with two 100-mL portions of dichloromethane. The combined organic extracts were filtered through a 12-g pad of silica gel, rinsing with an additional 100 mL of dichloromethane. Concentration on the rotary evaporator provided 8.50 g of a brown solid, which was granulated overnight with 40 mL of methyl *tert*-butyl ether. Filtration provided 4.86 g of **1** as a tan solid (60% yield). Concentration of the filtrate and granulation in isopropyl ether provided an additional 0.68 g (8%), for a total of 5.54 g (68%). HPLC conditions: Symmetry C-8 reverse phase column, elution with 30/70 acetonitrile/0.2% aqueous phosphoric acid, monitor at 210 nm. Retention times were as follows: **43** (7.3 min), ethyl ester of **1** (4.8 min), **1** (2.2 min).

4-Oxo-5,6,7,8-tetrahydro-4H-cyclohepta[*b*]furan-3-carboxylic Acid (1). Method C (Scale-Up of Method B). A clean, dry, nitrogen-purged 50-L reactor was charged with **43** (3.00 kg, 12.5 mol) and 30 L of dichloroethane. Trifluoroacetic anhydride (5.3 L, 38 mol) was then added, and the solution stirred for 1 h at ambient temperature. A separate 100-L nitrogen-purged reactor was charged with triflic acid (650 mL, 8.4 mol) and 30 L of dichloroethane and warmed to reflux (jacket temperature was 85 °C). The gas outlet from this reactor was passed through a 5% NaOH scrubber. The mixed anhydride in the first reactor was then added to the triflic acid/DCE solution over a period of 45 min. After the addition, 10 L of trifluoroacetic anhydride/DCE was distilled atmospherically from the reactor, until the distillate temperature reached 83 °C. The reaction mixture was cooled and analyzed for cyclization completion by HPLC, which indicated complete conversion to the ethyl ester of the desired product. HCl (30 L, 1 N) was added, and the dichloroethane was removed by distillation at atmospheric pressure. HPLC analysis indicated complete ester hydrolysis to the desired product. The reaction mixture was cooled, diluted with 30 L of brine, and extracted with three portions of CH_2Cl_2 (30, 15, and 15 L, respectively). The combined organic extracts were filtered through 4.0 kg of silica gel, rinsing with an additional 16 L CH_2Cl_2. The filtrate was concentrated at atmospheric pressure to a volume of ca. 15 L and gradually displaced with 12 L of methyl *tert*-butyl ether, to a final volume of 10 L. After cooling to room temperature, the product was isolated via filtration to provide a free-flowing, tan solid (1.5 kg, 7.7 mol, 62% yield).

2-(4-Carboxybutyl)-furan-3,4-dicarboxylic Acid (19). 3-Oxooctanedioic acid methyl ester[9] (1.7 g, 7.8 mmol) was dissolved in 10 mL of MeOH and treated with ethyl bromopyruvate (0.98 mL, 7.8 mmol) and KOH pellets (0.50 g, 7.8 mmol), initially in an ice bath (0 °C), with gradually warming to room-temperature overnight. After 16 h, TLC indicated complete consumption of starting material. The reaction mixture was poured onto ice and extracted with CH_2Cl_2 (4 × 25 mL). The organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide 2.13 g of a reddish brown oil. This material was treated with 16 mL of 1 N H_2SO_4 and warmed to reflux. After 16 h, TLC indicated complete conversion to a more polar material. The reaction mixture was cooled and extracted with CH_2Cl_2 (5 × 25 mL), followed by 10:1 CH_2Cl_2−MeOH (5 × 25 mL). The organic extracts were combined, dried over MgSO4, filtered, and concentrated to provide the desired triacid as an orange-white solid (1.23 g, 62% yield). This material was suitable for the next reaction or could be further purified by recrystallization from CH_2Cl_2 to provide a white, free-flowing solid, albeit in modest recovery (25%). ^{1}H NMR (CD_3OD) δ 8.22 (s, 1H), 3.11−3.06 (m, 2H), 2.34−2.28 (m, 2H), 1.76−1.67 (m, 2H), 1.65−1.57 (m, 2H). ^{13}C NMR (CD_3OD) δ 177.2, 168.3, 168.2, 167.2, 150.8, 118.7, 112.4, 34.4, 28.5, 28.2, 25.4.

2-(4-Methoxycarbonylbutyl)-furan-3,4-dicarboxylic Acid Dimethyl Ester (21). 2-(4-Carboxybutyl)-3,4-dicarboxyfuran (**19**) (0.77 g, 3.0 mmol) was dissolved in 15 mL of MeOH and treated with 5 drops of concentrated H_2SO_4 and then warmed to reflux for 3 h. After cooling to room-temperature overnight, the solution was diluted with 50 mL of 1:1 isopropyl ether−ethyl acetate, washed with aqueous $NaHCO_3$ (2 portions) and brine, dried over $MgSO_4$, filtered, and

concentrated to provide 0.83 g of a clear, orange oil. Column chromatography (20 mm column, eluting with 7:1 to 5:1 hexanes−ethyl acetate) provided the desired product as a clear, yellow oil (0.36 g, 1.20 mmol, 40% yield). Spectral data were consistent with that previously reported.[10]

2-(2-Oxocyclopentyl)-furan-3,4-dicarboxylic Acid Dimethyl Ester (22). 2-(4-Methoxycarbonylbutyl)-furan-3,4-dicarboxylic acid dimethyl ester (**21**) (155 mg, 0.52 mmol) was dissolved in 5 mL of THF and treated with KOtBu (117 mg, 1.04 mmol). After 20 h at ambient temperature, the solution was quenched with 5 mL of 1 N HCl, and extracted with two 10-mL portions of EtOAc. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide 154 mg of a dark red oil. The major nonbaseline spot was isolated by flash chromatography (gradient elution from 4:1 to 2:1 hexanes−EtOAc), to provide the title compound as a clear, pale yellow oil (23 mg, 0.086 mmol, 17%). IR (thin film): ν (cm^{-1}) 1745. ^1H NMR ($CDCl_3$) δ 7.76 (s, 1H), 3.97−3.92 (m, 1H), 3.81 (s, 6H), 2.46−2.16 (m, 5H), 1.95−1.87 (m, 1H). ^{13}C NMR ($CDCl_3$, results of a DEPT experiment are in parentheses, where C is quarternary, CH is methine, CH_2 is methylene, and CH_3 is methyl) δ 213.4 (C), 163.3 (C), 162.3 (C), 158.5 (C), 146.3 (CH), 118.9 (C), 114.7 (C), 52.0 (CH_3), 51.9 (CH_3), 48.7 (CH), 37.7 (CH_2), 29.2 (CH_2), 21.0 (CH_2). MS (CI): *m*/*z* 267 (M + 1, 25), 235 (M − OCH_3, 100).

4-Trimethylsilyloxy-6,7-dihydro-benzofuran-3-carboxylic Acid Methyl Ester (26). Keto ester **25**[4] (283 mg, 1.46 mmol) was dissolved in 2 mL of CH_3CN and treated with Et_3N (0.25 mL, 1.8 mmol), NaI (273 mg, 1.8 mmol), and TMSCl (0.23 mL, 1.8 mmol). After 48 h, the reaction mixture was diluted with 1:1 hexanes−ethyl acetate, washed with aqueous $NaHCO_3$ and brine, dried over K_2CO_3, filtered, and concentrated to provide the desired enol ether as a clear, pale yellow oil (320 mg, 1.20 mmol, 82%). ^1H NMR ($CDCl_3$) δ 7.73 (s, 1H), 4.78 (t, J = 5 Hz, 1H), 3.76 (s, 3H), 2.65 (t, J = 9 Hz, 2H), 2.42−2.36 (m, 2H), 0.19 (s, 9H). MS (EI): *m*/*z* 266 (M + 1, 30), 251 (M-CH_3, 100).

Dichlorocarbene Ring Expansion of TMS Enol Ether 26. TMS enol ether **26** (1.81 g, 6.81 mmol) and Cl_3CO_2Na (2.53 g, 13.6 mmol) were combined in tetrachloroethylene (16 mL) and dimethoxyethane (4 mL), and the resulting slurry was warmed to reflux. After 4 h, the mixture was cooled to room temperature and concentrated to provide a viscous, dark brown oil. This material was dissolved in THF (20 mL) and 1 N HCl (20 mL), and stirred at room temperature. After 3 h, the solution was diluted with isopropyl ether (50 mL), washed with brine (filtration through Celite was required at this point to break an emulsion), dried over $MgSO_4$, filtered, and concentrated to provide 1.69 g of a dark brown oil. Flash chromatography provided two products.

R_f = 0.40 was 5-chloro-4-oxo-7,8-dihydro-4H-cyclohepta-[*b*]furan-3-carboxylic acid methyl ester (**29**): 93 mg clear, pale yellow oil (0.39 mmol, 6% yield). ^1H NMR ($CDCl_3$) δ 7.61 (s, 1H), 7.03 (t, J = 7 Hz, 1H), 3.80 (s, 3H), 3.01−2.98 (m, 2H), 2.65−2.60 (m, 2H). MS (CI): *m*/*z* 241 (M + 1, 50).

R_f = 0.23 was 4-oxo-4H-cyclohepta[*b*]furan-3-carboxylic acid methyl ester (**30**): 183 mg clear, orange oil (0.90 mmol, 13% yield). ^1H NMR ($CDCl_3$) δ 7.94 (s, 1H), 7.36 (d, J = 11 Hz, 1H), 7.10 (dd, J = 12, 8 Hz, 1H), 7.02 (d, J = 12 Hz, 1H), 6.83 (dd, J = 11, 8 Hz, 1H), 3.86 (s, 3H). MS (CI): *m*/*z* 205 (M + 1, 100).

5-(2-Furanyl)-pentanal (35). To a solution of 5-furan-2-yl-pentan-1-ol (537 mg, 3.48 mmol) in CH_2Cl_2 (25 mL) were added 4 Å molecular sieves (1.75 g), *N*-methylmorpholine-*N*-oxide (612 mg, 5.22 mmol) and tetrapropylammonium perruthanate (122 mg, 0.35 mmol). After 60 min no starting material was observed by TLC. The reaction mixture was concentrated in vacuo to a thick slurry and filtered through a pad of Celite. The filter cake was washed with ethyl acetate (2 × 10 mL). The filtrate was concentrated in vacuo to give the desired product as a light brown oil: IR (film) 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.75 (t, J = 1.7 Hz, 1 H), 7.29−7.28 (m, 1 H), 6.27−6.26 (m, 1 H), 5.99−5.96 (m, 1 H), 2.66−2.60 (m, 2 H), 2.47−2.43 (m, 2 H), 1.70−1.62 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 202.7, 155.8, 141.1, 110.3, 105.2, 43.8, 27.9, 27.7, 21.7.

8-Furan-2-yl-4-hydroxy-oct-2-ynoic Acid Ethyl Ester (36). Lithium bis(trimethylsilyl)amide (4.13 mL of a 1.0 M solution in THF, 4.13 mmol) was dissolved in THF (20 mL) and cooled to −78 °C. Ethyl propynoate (405 mg, 4.13 mmol) dissolved in THF (10 mL) was added slowly via addition funnel, and the resulting solution was stirred for 10 minutes. 5-(2-Furanyl)-pentanal (**35**) was dissolved in THF (10 mL) and added slowly to the reaction mixture via additon funnel. After 60 min no starting material was observed by TLC. HCl (20 mL, 1 N) was added, and the reaction was warmed to room temperature. The phases were separated, and the aqueous portion was washed with EtOAc (2 × 25 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo to produce the desired product as a brown oil (537 mg, 2.15 mmol, 52% yield): IR (film) 3407, 2236, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 (dd, J = 1.7, 0.9 Hz, 1 H), 6.27 (dd, J = 2.9, 1.6 Hz, 1 H), 5.98 (dd, J = 2.9, 0.8 Hz, 1 H), 4.48 (dd, J = 6.7, 6.7 Hz, 1 H), 4.24 (q, J = 7.1 Hz, 2 H), 2.64 (t, J = 7.5 Hz, 2 H), 2.10 (br s, 1 H), 1.82−1.76 (m, 2 H), 1.71−1.64 (m, 2 H), 1.56−1.47 (m, 2 H), 1.31 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.1, 153.6, 141,0, 110.3, 105.1, 87.8, 76.9, 62.5, 62.2, 36.7, 28.0, 27.8, 24.7, 14.2. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.85; H, 7.23.

6-Oxo-12-oxatricyclo[7.2.1.0^{1,7}]dodeca-7,10-diene-8-carboxylic Acid Ethyl Ester (32). 8-Furan-2-yl-4-hydroxy-oct-2-ynoic acid ethyl ester (**36**) (50 mg, 0.20 mmol) was dissolved in CH_2Cl_2 (10 mL), and MnO_2 (695 mg, 7.99 mmol) was added. After the mixture stirred for 15 min, no starting material was observed by TLC. The reaction was filtered through a pad of Celite, the cake was washed with CH_2Cl_2 (2 × 5 mL), and the filtrate was concentrated in vacuo. NMR in DMSO-d_6 showed a 1:1 mixture of two products. After heating for 1 h at 100 °C, NMR showed conversion to a single product, assigned as [4 + 2] cycloadduct **32**. IR (film) 1709, 1626 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 (dd, J = 5.2, 1.9 Hz, 1 H), 7.02 (d, J = 5.2

Hz, 1 H), 5.61 (d, J = 1.9 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 2 H), 2.67−2.61 (m, 1 H), 2.54−2.48 (m, 1 H), 2.31−2.24 (m, 1 H), 2.22−2.15 (m, 1 H), 2.01−1.82 (m, 3 H), 1.67−1.62 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 202.0, 165.7, 162.8, 148.8, 146.2, 143.6, 95.4, 83.6, 61.5, 43.4, 30.3, 25.8, 24.4, 14.2; MS (CI), m/z 249.2 (M^+).

Furan-3-carboxylic Acid Ethyl Ester (38).[31] To a clean and dry glass-lined reactor was charged 87 L of 2B ethanol and 3-carboxyfuran (8.7 kg, 78 mol). Concentrated H_2SO_4 (4.3 L, ca. 77 mol) was added, and the resulting reaction mixture was warmed to reflux for 16 h, at which point HPLC analysis indicated complete conversion. The reaction was cooled to below 75 °C and concentrated under reduced pressure to approximately half the original volume (ca. 50 L). After cooling to room temperature, 87 L of CH_2Cl_2 was added, followed by slow addition of a 10% aqueous $NaHCO_3$ solution (125 L). After stirring for 30 min, the organic layer was separated and concentrated under reduced pressure to give the desired product as a brown oil (6.8 kg, 49 mmol, 63% yield), which was used without further purification in the next step. ^{1}H NMR data for this compound was consistent with that reported previously.[32]

5-(4-Carboxybutyryl)-furan-3-carboxylic Acid (39). 3-Carboethoxyfuran (50 g, 360 mmol) was dissolved in acetonitrile (500 mL), and monomethyl glutarate (57 g, 390 mmol) and 85% phosphoric acid (27 mL) were added. Trifluoroacetic anhydride (300 g, 1.43 mol) was added slowly via addition funnel over 30 min to ensure the temperature remained below 30 °C. After the mixture stirred overnight, no starting material remained, and the reaction was cooled to 0 °C. The solution was neutralized (pH 8) by slow addition of 50% aqueous NaOH. This solution was stirred overnight. Concentrated HCl was used to adjust to pH 4, and the resulting mixture was extracted with EtOAc (3 × 1000 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated to about 1/10 volume and diluted with hexanes (200 mL). The resulting heterogeneous solution was heated on a steam bath until homogeneous and was then cooled with vigorous stirring and solids began forming. This solution was granulated overnight and then filtered to provide the title compound as an off-white solid (52 g, 230 mmol, 64% yield). IR (film) 3422, 1682 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.16 (s, 1 H), 7.46 (s, 1 H), 2.81 (t, J = 7.5 Hz, 2 H), 2.24 (t, J = 7.5 Hz, 2 H), 1.76 (dd, J = 7.5, 7.5 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 189.1, 175.0, 165.2, 152.2, 150.2, 140.0, 119.1, 37.5, 33.7, 20.0; MS (CI), m/z 225.1 (M^-).

5-(4-Carboxybutyl)-furan-3-carboxylic Acid (40). 5-(4-Carboxybutyryl)-furan-3-carboxylic acid (**39**) (5.81 g, 25.7 mmol) was suspended in dichloromethane (116 mL) followed by addition of BF_3·OEt_2 (43.8 g, 308 mmol) and triethylsilane (12.0 g, 103 mmol). The resulting mixture was refluxed overnight at which time the reaction was homogeneous. The reaction was cooled to room temperature and quenched with H_2O (110 mL). This solution was stirred vigorously as solids began crashing out. After 3 h the mixture was filtered and washed with H_2O. The solids were air-dried to provide the desired product as an off-white solid (4.47 g, 21.1 mmol, 82% yield): IR (film) 1692 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.10 (s, 1 H), 6.33 (s, 1 H), 2.58 (t, J = 7.1 Hz, 2 H), 2.20 (t, J = 7.1 Hz, 2 H), 1.57−1.47 (m, 4 H); ^{13}C NMR (DMSO-d_6) δ 175.1, 164.7, 157.8, 147.4, 120.8, 105.8, 33.9, 27.4, 27.3, 24.5; MS (CI), m/z 211.2 (M^-).

5-(4-Methoxycarbonylbutyryl)-furan-3-carboxylic Acid Ethyl Ester (41). A clean, dry, 200-L reactor attached to a 5% NaOH off-gas scrubber was purged with nitrogen and then charged with trifluoroacetic anhydride (22.5 L, 160 mol), monomethylglutarate (7.5 L, 60 mol), and furan-3-carboxylic acid ethyl ester (**38**) (5.6 kg, 40 mol). The resulting solution was warmed to a gentle reflux while phosphoric acid (85% w/w in H_2O, 500 mL, 7.3 mol) was added dropwise. (Caution: exothermic!) The solution was refluxed for an additional 2 h post-addition, at which point HPLC analysis of an aliquot indicated complete conversion. The reaction mixture was cooled to 15 °C, and water (56 L, 10 volumes) was slowly added at a rate such that the internal temperature remained <35 °C. Ethyl acetate (57 L) was then added, and the resulting mixture stirred for 30 min. The layers were separated (addition of brine facilitated separation of the layers), and the organic extract was carefully treated with 10% aqueous $NaHCO_3$ solution (sufficient to reach pH 8). The layers were separated (with brine additions as needed), and the aqueous layer was extracted with an additional 11 L of ethyl acetate. The combined organic layers were concentrated under reduced pressure to provide the product as a brown oil, which solidified upon standing (10.7 kg, 40 mol, 100% yield). This material was used in the next reaction without further purification: IR (film) 1723, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.09 (s, 1 H), 7.45 (s, 1 H), 4.30 (q, J = 7.1 Hz, 2 H), 3.65 (s, 3 H), 2.89 (t, J = 7.3 Hz, 2 H), 2.40 (t, J = 7.3 Hz, 2 H), 2.02 (dd, J = 7.3, 7.3 Hz, 2 H), 1.33 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 188.7, 173.8, 162.2, 153.1, 150.3, 121.7, 116.4, 61.3, 51.9, 37.5, 33.1, 19.1, 14.5; MS (CI), m/z 269 (M + H). HRMS (FAB) m/e calcd for $C_{13}H_{16}O_6$ (M + H) 269.1025, found 269.1023.

5-(4-Ethoxycarbonyl-1-hydroxybutyl)-furan-3-carboxylic Acid Ethyl Ester (42). A clean, dry, glass-lined 200-L reactor was charged with 58 L of 2B ethanol, 58 L of THF, 660 mL of methanol (16.3 mol), and 5-(4-methoxycarbonylbutyryl)-furan-3-carboxylic acid ethyl ester (**41**) (10.7 kg, 40 mol). The reaction mixture was cooled to 0−5 °C, and $NaBH_4$ pellets were added in three portions (total of 616 g, 16.3 mol) such that the internal temperature remained below 5 °C. The reaction mixture was stirred for 6 h at 0−5 °C, at which point HPLC analysis indicated complete reduction to the secondary alcohol. ^{1}H NMR and HPLC of a concentrated aliquot were consistent with the desired alcohol. The toluene solution was carried directly into the next reaction lactonization.

An earlier run in straight EtOH (which upon workup transesterified to the bis-ethyl ester) was purified to provide 5-(4-ethoxycarbonyl-1-hydroxybutyl)-furan-3-carboxylic acid ethyl ester (**42**) for characterization: IR (film) 3459, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1 H), 6.57 (s, 1 H), 4.66 (t, J = 6.6 Hz, 1 H), 4.28 (q, J = 7.1 Hz, 2 H), 4.10 (q, J = 7.1 Hz,

(31) Kubota, T.; Matsuura, T. *J. Chem. Soc.* **1958**, 3667−3673.
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2 H), 3.66 (s, 1 H), 2.42−2.31 (m, 2 H), 1.95−1.64 (m, 4 H), 1.32 (t, J = 7.1 Hz, 3 H), 1.23 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.8, 163.4, 158.1, 147.2, 120.2, 106.2, 67.3, 60.8, 60.7, 34.8, 34.0, 20.9, 14.5, 14.4.

5-(4-Carboxybutyl)-furan-3-carboxylic Acid Ethyl Ester (43). The solution of 5-(4-methoxycarbonyl-1-hydroxybutyl)-furan-3-carboxylic acid ethyl ester in toluene from above (ca. 40 mol) was treated with 10 L of acetic acid, and warmed to reflux at a rate whereby 10 L of distillate per hour was collected. After 6 h, an additional 90 L of toluene and 10 L of acetic acid were added, and the distillation was continued. After an additional 60 L of distillate was collected, lactonization was complete by HPLC analysis. Toluene (30 L) was added, and atmospheric distillation was continued to a volume of ca. 20 L. Another 30 L of toluene was added, and distillation continued until the distillate boiling point reached 111 °C, indicating complete removal of acetic acid. The toluene solution was used directly in the hydrogenolysis.

A clean, water-rinsed, glass-lined reactor was charged with 590 g of 10% Pd/C under a nitrogen atmosphere, followed by addition of the toluene solution of lactone from above and an additional 165 L of toluene. The resulting reaction mixture was subjected to 50 psi hydrogen for 40 h, at which point HPLC analysis indicated complete conversion. The mixture was filtered through Celite, concentrated to a volume of ca. 40 L, and 35 L of saturated aqueous $NaHCO_3$ was carefully added. The mixture was stirred for 60 min, the layers were separated, and the toluene layer was extracted with an additional 15 L of saturated aqueous $NaHCO_3$. The combined aqueous extracts were washed with toluene (2 × 30 L) and then adjusted to pH 1.5 by careful addition of concentrated HCl. The resulting solids were filtered, and the filter cake was rinsed with 10 L of water. After drying (45 °C vacuum oven for 48 h, Karl Fischer analysis showed <0.1% water), the desired acid was obtained as a pale yellow solid (4.0 kg, 16.7 mol, 42% over three steps, from **41**: IR (film) 3487, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.86 (s, 1 H), 6.33 (s, 1 H), 4.25 (q, J = 7.1 Hz, 2 H), 2.65−2.57 (m, 2 H), 2.40−2.30 (m, 2 H), 1.71−1.60 (m, 4 H), 1.31 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.7, 163.9, 157.3, 146.5, 120.1, 105.3, 60.6, 33.9, 27.7, 27.3, 24.2, 14.5. Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.45; H, 6.90. HRMS (FAB) *m*/*e* calcd for $C_{12}H_{16}O_5$ (M + H) 241.1076, found 241.1087.

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