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Proline-Catalyzed Knoevenagel Condensation/[4+2] Cycloaddition Cascade Reaction: Application to Formal Synthesis of Averufin

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A remarkable proline-catalyzed method for the construction of biologically interesting oxygen-bridged tricyclic ketal skeletons was uncovered by starting from a variety of readily available cyclic 1,3-diketones and either 1,4- or 1,5-dicarbonyl substrates. The approach, which mimics a biosynthetic Knoevenagel condensation/[4+2] cycloaddition sequence, establishes a viable synthetic strategy for the efficient formal synthesis of averufin.

Introduction

Tricyclic ketal skeletons and their architectural derivatives represent a diverse family of structurally complex and biologically significant motifs[1] that are widely found in many interesting bioactive natural products (Scheme 1A).[2] These natural products most likely result from a biogenetic pathway involving a Knoevenagel condensation/[4+2] cycloaddition sequence that starts from 1,3-benzenediols and 1,4- versus 1,5-dicarbonyl compounds (Scheme 1, B). Among them, averufin (**1**),[2e] dactyloidin (**2**),[2b] and demethyldactyloidin (**3**)[2c] have been isolated from traditional medicinal plants or fungi with medical potential. In particular, averufin (**1**), a pivotal intermediate in the biogenesis of sterigmatocystin and aflatoxins,[3] has a potent uncoupling effect on mitochondrial respiration and an inhibitory effect towards cAMP phosphodiesterase (cAMP = cyclic adenosine monophosphate).[4] The significant biomedical activity of these natural products has inspired many synthetic efforts to explore elegant strategies and construct these complex motifs directly.[5–8] Arseniyadis has developed a creative method that leads to the formation of this tricyclic ketal skeleton by taking advantage of a sequential oxidative cleavage/intramolecular [4+2] cycloaddition reaction. However, a major disadvantage of this strategy is the requirement of strong oxidants and complex diol substrates.[7] Yoshida and co-workers have also observed that the treatment of cyclic 1,3-diketones with aliphatic aldehydes in the presence of BF_3–Et_2O can lead to cyclic ketals in good to excellent yields, but the resultant products were often obtained as inseparable diastereomeric mixtures.[8] Nonetheless, there is still no adequate or practical method to rapidly access these cyclic ketals from the perspective of the atom economy and synthetic aspects.

In the last decade, remarkable progress has been made toward the development of atom-economic reactions by using organocatalysts under operationally simple and environmentally friendly reaction conditions. A few classic organocatalytic reactions for ketal formation have also been developed.[9,10] On the basis of literature precedent[7,8] and inspired by the proposed biosynthetic pathway of the natural compounds shown in Scheme 1 (B),[11] we designed a Knoevenagel condensation/[4+2] cycloaddition sequence that uses an organocatalyst, 1,3-diketones, and either 1,4- or 1,5-dicarbonyl substrates to rapidly construct the oxygen-bridged tricyclic ketal frameworks under mild conditions, which provides direct access to the formal synthesis of averufin (**1**).

Results and Discussion

To test our hypothesis, we began by treating the model substrates cyclohexane-1,3-dione (**9a**) and 4-oxopentanal (**10a**, R_2 = Me), readily prepared by a Swern oxidation of 5-hydroxypentan-2-one,[12] with L-proline (10 mol-%) in dichloromethane (DCM) at room temperature under air.[13] Satisfactorily, the reaction was complete in 3 h and led to formation of the desired **11b** as the major product in 78% yield (20% *ee* value) along with a small amount of a by-product from a Knoevenagel condensation/Michael addition reaction.[14] In an attempt to improve the selectivity of this reaction under similar conditions, the solvents, substrate loadings, and potential catalysts including proline derivatives[15] and the MacMillan catalyst[16] were screened.[17]

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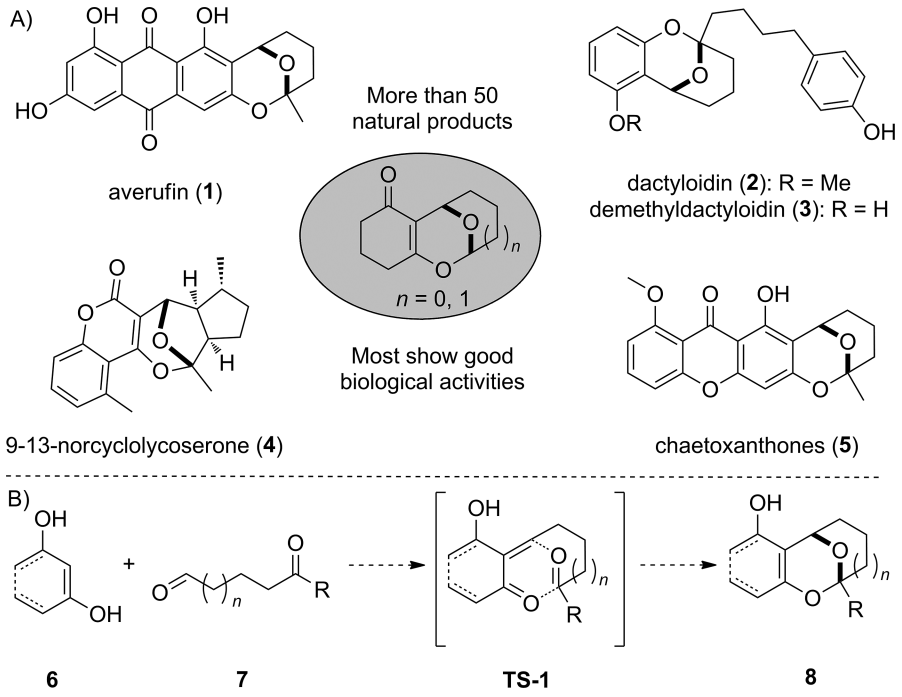


Scheme 1. (A) Biologically active natural products that feature a tricyclic ketal ring system. (B) Biosynthetic hypothesis of tricyclic ketal formation.

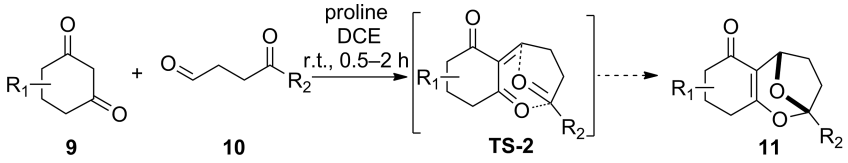
When we gradually increased the loading of 4-oxopentanal (**10a**, R_2 = Me) to 2.0 equiv. and used 1,2-dichloroethane (DCE) as the solvent and proline (10 mol-%) as the catalyst, the yield markedly increased to greater than 90%. Reducing the loading of proline to 5 mol-% did not lead to a notable decrease in the yield. Nevertheless, we employed 10 mol-% of proline in the following reactions to achieve a practical reaction time and product yield. (The details for the screening of the reaction conditions are provided in the Supporting Information).

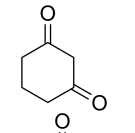
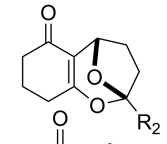
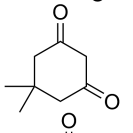
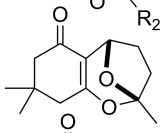
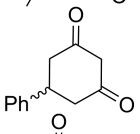
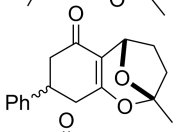
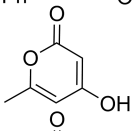
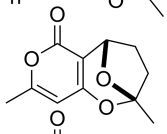
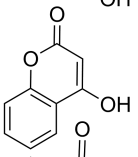
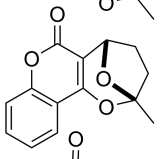
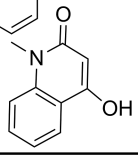
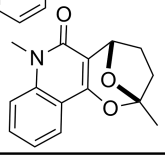
With the optimal conditions established, we surveyed the scope of this reaction by employing various 1,4-dicarbonyl substrates **10** and cyclic 1,3-dicarbonyl derivatives **9** (Table 1). When cyclohexane-1,3-dione (**9a**) was treated with different 1,4-dicarbonyl substrates **10**, all of the reactions proceeded smoothly to deliver the desired tricyclic ketal derivatives **11a**–**11d** in excellent yields (Table 1, Entries 1–4). Notably, we observed that the steric hindrance of substituents on 1,4-dicarbonyl substrates **10** had little influence on the yield of this cascade reaction. The reactivity of cyclic 1,3-diketones **9** were also evaluated by using 4-oxopentanal (**10a**, R_2 = Me) as the standard substrate. To our delight, disubstituted cyclohexane-1,3-dione **9b** also proceeded smoothly in the reaction to afford tricycle **11e** in 87% yield (Table 1, Entry 5). Monosubstituted dione **9c** underwent the reaction more efficiently than counterpart **9b** and afforded the desired tricycle **11f** in 90% yield as a mixture of diastereomers (1:2 ratio, Table 1, Entry 6). However, 4-hydroxy-6-methyl-2*H*-pyran-2-one (**9d**), 4-hydroxy-2*H*-chromen-2-one (**9e**), and 4-hydroxy-1-methylquinolin-2(1*H*)-one (**9f**) were converted into the expected tricyclic ketal products **11g**–**11i** in lower yields (57–83%) than the common cyclic 1,3-dicarbonyl derivatives **9a**–**9c**. The notable loss in the reactivity and selectivity of **9d**–**9f** is presumably because of their greater nucleophilicity, which tends to give a higher ratio of the Knoevenagel condensation/Michael addition byproducts.

When cycloheptane-1,3-dione (**9g**) was examined, the reaction proceeded cleanly in 36 h and afforded the product in 86% yield. In addition to the expected product **11j**, a new inseparable equilibrium species **12** was also obtained (**11j/12**, 1:1). The structure of **12** was spectroscopically assigned to be the Knoevenagel condensation intermediate (Scheme 2). The equilibrium between **11j** and **12** may be attributed to the high energy of the unstable 7/6/5-fused ring system, which is in agreement with Bischofberger's observation.[18] The result suggests that the [4+2] cycloaddition reaction might be reversible. Indeed, when the noncyclic pentane-2,4-dione (**9h**) was used as the substrate, the [4+2] cycloaddition did not proceed, but instead the corresponding linear Knoevenagel condensation product **13** was isolated in 84% yield. When we heated product **13** in toluene at 90 °C under nitrogen for 3 h, still no cycloaddition product **11k** was observed. However, it merits attention that when **13** was heated under air, it provided α-hydroxy-1,3-diketone **15** in 73% yield based on recovered starting material (brsm) through aerobic oxidation. This discovery can be used as a green method to synthesize biologically significant 3-hydroxy-2,4-dione derivatives.[19]

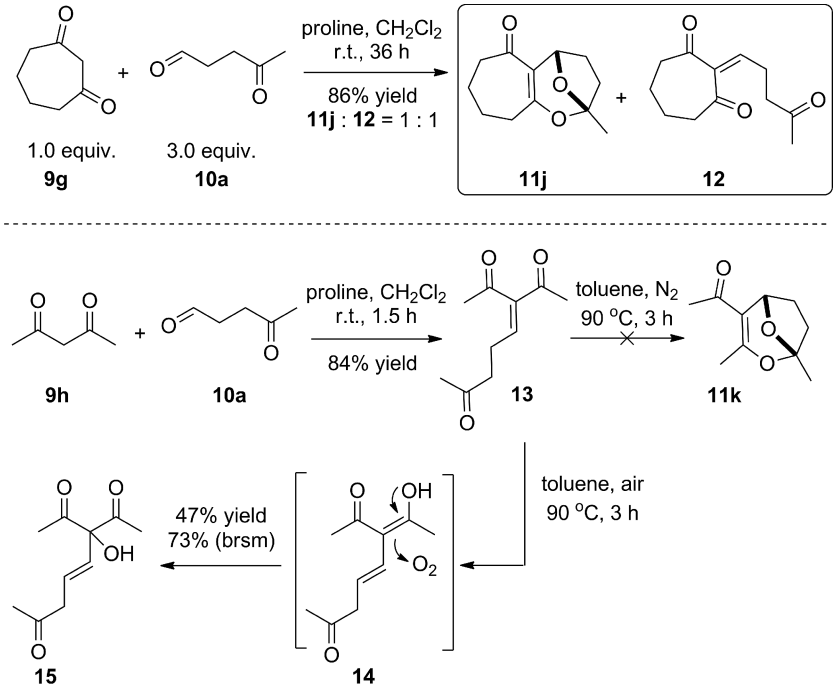
To further extend the scope of this reaction, various 1,5-dicarbonyl substrates **16** were examined (Table 2). The corresponding tricyclic ketal products **17a**–**17i** were consistently isolated in good to excellent yields. However, the yields in most cases were slightly lower than those of 1,4-

Table 1. Surveying the reaction scope of 1,4-dicarbonyl substrates.[a]



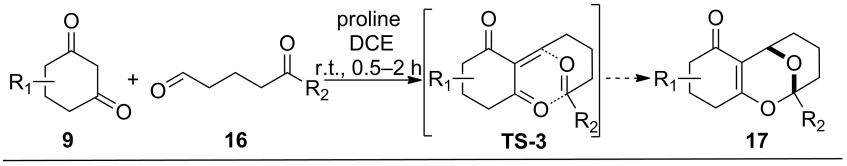
Entry	Substrate		R_2	Product		Yield[b] [%]
1		**9a**	H		**11a**	93
2		**9a**	Me		**11b**	91
3		**9a**	Et		**11c**	89
4		**9a**	*i*Pr		**11d**	90
5		**9b**	Me		**11e**	87
6		**9c**	Me		**11f**	90[c]
7		**9d**	Me		**11g**	68
8		**9e**	Me		**11h**	83
9		**9f**	Me		**11i**	57

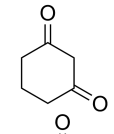
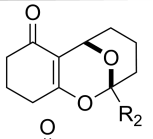
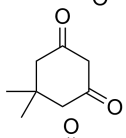
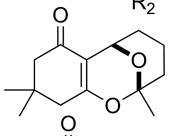
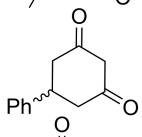
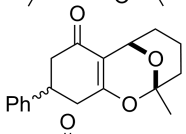
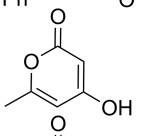
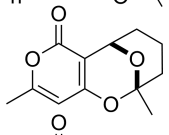
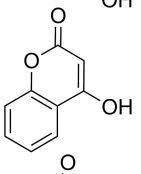
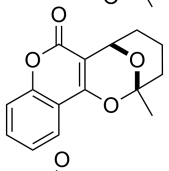
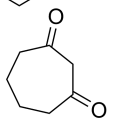
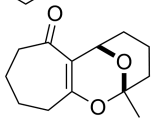
[a] Reagents and conditions: 1,3-diketone (0.5 mmol), 1,4-dicarbonyl substrate (1.0 mmol), proline (0.05 mmol), DCE (10 mL), room temp., 0.5–2 h. [b] Yield of isolated product. [c] The product isolated as a mixture of diastereomers (ratio: 1:2).



Scheme 2. Reactivity of strain and noncyclic 1,3-diketones.

Table 2. Surveying the reaction scope of 1,5-dicarbonyl substrates.[a]

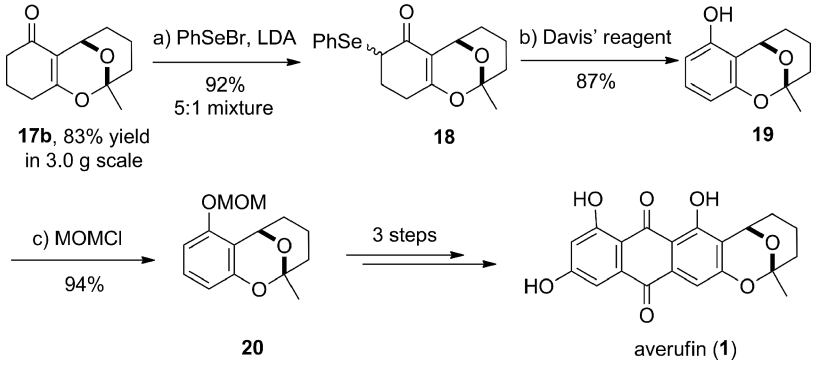


Entry	Substrate		R_2	Product		Yield[b] [%]
1		**9a**	H		**17a**	67
2		**9a**	Me		**17b**	87
3		**9a**	Et		**17c**	85
4		**9a**	*i*Pr		**17d**	82
5		**9b**	Me		**17e**	78
6		**9c**	Me		**17f**	81[c]
7		**9d**	Me		**17g**	78
8		**9e**	Me		**17h**	80
9		**9g**	Me		**17i**	77

[a] Reagents and conditions: 1,3-diketone (0.5 mmol), 1,5-dicarbonyl substrate (1.0 mmol), proline (0.05 mmol), DCE (10 mL), room temp., 0.5–2 h. [b] Yield of isolated product. [c] The product was isolated as a mixture of diastereomers (1:2).

dicarbonyl substrates **10** (with the exception of Table 2, Entry 7). Moreover, substituents on 1,5-dicarbonyl substrates **16** and cyclic 1,3-dicarbonyl substrates **9** had little influence on the efficiency of the catalysis. An obvious decrease in the yield was observed when the steric bulk of substituent increased (Table 2, Entries 2–6). It was notable that in contrast to the reaction of **9g** and 4-oxopentanal (**10a**, R_2 = Me), the corresponding inseparable Knoevenagel condensation intermediate was not observed in the reaction of **9g** and 5-oxohexanal. Instead, the desired [4+2] cycloaddition product **17i** was obtained in 77% yield as the only product (Table 2, Entry 9).

After establishing the synthetic methodology, we moved directly to the formal synthesis of averufin (**1**, Scheme 3).



Scheme 3. The formal total synthesis of averufin (**1**). Reagents and conditions: (a) PhSeBr (1.5 equiv.), lithium diisopropylamide (LDA, 1.2 equiv.), tetrahydrofuran (THF), –78 °C, 20 min; (b) 2-(phenylsulfonyl)-3-phenyloxaziridine (Davis' reagent, 1.2 equiv.), 3,5-dimethoxyaniline (2.0 equiv.), $CHCl_3$, room temp., 30 min; (c) NaH (1.5 equiv.), MOMCl (1.5 equiv.), tetra-*n*-butylammonium bromide (TBAB, 1.0 equiv.), THF, room temp., 5 h.

As expected, the desired starting material **17b** was readily obtained in 83% yield by the proline-mediated Knoevenagel condensation/[4+2] cycloaddition sequence when the reaction was scaled up from 100 mg to 3.0 g. Treating **17b** under standard conditions with phenylselenyl bromide gave α-benzeneselenenylation product **18** (92% yield, 5.0 g scale), which was then treated with the Davis reagent in the presence of 3,5-dimethoxyaniline to afford phenol **19** (87% yield, 2.0 g scale).[20] The simple protection of the hydroxy group of phenol **19** by using chloromethyl methyl ether (MOMCl) under basic conditions transforms it into key precursor **20** (94% yield, 1.5 g scale). The analytical data of **20** were identical to those previously reported,[5c] and **20** could be further converted into the natural product averufin (**1**) in three steps.[5c]

Conclusions

In summary, we have developed a remarkable proline-catalyzed approach, which mimics a biosynthetic Knoevenagel condensation/[4+2] cycloaddition reaction sequence, for the construction of biologically significant oxygen-bridged tricyclic ketal skeletons. The rapid construction of this architecture has potential uses in medicinal chemistry as well as natural product and diversity-oriented synthesis. By applying this methodology, we have successfully established a viable synthetic strategy to complete the formal synthesis of averufin (**1**). The preparation of a variety of other oxygen-bridged tricyclic ketal skeleton containing natural products and analogous derivatives are now underway and will be reported in due course.

Experimental Section

General Methods: All reactions were carried out in dry solvents under nitrogen and anhydrous conditions, unless otherwise noted. Reagents of high commercial quality were purchased and used without further purification. Thin layer chromatography was conducted with Tsingdao silica gel plates (60 F-254, 0.25 mm) and visualized either by exposure to UV light (254 nm) or staining with potassium permanganate. Silica gel (ZCX-II, 200–300 mesh) for flash column chromatography was purchased from Qing Dao Hai Yang Chemical Industry Co. of China. The ^{1}H and ^{13}C NMR spectroscopic data were recorded with a Bruker Advance 300 (for ^{1}H NMR, 300 MHz; for ^{13}C NMR, 75 MHz), a Bruker Advance 400 (for ^{1}H NMR, 400 MHz; for ^{13}C NMR, 100 MHz), or a Bruker Advance 500 (for ^{1}H NMR, 500 MHz; for ^{13}C NMR, 125 MHz) spectrometer. Chemical shifts are reported in parts per million relative to the residual protio solvent or $CDCl_3$ (for ^{1}H NMR, δ = 7.27 ppm; for ^{13}C NMR, δ = 77.00 ppm). Mass spectrometric data were obtained by using an ABI-Q Star Elite high resolution mass spectrometer. Anhydrous THF was distilled from sodium-benzophenone until a deep blue color persisted. CH_2ClCH_2Cl (DCE) was distilled from calcium hydride, yields refer to chromatographically purified products, unless otherwise stated. The following abbreviations were used for the multiplicities of spectral signals: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br. (broad).

General Procedure for Knoevenagel/[4+2] Cascade Reaction: A flame-dried 50 mL flask was charged with the aldehyde (1.0 mmol) and DCE (10 mL). The 1,3-diketone (0.5 mmol) was added followed by proline (6 mg, 0.05 mmol). The resulting solution was then stirred at room temperature for 0.5–2 h until the starting material was consumed. After 10 min, the mixture was concentrated in vacuo, and the crude product was purified by short-column flash chromatography (silica gel; hexane/EtOAc, 3:l) to afford the corresponding product **11–13** and **17**.

3,4,5,6,9,10-Hexahydro-2*H*-2,6-epoxybenzo[*b*]oxocin-7(8*H*)-one (11a): Following the general procedure afforded **11a** (93% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83 (dd, J = 3.0, J = 1.0 Hz, 1 H), 5.14 (t, J = 2.0 Hz, 1 H), 2.28 (m, 4 H), 2.18 (m, 2 H), 2.06 (m, 2 H), 1.97 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.9, 168.6, 117.5, 101.6, 72.4, 36.1, 34.6, 34.1, 27.2, 20.7 ppm. HRMS (ESI): calcd. for $C_{10}H_{13}O_3^+$ $[M + H]^+$ 181.0865; found 181.0858.

2-Methyl-2,3,4,5,8,9-hexahydro-2,5-epoxybenzo[*b*]oxepin-6(7*H*)-one (11b): Following the general procedure afforded **11b** (91% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.12 (d, J = 6.0 Hz, 1 H), 2.27–2.32 (m, 5 H), 2.11–2.19 (m, 1 H), 1.96–2.05 (m, 4 H), 1.66 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.0, 169.8, 116.6, 109.6, 73.7, 38.4, 36.2, 35.7, 27.3, 22.9, 20.8 ppm. HRMS (ESI): calcd. for $C_{11}H_{15}O_3^+$ $[M + H]^+$ 195.1021; found 195.1018.

2-Ethyl-2,3,4,5,8,9-hexahydro-2,5-epoxybenzo[*b*]oxepin-6(7*H*)-one (11c): Following the general procedure afforded **11c** (89% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.15 (d, J = 5.5 Hz, 1 H), 2.30–2.35 (m, 4 H), 1.97–2.24 (m, 8 H), 1.07 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.0, 170.0, 117.0, 111.8, 73.6, 36.4, 36.3, 35.4, 29.4, 27.4, 20.9, 7.7 ppm. HRMS (ESI): calcd. for $C_{12}H_{17}O_3^+$ $[M + H]^+$ 209.1178; found 209.1172.

2-Isopropyl-2,3,4,5,8,9-hexahydro-2,5-epoxybenzo[*b*]oxepin-6(7*H*)-one (11d): Following the general procedure afforded **11d** (90% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.14 (s, 1 H), 2.32 (m, 4 H), 1.85–2.25 (m, 7 H), 1.06 (t, J = 5.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.1, 170.2, 116.9, 113.7, 73.6, 36.2, 35.3, 34.6, 34.0, 27.4, 20.8, 16.8, 16.5 ppm. HRMS (ESI): calcd. for $C_{13}H_{19}O_3^+$ $[M + H]^+$ 223.1334; found 223.1333.

2,8,8-Trimethyl-2,3,4,5,8,9-hexahydro-2,5-epoxybenzo[*b*]oxepin-6(7*H*)-one (11e): Following the general procedure afforded **11e** (87% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.13 (d, J = 5.6 Hz, 1 H), 2.26 (m, 1 H), 2.18 (m, 5 H), 2.04 (m, 2 H), 1.67 (m, 3 H), 1.06 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.8, 168.3, 115.4, 109.6, 73.7, 50.2, 41.1, 38.5, 35.8, 32.5, 28.6, 28.2, 22.9 ppm. HRMS (ESI): calcd. for $C_{13}H_{19}O_3^+$ $[M + H]^+$ 223.1334; found 223.1325.

2-Methyl-8-phenyl-2,3,4,5,8,9-hexahydro-2,5-epoxybenzo[*b*]oxepin-6(7*H*)-one (11f): Following the general procedure afforded **11f** (90% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 2 H), 7.26 (m, 3 H), 5.20 (t, J = 7.0 Hz, 1 H), 3.36 (m, 1 H), 2.00–2.80 (m, 8 H), 1.71 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.0, 169.2, 168.9, 142.7, 142.6, 128.8, 128.8, 127.0, 126.6, 126.6, 116.7, 116.3, 110.0, 109.9, 74.0, 73.6, 43.5, 43.3, 39.4, 38.7, 38.3, 35.8, 35.6, 34.9, 23.0, 22.8 ppm. HRMS (ESI): calcd. for $C_{17}H_{19}O_3^+$ $[M + H]^+$ 271.1334; found 271.1331.

2,8-Dimethyl-4,5-dihydro-2*H*-2,5-epoxypyrano[4,3-*b*]oxepin-6(3*H*)-one (11g): Following the general procedure afforded **11g** (68% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.71 (s,

1 H), 5.17 (s, J = 4.4 Hz, 1 H), 2.37 (m, 1 H), 2.00–2.35 (m, 6 H), 1.71 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.5, 162.6, 161.8, 110.3, 102.3, 99.5, 74.3, 38.5, 35.8, 22.9, 20.0 ppm. HRMS (ESI): calcd. for $C_{11}H_{13}O_4^+$ [M + H]$^+$ 209.0814; found 209.0809.

2-Methyl-4,5-dihydro-2*H*-2,5-epoxyoxepino[3,2-*c*]chromen-6(3*H*)-one (11h): Following the general procedure afforded **11h** (83% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (dd, J = 8.0 Hz, J = 1.6 Hz, 1 H), 7.54 (dt, J = 8.0 Hz, J = 1.6 Hz, 1 H), 7.28 (m, 2 H), 5.33 (m, J = 1.6 Hz, 1 H), 2.49 (m, 1 H), 2.31 (m, 2 H), 2.18 (m, 1 H), 1.86 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 158.8, 153.3, 132.1, 123.9, 122.4, 116.9, 114.9, 111.0, 105.1, 74.6, 38.7, 36.0, 23.0 ppm. HRMS (ESI): calcd. for $C_{14}H_{13}O_4^+$ [M + H]$^+$ 245.0814; found 245.0801.

2,7-Dimethyl-2,3,4,5-tetrahydro-2,5-epoxyoxepino[3,2-*c*]quinolin-6(7*H*)-one (11i): Following the general procedure afforded **11i** (57% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (dd, J = 8.0 Hz, J = 1.6 Hz, 1 H), 7.56 (dt, J = 7.2 Hz, J = 1.6 Hz, 1 H), 7.32 (dt, J = 7.6 Hz, 1 H), 7.21 (dt, J = 8.0 Hz, J = 0.8 Hz, 1 H), 5.44 (d, J = 4.2 Hz, 1 H), 3.67 (s, 1 H), 2.05–2.50 (m, 4 H), 1.84 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5, 154.5, 139.3, 130.8, 122.6, 121.6, 115.3, 114.0, 110.6, 109.5, 74.9, 38.5, 36.2, 28.9, 23.4 ppm. HRMS (ESI): calcd. for $C_{15}H_{16}NO_3^+$ [M + H]$^+$ 258.1130; found 258.1128.

2-Methyl-4,5,7,8,9,10-hexahydro-2*H*-2,5-epoxycyclohepta[*b*]oxepin-6(3*H*)-one (11j) and 2-(4-Oxopentylidene)cycloheptane-1,3-dione (12): Following the general procedure afforded **11j** and **12** was (86% total yield) as colorless oils. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88 (t, J = 8.0 Hz, 1 H), 5.16 (t, J = 6.0 Hz, 1 H), 2.65 (m, 4 H), 2.56 (m, 6 H), 2.53 (m, 2 H), 2.28 (m, 1 H), 2.16 (s, 3 H), 2.15 (m, 1 H), 1.70–2.10 (m, 10 H), 1.66 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.0, 169.2, 168.9, 142.7, 142.6, 128.8, 128.8, 127.0, 126.6, 126.6, 116.7, 116.3, 110.0, 109.9, 74.0, 73.6, 43.5, 43.3, 39.4, 38.7, 38.3, 35.8, 35.6, 34.9, 23.0, 22.8 ppm. HRMS (ESI): calcd. for $C_{12}H_{17}O_3^+$ [M + H]$^+$ 209.1178; found 209.1173.

3-Acetyloct-3-ene-2,7-dione (13): Following the general procedure afforded **13** (84% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.67 (t, J = 8.0 Hz, 1 H), 2.66 (t, J = 7.0 Hz, 2 H), 2.44 (q, J = 6.0 Hz, 2 H), 2.32 (s, 3 H), 2.28 (s, 3 H), 2.15 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.5, 203.2, 197.0, 145.7, 145.1, 42.0, 31.4, 29.7, 26.0, 23.6 ppm. HRMS (ESI): calcd. for $C_{10}H_{15}O_3^+$ [M + H]$^+$ 183.1021; found 183.1013.

3,4,5,6,9,10-Hexahydro-2*H*-2,6-epoxybenzo[*b*]oxocin-7(8*H*)-one (17a): Following the general procedure afforded **17a** (67% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.57 (m, 1 H), 4.86 (m, J = 3.6 Hz, 1 H), 2.52 (m, 2 H), 2.40 (m, 2 H), 1.80–2.10 (m, 4 H), 1.50–1.75 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.1, 171.5, 112.6, 96.7, 65.3, 36.4, 31.3, 27.7, 27.6, 20.9, 14.4 ppm. HRMS (ESI): calcd. for $C_{11}H_{15}O_3^+$ [M + H]$^+$ 195.1021; found 195.1017.

2-Methyl-3,4,5,6,9,10-hexahydro-2*H*-2,6-epoxybenzo[*b*]oxocin-7(8*H*)-one (17b): Following the general procedure afforded **17b** (87% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.93 (d, J = 4.0 Hz, 1 H), 2.38–2.48 (m, 2 H), 2.37 (t, J = 6.2 Hz, 2 H), 1.86–2.06 (m, 4 H), 1.55–1.80 (m, 4 H), 1.48 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.0, 171.8, 111.9, 102.0, 66.9, 36.5, 36.1, 27.9, 27.6, 27.1, 21.1, 15.9 ppm. HRMS (ESI): calcd. for $C_{12}H_{17}O_3^+$ [M + H]$^+$ 209.1178; found 209.1173.

2-Ethyl-3,4,5,6,9,10-hexahydro-2*H*-2,6-epoxybenzo[*b*]oxocin-7(8*H*)-one (17c): Following the general procedure afforded **17c** (85% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.92 (d, J = 4.0 Hz, 1 H), 2.30–2.60 (m, 4 H), 1.80–2.20 (m, 4 H), 1.50–1.80 (m, 6 H), 0.94 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.1, 172.2, 112.0, 103.3, 66.6, 36.5, 34.1, 33.3, 27.8, 27.4, 21.0, 15.7, 6.7 ppm. HRMS (ESI): calcd. for $C_{13}H_{19}O_3^+$ [M + H]$^+$ 223.1334; found 223.1334.

2-Isopropyl-3,4,5,6,9,10-hexahydro-2*H*-2,6-epoxybenzo[*b*]oxocin-7-(8*H*)-one (17d): Following the general procedure afforded **17d** (82% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.89 (d, J = 4.0 Hz, 1 H), 2.30–2.60 (m, 4 H), 2.06 (m, 2 H), 1.87 (m, 3 H), 1.59 (m, 4 H), 0.95 (q, J = 4.0 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.1, 172.3, 112.2, 104.9, 66.5, 37.1, 36.4, 31.2, 27.7, 27.4, 21.0, 16.3, 15.9, 15.6 ppm. HRMS (ESI): calcd. for $C_{14}H_{21}O_3^+$ [M + H]$^+$ 237.1491; found 237.1484.

2,9,9-Trimethyl-3,4,5,6,9,10-hexahydro-2*H*-2,6-epoxybenzo[*b*]oxocin-7(8*H*)-one (17e): Following the general procedure afforded **17e** (78% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.91 (d, J = 4.0 Hz, 1 H), 2.26–2.35 (m, 2 H), 2.14 (q, J = 16.0 Hz, 2 H), 1.87–1.93 (m, 2 H), 1.62–1.72 (m, 4 H), 1.46 (s, 3 H), 1.10 (s, 3 H), 1.08 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.7, 170.0, 110.6, 102.0, 66.8, 50.4, 41.7, 36.0, 32.2, 28.9, 28.1, 27.5, 27.1, 16.0 ppm. HRMS (ESI): calcd. for $C_{12}H_{25}O_2Si^+$ [M + H]$^+$ 229.1618; found 229.1617. HRMS (ESI): calcd. for $C_{14}H_{21}O_3^+$ [M + H]$^+$ 237.1491; found 237.1493.

2-Methyl-9-phenyl-3,4,5,6,9,10-hexahydro-2*H*-2,6-epoxybenzo[*b*]oxocin-7(8*H*)-one (17f): Following the general procedure afforded **17f** (81% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 2 H), 7.26 (m, 3 H), 4.98 (s, 1 H), 3.25–3.55 (m, 1 H), 2.60–2.95 (m, 4 H), 1.94 (m, 2 H), 1.55–1.85 (m, 4 H), 1.50 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.1, 194.0, 171.2, 170.8, 142.7, 142.7, 128.8, 128.7, 127.0, 126.9, 126.6, 111.8, 111.3, 110.0, 102.4, 102.2, 67.0, 66.8, 43.8, 43.3, 39.2, 39.1, 36.0, 35.9, 35.5, 35.2, 27.6, 27.4, 27.2, 26.8, 15.9, 15.7 ppm. HRMS (ESI): calcd. for $C_{18}H_{21}O_3^+$ [M + H]$^+$ 285.1491; found 285.1481.

2,9-Dimethyl-3,4,5,6-tetrahydro-2,6-epoxypyrano[4,3-*b*]oxocin-7(2*H*)-one (17g): Following the general procedure afforded **17g** (78% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (s, 1 H), 4.99 (d, J = 2.8 Hz, 1 H), 2.10 (s, 1 H), 1.96 (m, 1 H), 1.50–1.80 (m, 4 H), 1.51 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 161.8, 161.7, 102.5, 99.4, 98.1, 67.1, 35.7, 27.4, 26.6, 20.0, 15.6 ppm. HRMS (ESI): calcd. for $C_{12}H_{15}O_4^+$ [M + H]$^+$ 223.0970; found 223.0969.

2-Methyl-3,4,5,6-tetrahydro-2,6-epoxyoxocino[3,2-*c*]chromen-7(2*H*)-one (17h): Following the general procedure afforded **17h** (80% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (dd, J = 8.0 Hz, J = 1.6 Hz, 1 H), 7.54 (dt, J = 8.0 Hz, J = 1.6 Hz, 1 H), 7.28 (m, 2 H), 5.13 (dd, J = 4.0 Hz, J = 1.6 Hz, 1 H), 2.07 (m, 2 H), 1.86 (m, 2 H), 1.75 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 160.2, 153.0, 131.9, 123.8, 122.4, 116.8, 114.7, 103.2, 100.8, 67.5, 35.8, 27.4, 26.6, 15.6 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}O_4^+$ [M + H]$^+$ 259.0970; found 259.0964.

2-Methyl-3,4,5,6,8,9,10,11-octahydro-2,6-epoxycyclohepta[*b*]oxocin-7(2*H*)-one (17i): Following the general procedure afforded **17i** (77% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.93 (d, J = 4.0 Hz, 1 H), 2.56–2.62 (m, 4 H), 1.78–1.92 (m, 6 H), 1.65–1.67 (m, 4 H), 1.46 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.4, 171.2, 113.9, 101.2, 68.3, 41.6, 36.3, 32.4, 27.6, 27.3, 23.5, 21.0, 16.0 ppm. HRMS (ESI): calcd. for $C_{13}H_{19}O_3^+$ [M + H]$^+$ 223.1334; found 223.1327.

(*E*)-6-Acetyl-6-hydroxyoct-4-ene-2,7-dione (15): Unsaturated 1,3-diketone **13** (36 mg, 0.20 mmol) was dissolved in toluene (5 mL), and the resulting solution was heated to 90 °C under air. After stirring at this temperature for 3 h, the mixture was cooled to room tem-

perature and purified directly by flash chromatography (silica gel; hexane/EtOAc, 5:l) to afford the corresponding starting material **13** (9.8 mg, 0.05 mmol) and product **15** (18 mg, 47% yield, 73% brsm) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.11 (d, J = 15.6 Hz, 1 H), 5.65 (dt, J = 15.6 Hz, J = 7.2 Hz, 1 H), 3.31 (dd, J = 7.2 Hz, J = 1.0 Hz, 2 H), 2.21 (s, 3 H), 2.16 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.3, 191.0, 127.9, 127.8, 110.9, 47.6, 29.7, 24.1 ppm. HRMS (ESI): calcd. for $C_{10}H_{15}O_3^+$ $[M + H]^+$ 202.1160; found 202.1173.

Formal Synthesis of Averufin

2-Methyl-3,4,5,6,9,10-hexahydro-2*H*-2,6-epoxybenzo[*b*]oxocin-7(8*H*)-one (17b): A flame-dried 250 mL flask was charged with aldehyde **16a** (1.14 g, 10.0 mmol), DCE (100 mL), and cyclohexane-1,3-dione (**9a**, 506 mg, 5.0 mmol). Proline (115 mg, 1.0 mmol) was then added. The resulting mixture was stirred at room temperature for 15 min, and then a second portion of cyclohexane-1,3-dione (**9a**, 258 mg, 2.5 mmol) was added. After 15 min, a third portion of cyclohexane-1.3-dione (**9a**, 258 mg, 2.5 mmol) was added. The solution was stirred at room temperature for 20 min until the starting material was consumed. After 10 min, the resulting mixture was concentrated in vacuo, and the crude product was purified by flash chromatography (silica gel; hexane/EtOAc, 3:l) to afford product **17b** (1.73 g, 83% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.93 (d, J = 4.0 Hz, 1 H), 2.38–2.48 (m, 2 H), 2.37 (t, J = 6.2 Hz, 2 H), 1.86–2.06 (m, 4 H), 1.55–1.80 (m, 4 H), 1.48 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.0, 171.8, 111.9, 102.0, 66.9, 36.5, 36.1, 27.9, 27.6, 27.1, 21.1, 15.9 ppm. HRMS (ESI): calcd. for $C_{12}H_{17}O_3^+$ $[M + H]^+$ 209.1178; found 209.1173.

2-Methyl-8-(phenylselenyl)-3,4,5,6,9,10-hexahydro-2*H*-2,6-epoxybenzo[*b*]oxocin-7(8*H*)-one (18): To a solution of LDA, which was freshly prepared from *n*BuLi (2.5 M solution in hexane, 0.6 mL, 1.5 mmol) and diisopropylamine (152 mg, 1.5 mmol) in dry THF (10 mL), was slowly added ketone **17b** (208 mg, 1.0 mmol) at –78 °C under nitrogen. After 20 min, a solution of benzeneselenenyl bromide (354 mg, 1.5 mmol) in THF (1 mL) was added dropwise, and the resulting mixture was stirred at –78 °C for another 20 min. The mixture was then warmed room temperature, and the reaction was quenched with water (10 mL). The resulting mixture was extracted with EtOAc (4× 10 mL), and the combined organic phases were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (silica gel; hexane/EtOAc, 5:l) to afford **18** (334 mg, 92% yield, approximately 5:1 mixture) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (m, 2 H), 7.27 (m, 3 H), 4.95 (m, J = 4.0 Hz, 1 H), 4.03 (m, 1 H), 2.60–2.95 (m, 1 H), 2.10–2.50 (m, 4 H), 1.55–2.0 (m, 6 H), 1.47 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.3, 191.2, 170.4, 135.5, 135.3, 129.1, 129.0, 128.2, 127.9, 110.6, 102.3, 102.0, 66.9, 66.8, 46.5, 46.3, 35.9, 27.5, 27.4, 27.0, 27.0, 26.6, 26.0, 25.4, 15.7, 15.7 ppm. HRMS (ESI): calcd. for $C_{18}H_{21}O_3Se^+$ $[M + H]^+$ 365.0656; found 365.0654.

2-Methyl-3,4,5,6-tetrahydro-2*H*-2,6-epoxybenzo[*b*]oxocin-7-ol (19): To a solution of ketone **18** (181 mg, 0.5 mmol) in $CHCl_3$ (3 mL) were added 3,5-dimethoxyaniline (153 mg, 1.0 mmol) and the Davis reagent (165 mg, 0.6 mmol). The resulting mixture was stirred at room temperature for 30 min and was then concentrated in vacuo. The crude product was purified by flash chromatography (silica gel; hexane/EtOAc, 4:1) to afford product **19** (158 mg, 87% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.08 (dt, J = 8.5 Hz, J = 0.5 Hz, 1 H), 6.58 (d, J = 7.5 Hz, 1 H), 6.49 (d, J = 7.5 Hz, 1 H), 5.29 (d, J = 3.5 Hz, 1 H), 5.17 (m, 2 H), 3.46 (d, J = 1.0 Hz, 3 H), 2.02 (m, 2 H), 1.78 (m, 2 H), 1.62 (m, 2 H), 1.54 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.5, 152.5, 128.1, 111.8, 108.7, 104.3, 98.9, 94.1, 67.2, 56.0, 36.2, 28.3, 28.2, 16.1 ppm. HRMS (ESI): calcd. for $C_{12}H_{15}O_3^+$ $[M + H]^+$ 206.0623; found 206.0622.

7-(Methoxymethoxy)-2-methyl-3,4,5,6-tetrahydro-2*H*-2,6-epoxybenzo[*b*]oxocine (20): NaH (60% in mineral oil, 42 mg, 1.05 mmol) was slowly and carefully added to a solution of phenol **19** (141 mg, 0.7 mmol) in THF (10 mL) at 0 °C. The resulting mixture was stirred at this temperature for 10 min under nitrogen, and then MOMCl (85 mg, 1.05 mmol) was added followed by TBAB (225 mg, 0.7 mmol). The ice bath was removed, and the mixture was stirred at room temperature for an additional 5 h. The crude mixture was diluted with EtOAc (20 mL), and the reaction was then quenched with saturated aqueous NH_4Cl (10 mL). The resulting mixture was extracted with EtOAc (4× 15 mL), and the combined organic phases were washed with brine and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel; hexane/EtOAc, 4:l) to afford **20** (165 mg, 94% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.08 (m, 1 H), 6.59 (d, J = 8.5 Hz, 1 H), 6.49 (d, J = 8.5 Hz, 1 H), 5.29 (d, J = 3.5 Hz, 1 H), 5.18 (m, 2 H), 3.46 (d, J = 1.0 Hz, 3 H), 2.05–1.99 (m, 2 H), 1.75–1.82 (m, 2 H), 1.62–1.65 (m, 2 H), (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.5, 152.5, 128.1, 111.8, 108.7, 104.3, 98.9, 94.1, 67.2, 56.0, 36.18, 28.3, 28.2, 16.1 ppm. HRMS (ESI): calcd. for $C_{14}H_{19}O_4^+$ $[M + H]^+$ 251.1283; found 251.1273.

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[1] a) L. E. Brown, K. C.-C. Cheng, W. G. Wei, P. W. Yuan, P. Dai, R. Trilles, F. Ni, J. Yuan, R. MacArthur, R. Guha, R. L. Johnson, X. Z. Su, M. M. Dominguez, J. K. Snyder, A. B. Beeler, S. E. Schaus, J. Inglese, J. A. Porco Jr., *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6775–6780; b) W. M. zu Reckendorf, *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 665; c) M. Shibuya, F. Jaisli, A. Eschenmoser, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 636–637; *Angew. Chem.* **1979**, *91*, 672–673; d) F. Jaisli, D. Sternbach, M. Shibuya, A. Eschenmoser, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 637–638; *Angew. Chem.* **1979**, *91*, 673–675; e) W. W. Epstein, F. W. Sweat, C. VanLear, F. M. Lovell, E. J. Gabe, *J. Am. Chem. Soc.* **1979**, *101*, 2748–2750; f) K. Kojiri, S. Nakajima, A. Fuse, H. Suzuki, H. Suda, *J. Antibiot.* **1995**, *48*, 1506–1508; g) J. Aiguade, J. L. Hao, C. J. Forsyth, *Org. Lett.* **2001**, *3*, 979–982; h) L. A. Paquette, D. Backhaus, R. Braun, T. L. Underiner, K. Fuchs, *J. Am. Chem. Soc.* **1997**, *119*, 9662–9671; i) R. W. Huigens 3rd, K. C. Morrison, R. W. Hicklin, T. A. Flood Jr., M. F. Richter, P. J. Hergenrother, *Nature Chem.* **2013**, *5*, 195–202.

[2] For selected bioactive natural products featuring an oxygen-bridged tricyclic ketal skeleton, see: a) F. Bohlmann, J. Jakupovic, L. N. Misra, V. Castro, *Liebigs Ann. Chem.* **1985**, 1367–1376; b) H. M. T. B. Herath, A. M. A. Priyadarshani, J. Jamie, *Nat. Prod. Lett.* **1998**, *12*, 91–95; c) H. M. T. B. Herath, W. Padmasiri, *Nat. Prod. Lett.* **1999**, *14*, 141–146; d) A. Pontius, A. Krick, S. Kehraus, R. Brun, G. M. König, *J. Nat. Prod.* **2008**, *71*, 1579–1584; e) J. S. E. Holker, S. A. Kagal, L. J. Mulheirn, P. M. White, *J. Chem. Soc., Chem. Commun.* **1966**, 911–913; f) R. J. Li, R. X. Zhu, Y. Y. Li, J. C. Zhou, J. Z. Zhang, S. Wang, J. P. Ye, Y. H. Wang, S. L. Morris-Natschke, K. H. Lee, H. X. Lou, *J. Nat. Prod.* **2013**, *76*, 1700–1708; g) A.

Fredenhagen, P. Hug, H. Sauter, H. H. Peter, *J. Antibiot.* **1995**, *48*, 199–204; h) S. B. Singh, D. L. Fink, D. S. Quamina, F. Pelaez, A. Teran, P. Felock, D. J. Hazuda, *Tetrahedron Lett.* **2002**, *43*, 2351–2354.

[3] a) C. A. Townsend, S. B. Christensen, S. G. Davis, *J. Am. Chem. Soc.* **1982**, *104*, 6152–6153; b) C. A. Townsend, S. B. Christensen, S. G. Davis, *J. Am. Chem. Soc.* **1982**, *104*, 6154–6155; c) M. T. Lin, D. P. H. Hsieh, *J. Am. Chem. Soc.* **1973**, *95*, 1668–1669; d) D. P. H. Hsieh, R. Singh, R. C. Yao, J. W. Bennett, *Appl. Environ. Microbiol.* **1978**, *35*, 980–982.

[4] a) T. Nikaido, T. Ohmoto, U. Sankawa, S. Kitanka, M. Takido, *Chem. Pharm. Bull.* **1984**, *32*, 3075–3078; b) K. Kawai, Y. Nozawa, Y. Maebayashi, M. Yamazaki, T. Hamasaki, *Appl. Environ. Microbiol.* **1984**, *47*, 481–483.

[5] For reports on the total synthesis of averufin or constructing its tricyclic ketal skeleton, see: a) P. Roffey, M. V. Sargent, J. A. Knight, *J. Chem. Soc. C* **1967**, 2328–2331; b) A. Castonguay, P. Brassard, *Can. J. Chem.* **1977**, *55*, 1324–1332; c) C. A. Townsend, S. G. Davis, S. B. Christensen, J. C. Linc, C. P. Lewis, *J. Am. Chem. Soc.* **1981**, *103*, 6885–6888; d) R. A. Murphy Jr., M. P. Cava, *J. Am. Chem. Soc.* **1984**, *106*, 7630–7632; e) M. Koreeda, B. Hulin, M. Yoshihara, C. A. Townsend, S. B. Christensen, *J. Org. Chem.* **1985**, *50*, 5426–5428; f) C. A. Townsend, S. G. Davis, M. Koreeda, B. Hulin, *J. Org. Chem.* **1985**, *50*, 5428–5430; g) G. J. O'Malley, R. A. Murphy Jr., M. P. Cava, *J. Org. Chem.* **1985**, *50*, 5533–5537.

[6] For recent work on constructing oxygen-bridged tricyclic ketal skeletons, see: a) S. Y. Xing, Y. Li, Z. Li, C. Liu, J. Ren, Z. W. Wang, *Angew. Chem. Int. Ed.* **2011**, *50*, 12605–12609; b) A. B. Beeler, S. Su, C. A. Singleton, J. A. Porco Jr., *J. Am. Chem. Soc.* **2007**, *129*, 1413–1419; c) C. V. Ramana, C. N. Reddy, R. G. Gonnade, *Chem. Commun.* **2008**, 3151–3153; d) J. Janas, T. P. Forrest, *J. Org. Chem.* **1970**, *35*, 836–838; e) J. S. Foot, G. M. P. Giblin, R. J. K. Taylor, *Org. Lett.* **2003**, *5*, 4441–4444; f) A. Nath, J. Mal, R. V. Venkateswaran, *J. Chem. Soc., Chem. Commun.* **1993**, 1374–1375; g) J. Mal, A. Nath, R. V. Venkateswaran, *J. Org. Chem.* **1996**, *61*, 9164–9167; h) N. Bischofberger, B. Frei, O. Jeger, *Helv. Chim. Acta* **1983**, *66*, 1061–1067.

[7] For a selection of some representative oxidative cleavage/intramolecular [4+2] cycloaddition cascade reactions, see: a) M. Aquino, I. Safir, Z. Elkhayat, Z. Gandara, M. Perez, P. Retailleau, S. Arseniyadis, *Org. Lett.* **2009**, *11*, 3610–3613; b) R. R. Castillo, M. Aquino, Z. Gandara, I. Safir, Z. Elkhayat, P. Retailleau, S. Arseniyadis, *Org. Lett.* **2012**, *14*, 1628–1631; c) Z. Elkhayat, I. Safir, P. Retailleau, S. Arseniyadis, *Org. Lett.* **2007**, *9*, 4841–4844; d) R. R. Castillo, V. Abet, M. Aquino, Z. Gandara, P. Retailleau, S. Arseniyadis, *Eur. J. Org. Chem.* **2013**, 2389–2400.

[8] a) M. L. Bolte, W. D. Crow, S. Yoshida, *Aust. J. Chem.* **1982**, *35*, 1411–1419; b) A. B. Smith, B. D. Dorsey, M. Ohba, A. T. Lupo, M. S. Malamas, *J. Org. Chem.* **1988**, *53*, 4314–4325.

[9] For selected reviews and papers of organocatalysis, see: a) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171; *Angew. Chem.* **2008**, *120*, 6232–6265; b) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308; c) A. Moyano, R. Rios, *Chem. Rev.* **2011**, *111*, 4703–4832; d) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178–2189.

[10] For selected reviews and papers of organocatalytic ketal formation, see: a) I. Čorić, B. List, *Nature* **2012**, *483*, 315–319; b) Z. K. Sun, G. A. Winschel, A. Borovika, P. Nagorny, *J. Am. Chem. Soc.* **2012**, *134*, 8074–8077; c) E. Mensah, N. Camasso, W. Kaplan, P. Nagorny, *Angew. Chem. Int. Ed.* **2013**, *52*, 12932–12936; d) J. S. Potuzak, S. B. Moilanen, D. S. Tan, *J. Am. Chem. Soc.* **2005**, *127*, 13796–13797.

[11] The proposed biosynthesis was successfully realized by Castonguay. In the reported Synthesis they used 1,3,6,8-tetrahydroxyanthraquinone to react with 5-oxohexanal in the presence of sodium hydrogen carbonate. However, this reaction provided averufin in as little as 6.5% yield. The details of this synthesis can be found in ref.[5b]

[12] a) G. E. Ferris, K. Hong, I. A. Roundtree, J. P. Morken, *J. Am. Chem. Soc.* **2013**, *135*, 2501–2504; b) M. J. Wanner, R. N. A. Boots, B. Eradus, R. de Gelder, J. H. van Maarseveen, H. Hiemstra, *Org. Lett.* **2009**, *11*, 2579–2581.

[13] For a selection of some representative amine-catalyzed cascade reactions, see: a) E. Reyes, G. Talavera, J. L. Vicario, D. Badía, L. Carrillo, *Angew. Chem. Int. Ed.* **2009**, *48*, 5701–5704; *Angew. Chem.* **2009**, *121*, 5811; b) A. Michrowska, B. List, *Nature Chem.* **2009**, *1*, 225–228; c) S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature* **2011**, *475*, 183–188.

[14] a) J. J. Yu, L. M. Wang, J. Q. Liu, F. L. Guo, Y. Liu, N. Jiao, *Green Chem.* **2010**, *12*, 216–219; b) S. Kokkirala, N. M. Sabbavarapu, V. D. N. Yadavalli, *Eur. J. Chem.* **2011**, *2*, 272–275.

[15] For recent work on reactions catalyzed by proline derivatives: a) I. Ibrahem, P. Breistein, A. Cordova, *Angew. Chem. Int. Ed.* **2011**, *50*, 12036–12041; b) Y. Hayashi, Y. Yasui, T. Kawamura, M. Kojima, H. Ishikawa, *Angew. Chem. Int. Ed.* **2011**, *50*, 2804–2807; c) S. Z. Lin, L. Deiana, G. L. Zhao, J. L. Sun, A. Córdova, *Angew. Chem. Int. Ed.* **2011**, *50*, 7624–7630; d) S. Cabrera, E. Reyes, J. Aleman, A. Milelli, S. Kobbelgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2008**, *130*, 12031–12037; e) J. L. Vicario, S. Reboredo, D. Badía, L. Carrillo, *Angew. Chem. Int. Ed.* **2007**, *46*, 5168–5170; *Angew. Chem.* **2007**, *119*, 5260.

[16] For selected recent work on MacMillan's organocatalyzed reactions, see: a) N. T. Jui, J. A. O. Garber, F. G. Finelli, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2012**, *134*, 11400–11403; b) A. Gualandi, E. Emer, M. G. Capdevila, P. G. Cozzi, *Angew. Chem. Int. Ed.* **2011**, *50*, 7842–7846; c) J. F. V. Humbeck, S. P. Simonovich, R. R. Knowles, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 10012–10014; d) T. D. Beeson, A. Mastracchio, J. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582–585.

[17] All of the other examined organocatalysts afforded unsatisfactory *ee* values (less than 20%) and low yields with increased amounts of byproducts.

[18] The dioxabicyclo[3.2.1]octene ring system of this cyclic ketal is thermally labile, as it can be transformed into the linear noncyclic product at room temperature through a thermal electrocyclic ring-opening mechanism; see ref.[6h]

[19] For a selection of some representative papers on the syntheses of 3-hydroxy-2,4-dione derivatives in recent years, see: a) S. Gundala, C. L. Fagan, J. F. Franz, S. J. Connon, K. Zeitler, *Chem. Sci.* **2012**, *3*, 735–740; b) J. Christoffers, T. Werner, W. Frey, A. Baro, *Chem. Eur. J.* **2004**, *10*, 1042–1045; c) J. Christoffers, A. Baro, T. Werner, *Adv. Synth. Catal.* **2004**, *346*, 143–51; d) C. B. Miao, Y. H. Wang, M. L. Xing, X. W. Lu, X. Q. Sun, H. T. Yang, *J. Org. Chem.* **2013**, *78*, 11584–11589.

[20] M. Krause, H. M. R. Hoffmann, *Synlett* **1990**, 485–486.

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