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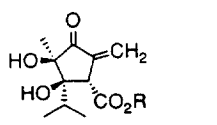
Synthesis of (±)-Xanthocidin

Marcus A. Tius,* and David J. Drake

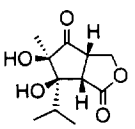
Department of Chemistry, University of Hawaii, 2545 The Mall, Honolulu, Hawaii 96822, U.S.A.

Abstract: An efficient total synthesis of (±)-xanthocidin, a complex and unstable cyclopentanoid antibiotic, is described. The success of the key cyclopentannelation step suggests much greater versatility for the general version of this reaction.

Xanthocidin (**1**) is the most complex of the cyclopentanone antibiotics.[1] It belongs to a class of compounds which includes sarkomycin, an antitumor antibiotic with activity in humans, and methylenomycin A, which is active against Lewis lung carcinoma in mice.[2] As a consequence of the two contiguous quaternary carbon atoms in the ring, xanthocidin is also an unstable molecule which undergoes, *inter alia*, loss of water upon exposure to base or acid. Although the appeal of its challenging structure has been sufficient to justify several synthetic efforts, there is a practical reason for undertaking a total synthesis as well: the producing strain of *Streptomyces xanthocidicus* from which the natural product was originally isolated has lost its ability to biosynthesize **1**.[3] Total synthesis is the only source for this material.



xanthocidin **1** R = H
3 R = CH_3



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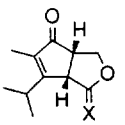


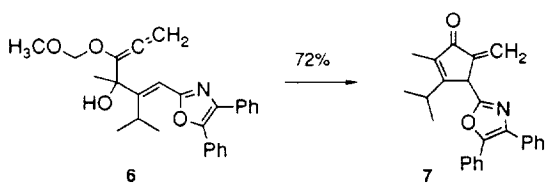
4 X = H_2
5 X = O

There have been three total syntheses and two formal syntheses of **1** to date. Amos Smith's pioneering work in 1981[4,5] was followed by our total synthesis in 1989.[6,7] In 1994 Mori was able to prepare each of the enantiomers of **1** by following the outline of Smith's earlier work, and resolving one of the intermediates.[3] An interesting formal synthesis is due to Au-Yeung;[8] more recently Jacobi has applied his fascinating enynone cyclization to the problem.[9] There were several motivations for the present work. First, we wished to improve the efficiency of our earlier route, which suffered from two low yielding steps at the very end of the sequence. Second, we wanted to demonstrate that the key reaction, the cationic cyclopentannelation, is far

more versatile than we had disclosed, and that the carboxylate need not be carried through in a protected form. Finally, we wished to provide the complete experimental details for our optimized synthesis.

Any successful total synthesis must address the problems posed by the presence of the *cis*-vicinal diol. The dihydroxylation must be performed toward the end of the sequence, since the presence of the vicinal diol in intermediate structures places limits on the types of reactions that can be performed subsequently. Also, the exocyclic methylene group must be masked during the dihydroxylation step. This makes it necessary to deprotect the methylene group in an intermediate which incorporates the unstable diol. The difficulty in performing this transformation can be appreciated by considering the yields for the base catalyzed conversion of **2** or **3** to xanthocidin (20-25% and 26%, respectively).[5,6]

A difficult step in Smith's synthesis was the low yielding and non-regioselective oxidation of **4** to a mixture of lactones. Only lactone **5** was carried on to **1**, following osmylation to **2**.[5] The necessity of having to adjust the oxidation state of the carboxylate carbon diminishes the overall efficiency of this approach. Our early synthesis of **1** also required oxidation at the same site.[6] We chose Wasserman's diphenyloxazole[10] as a photolabile carboxylate equivalent, because it was expected to stabilize the presumed pentadienyl cation intermediate derived from **6** (eq 1). This prediction was borne out, and the cyclization to **7** took place in good yield.



6 7 [1]

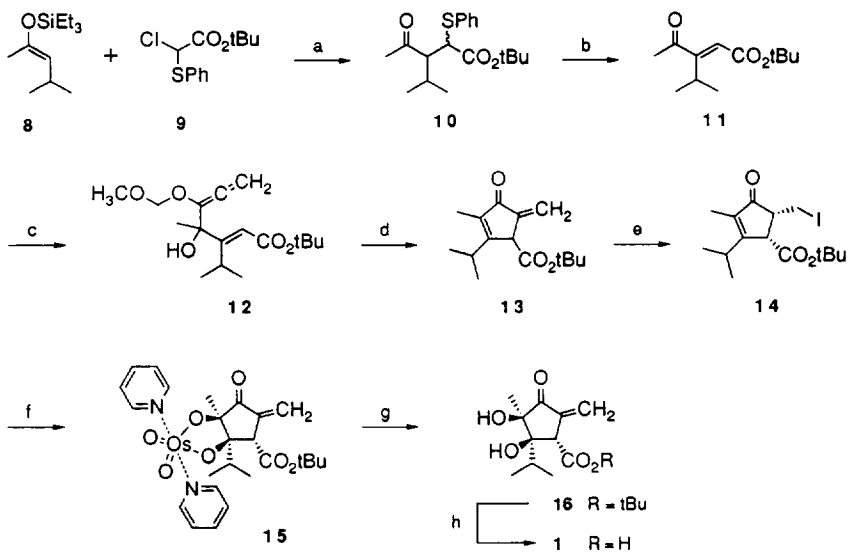
The starting point for our optimized synthesis was triethylsilyl enol ether **8** (Scheme 1), which is obtained in quantitative yield from the catalytic hydrosilylation of mesityl oxide.[11] Chlorination of *tert*-butyl phenylthioacetate with sulfuryl chloride produced chloride **9** in 78% yield.[12] The acylation reaction was catalyzed by $ZnCl_2$ and produced a mixture of diastereoisomers of **10** in 75% yield.[13-15] Oxidative elimination[13] of the thiophenyl group produced 41% of (E)-*tert*-butyl-3-isopropyl-4-oxo-2-pentenoate **11**, along with 43% of the Z isomer. The geometric isomers were easily separable by flash column chromatography. The recovered Z isomer could be isomerized to an E,Z isomeric mixture by exposure to thiophenol and 1,1'-azobis(cyclohexanenitrile) in refluxing benzene and recycled for a higher overall yield of **11**.[16] Selective addition of lithio (methoxy)methoxyallene to the ketone carbonyl group of **11** produced tertiary alcohol **12** in 78% yield.[7]

The cationic cyclopentannelation of substrates bearing electron-releasing substituents on the alkene had been shown to be a rapid and high-yielding process.[7,17] Therefore, the presence of electron-withdrawing functionality in **12** might have been expected to suppress the generation of the pentadienyl cation. This, in turn, might allow competing processes to take place, for example hydrolysis of the methoxymethyl enol ether moiety, in preference to cyclization. In the event, exposure of **12** to an excess of 2,6-lutidine and trifluoroacetic anhydride in CH_2Cl_2 at -20 °C, followed by warming to room temperature and treatment with

silica gel for 3 h, led to ketoester **13** in 62% yield following column chromatography. In the absence of silica gel, the yield of **13** was much lower and multiple products were observed. This key reaction assembles the entire carbon framework, including the exocyclic methylene and the carboxylate.

Ketoester **13** was also converted to lactone **5** in an unoptimized process. Cleavage of the *tert*-butyl ester with trifluoroacetic acid, followed by exposure to iodotrimethylsilane, gave an unstable β-iodoketone, which was not purified. Exposure of the iodide to silver carbonate in ethanol at room temperature gave lactone **5** in 26% overall yield following column chromatography. Since **5** has been converted to **1**,[3,5] the synthesis of **5** also constitutes a formal synthesis of (±)-xanthocidin.

Scheme 1



(a) $ZnCl_2$, CH_2Cl_2, -20 °C to 0 °C, 75%; (b) $NaIO_4$, CH_3OH, H_2O, r.t., 3 d; CCl_4, K_2CO_3, 70 °C, 24 h, 41% E + 43% Z; (c) lithio (methoxy)methoxyallene, THF, ether, -78 °C, 15 min, 78%; (d) 2,6-lutidine, $(F_3CCO)_2O$, CH_2Cl_2, SiO_2, -20 °C to r.t., 62%; (e) $H_2C{=}CHCH_2SiMe_3$, I_2, CH_2Cl_2, -40 °C, 20 min, 62%; (f) OsO_4, pyr, -20 °C to r.t., 81% + 15% **13**; (g) H_2S, CH_2Cl_2, r.t.; de-gas; EtOH, Ag_2CO_3, 50%; (h) TBSOTf, CH_2Cl_2, r.t., 3 h; 2,6-lutidine, 0 °C, 30 min; 1N HCl, 88%.

To complete the total synthesis of **1**, it was necessary to protect the reactive exocyclic alkene in **13** prior to osmylation. Exposure of **13** to iodotrimethylsilane, followed by workup with aqueous thiosulfate, produced β-iodoketone **14** in 62% yield, along with ca. 20% of a mixture of unreacted **13** and the *trans* diastereomer of **14**.[18] The successful protection of the methylene group was followed by osmylation and subsequent purification by column chromatography to produce *bis*-pyridine osmate ester **15** in 81% yield as a brown oil. Recovered enone **13** (15% yield) was recycled, thus increasing the overall efficiency of the synthesis. There are several noteworthy features of this reaction. First, osmylation of **14** with one equivalent

of osmium tetraoxide at -20 °C leads to a complete reaction. Upon warming of the intermediate product to room temperature in pyridine, elimination of HI took place. Had the loss of HI taken place at -20 °C, *bis*-osmylated products would have been isolated. It is significant that unmasking of the methylene group took place during the osmylation reaction, since this operation had represented the most serious obstacle in earlier approaches.[3-5]

Reductive decomposition of this osmate was accomplished by exposure of **15** to H_2S, as evidenced by the appearance of a black precipitate of osmium salts. Michael addition of H_2S to the reactive methylene group also took place during this reaction, however, brief treatment with silver carbonate prior to workup led cleanly to xanthocidin *tert*-butyl ester **16** in 50% overall yield from **15**. Unmasking of the carboxylate, potentially a very challenging step, was left to the end. Although **16** would not be expected to tolerate prolonged exposure to protic or Lewis acids, we reasoned that treatment with a silyl triflate would convert the *tert*-butyl ester into a hydrolytically labile silyl ester with generation of isobutylene.[19,20] Brief exposure of the silyl ester to aqueous acid would lead to the final product, providing that decomposition of xanthocidin did not compete. We further predicted that neither the ketone carbonyl group of **16**, nor the two tertiary hydroxyl groups would interfere with this process. We were gratified to find that by first exchanging the *tert*-butyl for *tert*-butyldimethylsilyl, followed by brief treatment with aqueous HCl, the hydrolysis of **16** to **1** took place in a single operation in 88% yield. The xanthocidin which was produced was identical in all respects with material which we had prepared in our earlier synthesis.[6]

This synthesis of (±)-xanthocidin is brief (9 steps longest linear sequence) and efficient. Noteworthy features of this work include the cyclization step, the conversion of **14** to **15** and the hydrolysis of **16** to **1**. A focus of work in the future will be to develop an enantioselective version of the cyclopentannnelation reaction.

Acknowledgement is made to Sea Grant (Institutional Grant No. NA36RG0507, UNIHI-SEAGRANT-JC-95-27) for support of this work.

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded at 300 MHz ^{1}H (75 MHz ^{13}C) or 500 MHz ^{1}H (125 MHz ^{13}C) in deuteriochloroform ($CDCl_3$) with chloroform (7.26 ppm ^{1}H, 77.00 ppm ^{13}C) as an internal reference. Chemical shifts are given in δ; multiplicities are indicated as br (broadened), s (singlet), t (triplet), q (quartet), sext (sextet), sept (septet), m (multiplet); coupling constants (J) are reported in hertz (Hz). Infrared spectra were recorded on a Perkin-Elmer IR 1430 spectrometer. Electron impact (EI) and FAB mass spectra were performed on a VG-70SE mass spectrometer. Mass spectral data are reported in the form of m/e. Thin-layer chromatography (TLC) was performed on EM Reagents precoated silica gel 60 F-254 analytical plates (0.25 mm). Flash column chromatography was performed on Brinkmann silica gel (0.040-0.063 mm). Tetrahydrofuran (THF) and ether were distilled from sodium-benzophenone ketyl, dichloromethane (CH_2Cl_2) from phosphorus pentoxide and hexane from calcium hydride. Other reagents were obtained commercially and used as received unless otherwise specified. All reactions were performed under a static nitrogen or argon atmosphere in flame-dried glassware. The purity and homogeneity of the products on which the high

resolution mass spectral data are reported were determined on the basis of 300 MHz ^{1}H-NMR and multiple elution TLC analysis or HPLC analysis.

***tert*-Butyl(phenylthio)acetate.** Isobutylene (13 ml, 0.15 mol) was condensed into an argon flushed pressure bottle cooled to -78 °C. Phenylthioacetic acid (16.82 g, 0.10 mol) was rapidly added, followed by 10 ml ether and 1 ml concentrated H_2SO_4, and the bottle was fitted into a high pressure shaker apparatus. The reaction was shaken at r.t. for 6 h and attained a pressure of 25 psi. The pressure was bled from the system and the bottle quickly removed, stoppered and cooled to 0 °C. To a separatory funnel containing 50 ml water, 50 g ice and 14 g sodium hydroxide was added the reaction mixture and the organic phase was separated. The aqueous phase was extracted with ether and the combined ethereal extracts were dried (K_2CO_3), filtered and the solvent evaporated. The crude yellow liquid was distilled from K_2CO_3 to give the product as a colorless liquid (17.87 g, 80% yield): bp 120 °C @ 1.0 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.21 (m, 5H), 3.56 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 135.2, 129.8, 128.8, 126.6, 81.8, 37.7, 27.8; IR (neat) 3050, 2980, 2930, 1725, 1580, 1480, 1365, 1290, 1130, 740, 690 cm^{-1}; m/e (EI$^+$) 224 (M^+, 27), 168 (54), 151 (6), 123 (100), 109 (18), 77 (13); exact mass calculated for $C_{12}H_{16}O_2S$ 224.0867, found 224.0879.

***tert*-Butyl-2-chloro-2-(phenylthio)acetate 9.** To a refluxing solution of *tert*-butylphenylthioacetate (5.0 g, 22.5 mmol) in 18 ml CH_2Cl_2 at 45 °C was added a solution of sulfuryl chloride (1.8 ml, 22.0 mmol) in 5 ml CH_2Cl_2 dropwise at such a rate as to maintain a gentle reflux (ca. 1 h). Reflux was maintained for 2 h, the reaction was cooled to r.t. and powdered K_2CO_3 added. Filtration and solvent evaporation gave **9** as a pale yellow oil (4.45 g, 78% yield): bp 131 °C @ 1.0 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.58 (m, 2H), 7.39-7.37 (m, 3H), 5.44 (s, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 133.7, 129.3, 128.9, 83.9, 65.9, 27.7; IR (neat) 3050, 2980, 2930, 1740, 1580, 1475, 1370, 1290, 1140, 850, 740, 690 cm^{-1}; m/e (EI$^+$) 260 (M^+[^{37}Cl], 10), 258 (M^+[^{35}Cl], 27), 204 (12), 202 (32), 187 (4), 185 (10), 167 (16), 159 (37), 157 (100), 121 (51), 109 (39), 77 (43); exact mass calculated for $C_{12}H_{15}O_2ClS$ 258.0478, found 258.0516.

***tert*-Butyl-3-isopropyl-4-oxo-2-(phenylthio)pentanoate 10.** To a solution of (E)-4-methyl-2-(triethylsilyloxy)pent-2-ene (7.0 g, 32.5 mmol) and 2.8 g (10.8 mmol) *tert*-butyl-2-chloro-2-phenylthioacetate **9** in 25 ml CH_2Cl_2 at -20 °C was added 100 mg fused zinc chloride followed by zinc chloride solution (500 µl, approx. 10.8 mmol, bottom layer from Aldrich® 1M $ZnCl_2$ in ether solution) and the reaction was allowed to warm to 0 °C over 30 min. After stirring at 0 °C for an additional 30 min, TLC showed complete absence of starting material. The reaction was poured onto ice cold aqueous Na_2CO_3 and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated to give a pale yellow oil. Purification by flash chromatography (3% → 10% EtOAc in hexane) gave **10** as a colorless oil (2.6 g, 75% yield, *mixture of diastereoisomers*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.44 (m, 2H), 7.31-7.28 (m, 3H),

3.83 & 3.79 (d, J = 11.5 Hz, & d, J = 10.8 Hz, 1H), 3.05 & 2.97 (dd, J = 10.8, 5.5 Hz, & dd, J = 11.5, 3.5 Hz, 1H), 2.55 & 2.04 (sept d, J = 7.2, 3.5 Hz, & ap sext, J = 6.9 Hz, 1H), 2.29 & 2.20 (s & s, 3H), 1.36 & 1.33 (s & s, 9H), 1.13 & 1.01 & 0.93 & 0.87 (d & d & d & d, J = 7.2 Hz, & J = 7.2 Hz, & J = 6.9 Hz, & J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4 & 208.7, 171.0 & 170.2, 133.1 & 132.5, 128.6 & 127.9, 127.8, 81.4 & 81.3, 57.5 & 56.7, 52.6 & 51.9, 34.1 & 33.1, 29.4, 27.6 & 27.5, 26.8, 22.1 & 21.5, 17.6 & 16.9; IR (neat) 3060, 2970, 2935, 2875, 1725, 1710, 1580, 1475, 1465, 1365, 1285, 1250, 1140, 845, 740, 685 cm^{-1}; m/e (EI$^+$) 322 (M^+, 9), 266 (20), 248 (35), 223 (15), 221 (11), 205 (28), 179 (93), 110 (100); exact mass calculated for $C_{18}H_{26}O_3S$ 322.1596, found 322.1565.

(E)-*tert*-Butyl-3-isopropyl-4-oxo-2-pentenoate 11. To a solution of 2.94 g (9.1 mmol) *tert*-butyl-3-isopropyl-4-oxo-2-phenylthiopentanoate **10** in 81 ml methanol was added 9.9 g (45.5 mmol) sodium *meta*-periodate in 10 ml water and the mixture was stirred at r.t. for 3 d. The solid was removed by filtration, the filtrate evaporated and the aqueous residue extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and evaporated to give the sulfoxide as a colorless oil. The sulfoxide was dissolved in 30 ml CCl_4, K_2CO_3 was added and the mixture heated to 70 °C for 24h. The reaction was cooled to r.t., filtered and the solvent evaporated to give a 1:1 mixture of geometric isomers as a pale yellow oil. Purification by flash chromatography (5% ether in hexane) gave **11** as a yellow oily solid (800 mg, 41% yield), along with 827 mg (43% yield) of the Z isomer. **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (s, 1H), 3.56 (sept, J = 6.9 Hz, 1H), 2.31 (s, 3H), 1.51 (s, 9H), 1.18 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 165.2, 158.7, 125.3, 81.5, 28.6, 28.2, 28.0, 20.6; IR (neat) 2980, 2940, 2880, 1715, 1685, 1625, 1455, 1365, 1240, 1150 cm^{-1}; m/e (EI$^+$) no M^+, 156 (35), 138 (100), 110 (51), 99(90), 95 (58), 67 (68); exact mass calculated for $C_8H_{12}O_3$ (M^+ - $Me_2C{=}CH_2$) 156.0783, found 156.0819. [Z isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (d, J = 1 Hz, 1H), 2.54 (sept, J = 6.9 Hz, 1H), 2.35 (s, 3H), 1.45 (s, 9H), 1.12 (d, J = 6.9 Hz, 6H)].

(2E)-*tert*-Butyl-4-hydroxy-3-isopropyl-4-methyl-5-((methoxy)methoxy)hepta-2,5,6-trienoate 12. To a solution of 418 mg (4.18 mmol) methyloxymethyl allenyl ether in 20 ml THF/ether (1:1 v/v) was added *n*-butyllithium (1.72 ml, 3.35 mmol, 1.95M solution in hexane) at -78 °C. The solution was stirred for 1 h at -78 °C and then transferred via cannula into a solution of 470 mg (2.22 mmol) of ketone **11** in 10 ml THF/ether (1:1 v/v) at -78 °C. After 15 min TLC showed the complete absence of starting material, and the reaction was quenched with satd aqueous $NaHCO_3$ and allowed to warm to r.t. The mixture was extracted with ether and the combined ethereal extracts washed with brine, dried ($MgSO_4$) and evaporated to give a bright yellow oil. Purification by flash chromatography (15% ether in hexane + 1% triethylamine) gave **12** as a pale yellow oil (542 mg, 78% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (s, 1H), 5.59 (s, 2H), 4.84 (s, 2H), 3.42 (s, 3H), 2.71 (s, 1H), 2.66 (sept, J = 7.2 Hz, 1H), 1.49 (s, 9H), 1.38 (s, 3H), 1.28 (d, J = 7.2 Hz, 3H), 1.26 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 166.5, 165.3, 132.5, 117.1, 94.8, 92.2, 79.7, 76.9, 56.8, 29.4, 28.0, 24.8, 20.7, 20.5; IR (neat) 3460 br, 2970, 2930, 1960, 1715, 1640, 1450, 1360, 1150 br, 1050, 970, 885 cm^{-1}; m/e (EI$^+$) no M^+, 294 (0.5), 255 (<0.5), 239 (7), 221 (4), 213 (10), 194 (30), 157 (79), 149 (65), 139 (100), 125 (52), 111 (38); exact mass calculated for $C_{13}H_{19}O_4$

(M^+ -C_4H_9O) 239.1278, found 239.1309; exact mass calculated for $C_{13}H_{19}O_5$ (M^+ - C_4H_9) 255.1227, found 255.1269.

4-*tert*-Butyloxycarbonyl-3-isopropyl-2-methyl-5-methylene-2-cyclopentenone 13. To a solution of 540 mg (1.74 mmol) **12** in 30 ml CH_2Cl_2 at -20 °C was added 1.22 ml (10.42 mmol) 2,6-lutidine followed by 1.22 ml (8.69 mmol) trifluoroacetic anhydride and the reaction was stirred at -20 °C for 20 min. The reaction was allowed to warm to r.t., 315 mg silica gel was added and stirring continued for 3 h. after which time no change in reaction composition could be detected by TLC. The reaction was quenched by addition of satd aqueous $NaHCO_3$ and extracted with ether/hexane (1:1 v/v). The combined organic extracts were dried ($MgSO_4$) and evaporated to give a yellow/orange oil. Purification by flash chromatography (10% ether in hexane) gave **13** as a pale yellow oil (270 mg, 62% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 6.09 (d, J =1.2 Hz, 1H), 5.48 (s, 1H), 4.06 (s, 1H), 3.02 (sept, J = 7.2 Hz, 1H), 1.86 (d, J = 1.5 Hz, 3H), 1.42 (s, 9H), 1.19 (d, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 169.9, 169.5, 141.8, 139.6, 115.4, 81.6, 50.9, 29.6, 27.6, 20.2, 20.1, 8.7; IR (neat) 2970, 2930, 2870, 1725, 1690, 1620, 1465, 1390, 1365, 1310, 1250, 1145, 920 cm^{-1}; m/e (EI^+) no M^+, 194 (15), 177 (6), 150 (100), 135 (37), 121 (9), 107 (19), 91 (40); exact mass calculated for $C_{11}H_{14}O_3$ (M^+ - $Me_2C{=}CH_2$) 194.0939, found 194.0967; exact mass calculated for $C_{10}H_{14}O$ (M^+ - $Me_2C{=}CH_2$ - CO_2) 150.1041, found 150.1050.

4-*tert*-Butyloxycarbonyl-5-iodomethyl-3-isopropyl-2-methyl-2-cyclopentenone 14. To a solution of 200 mg (0.80 mmol) iodine in 5 ml CH_2Cl_2 at 0 °C and shielded from light was added allyltrimethylsilane (130 µl, 0.80 mmol) and the mixture stirred at 0 °C in the dark for 1 h. Two identical reactions were set up each containing a solution of 30 mg (0.12 mmol) **13** in 1.5 ml CH_2Cl_2, cooled to -40 °C and shielded from light. To each flask was added the freshly prepared iodotrimethylsilane solution (900 µl, 0.144 mmol) and the reactions were stirred at -40 °C in the dark for 20 min. The reactions were diluted with ether, washed with ice cold 5% aqueous sodium thiosulfate and brine, dried ($MgSO_4$) and evaporated to give a pale yellow oil. This material was immediately purified by flash chromatography (10% ether in hexane) to give the *cis* diastereomer **14** as the major product (56 mg, 62% yield) and 16 mg of a mixture of the *trans* diastereomer and recovered **13**. This mixture was treated with pyridine to yield 10 mg of **13**. The *cis* diastereomer **14** was obtained as a white crystalline solid: mp. 55 - 56 °C, ^1H NMR (500 MHz, $CDCl_3$) δ 3.89 (dd, J = 6.2, 1.2 Hz, 1H), 3.75 (dd, J = 10.5, 4.0 Hz, 1H), 3.07 (dd, J = 11.6, 10.5 Hz, 1H), 3.00 (sept, J = 6.9 Hz, 1H), 2.83 (ddd, J = 11.6, 6.2, 4.0 Hz, 1H), 1.76 (d, J = 1.5 Hz, 3H), 1.51 (s, 9H), 1.20 (d, J = 6.9 Hz, 3H), 1.12 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 171.6, 170.1, 136.6, 82.8, 54.4, 51.1, 29.7, 28.0, 20.4, 20.0, 8.7, -0.9; IR (neat) 2970, 2930, 2870, 1725, 1710, 1640, 1465, 1365, 1330, 1210, 1145, 1010, 840, 770 cm^{-1}; m/e (EI^+) 378 (M^+, <1), 322 (19), 277 (18), 195 (100), 150 (32), 135 (17), 128 (37), 107 (31), 91 (28), 79 (22), 69 (31); exact mass calculated for $C_{15}H_{23}O_3I$ 378.0685, found 378.0714; exact mass calculated for $C_{11}H_{15}O_3I$ (M^+ - $Me_2C{=}CH_2$) 322.0061, found 322.0093.

Osmate ester, *bis*-(pyridino) complex 15. To a flask containing 50 mg (0.13 mmol) iodide **14** at -20 °C was added a solution of OsO_4 in pyridine (1.3 ml, 0.13mmol, 0.1M solution) in a single portion. The solution was stirred at -20 °C for 15 min. The reaction was warmed to r.t. and stirring continued for 3 h. The reaction was diluted with $CHCl_3$ and washed with water. The aqueous phase was back extracted with $CHCl_3$ and the combined organic phases dried ($MgSO_4$) and evaporated to give a brown oil. Purification by flash chromatography (20% → 50% EtOAc in hexane → $CHCl_3$ → 2% MeOH in $CHCl_3$) gave 5 mg (15%) recovered **13**, followed by osmate ester **15** (70 mg, 81% yield) as a brown oil. The overall yield from **13** to **15** based on recovered starting material was 59% for the two steps. **15**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, *J* = 5.4 Hz, 4H), 7.83 (br s, 2H), 7.45 (t, *J* = 6.6 Hz, 4H), 6.27 (d, *J* = 2.1 Hz, 1H), 5.50 (d, *J* = 1.0 Hz, 1H), 4.09 (br s, 1H), 2.94 (sept, *J* = 6.6 Hz, 1H), 1.97 (s, 3H), 1.46 (s, 9H), 1.38 (d, *J* = 6.6 Hz, 3H), 1.18 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7, 171.7, 149.7, 143.0, 140.2, 125.2, 120.5, 98.7, 96.4, 81.0, 57.8, 33.0, 27.9, 19.7, 18.9, 17.9; IR (neat) 3110, 3080, 3050, 2985, 2930, 2880, 1725, 1710, 1630, 1605, 1480, 1450, 1365, 1310, 1150, 1025, 950, 835, 760, 690 cm^{-1}; m/e (FAB) 665 (MH^+ [^{192}Os], 22), 608 (30), 586 (95), 529 (29), 449 (23), 414 (40), 382 (51), 303 (100).

8-Isopropyl-7-methyl-3-oxabicyclo[3.3.0]oct-7-ene-2,6-dione 5. *tert*-Butyl ester **13** (10 mg, 0.04 mmol) was dissolved in trifluoroacetic acid and stirred at r.t. for 15 min. The trifluoroacetic acid was evaporated to give a yellow oil which was dissolved in CH_2Cl_2 and cooled to -40 °C. To this solution of the free acid was added freshly prepared iodotrimethylsilane solution (500 ml, 0.08 mmol, 0.16M solution in CH_2Cl_2) and the reaction stirred at -40 °C for 2 h. The reaction was diluted with ether, washed with ice cold 5% aqueous sodium thiosulfate and brine, dried ($MgSO_4$) and evaporated to give a brown oil. Purification by flash chromatography (20% EtOAc in hexane + 1% AcOH) gave iodide as a white solid (5 mg). To a solution of this iodide in ethanol was added silver carbonate and the flask stirred at r.t. in the dark for 3 h. The silver salts were removed by filtration through Celite and evaporated to give a light brown oily solid. Purification by flash chromatography (25% EtOAc in hexane) gave ketolactone **5** as a white solid (2 mg, 26% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (t, *J* = 9.6 Hz, 1H), 4.42 (dd, *J* = 9.6, 3.5 Hz, 1H), 3.85 (dddd, *J* = 7.5, 3.5, 3.5, 0.75, 1H), 3.29 (dddd, *J* = 9.6, 7.5, 3.5, 0.5, 1H), 3.13 (sept, *J* = 7.0 Hz, 1H), 1.80 (d, *J* = 1.75 Hz, 3H), 1.38 (d, *J* = 7.0 Hz, 3H), 1.25 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 173.8, 173.3, 136.5, 67.4, 46.1, 45.4, 30.2, 20.2, 19.4, 8.72; IR (neat) 2960, 2915, 2830, 1770, 1705, 1630, 1460, 1160, 1005 cm^{-1}; m/e (EI$^+$) 194 (M^+, 55), 149 (13), 135 (27), 107 (82), 91 (40); exact mass calculated for $C_{11}H_{14}O_3$ 194.0939, found 194.0961; exact mass calculated for $C_{10}H_{13}O$ (M^+ - HCO_2) 149.0963, found 149.0973.

(±) Xanthocidin, *t*-butyl ester 16. Hydrogen sulfide was bubbled through a solution of osmate ester **15** (70 mg, 0.106 mmol) in 30 ml CH_2Cl_2 for 10 min. A black precipitate settled leaving a colorless solution which was degassed with argon for 20 min. The osmium salts were removed by filtration through Celite and the colorless filtrate evaporated to give a pale yellow oil (22 mg). To a solution of oil in 5 ml absolute ethanol was added 20 mg (0.07 mmol) Ag_2CO_3 and the mixture stirred in the dark for 2h. TLC analysis showed the

presence of residual thiol, therefore another 1 equivalent of Ag_2CO_3 (20 mg, 0.07 mmol) was added and stirring was continued for 30 min. The silver salts were removed by filtration through Celite and washed with EtOAc. Solvent evaporation produced a brown oil. Purification by flash chromatography (25 % EtOAc in hexane) gave **16** as a colorless oil (15 mg, 50% yield over two steps): ^{1}H NMR (500 MHz, d^6-benzene) δ 6.22 (d, *J* = 2.5 Hz, 1H), 5.30 (dd, *J* = 2.2, 0.5 Hz, 1H), 3.82 (t, *J* = 2.3, 1H), 3.06 (br s, 1H), 2.92 (br s, 1H), 2.46 (sept, *J* = 6.7 Hz, 1H), 1.50 (s, 3H), 1.24 (s, 9H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, d^6-benzene) δ 206.6, 170.2, 141.1, 123.1, 82.1, 81.1, 55.4, 30.2, 29.3, 27.7, 20.5, 17.1, 16.6; IR (neat) 3500 br, 2980, 2940, 2885, 1735, 1725, 1640, 1460, 1375, 1330, 1160, 1035, 975, 850, 800 cm^{-1}; m/e (EI$^+$) no M$^+$, 228 (M$^+$ - $Me_2C{=}CH_2$, 5), 210 (8), 167 (19), 140 (52), 116 (100), 112 (14), 101 (17), 71 (75); exact mass calculated for $C_{11}H_{16}O_5$ 228.0993, found 228.1015; exact mass calculated for $C_{11}H_{14}O_4$ 210.0888, found 210.0907.

(±) **Xanthocidin 1**. To a solution of 7 mg (0.025 mmol) **16** in 500 µl CH_2Cl_2 was added a solution of *tert*-butyldimethylsilyltriflate (100 µl, 0.027 mmol, 0.27 M solution in CH_2Cl_2) and the yellow solution was stirred at r.t. for 3 h. The reaction was cooled to 0 °C and a solution of 2,6-lutidine was added (50 µl, 0.027 mmol, 0.54 M solution in CH_2Cl_2). The yellow color dissipated and the reaction was stirred at 0 °C for 30 min. The reaction was diluted with EtOAc, brine was added and the pH adjusted to 1-2 using 1N HCl. The aqueous phase was extracted with EtOAc, the organic extracts combined, dried (Na_2SO_4) and evaporated to give a brown oil. Purification by flash chromatography (10% water added to deactivate the SiO_2 before packing the column; eluant 33% → 50% EtOAc in hexane) gave 5 mg (88% yield) of xanthocidin **1** as a pale yellow oily solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (d, *J* = 2.25 Hz, 1H), 5.85 (d, *J* = 2.25 Hz, 1H), 3.87 (t, *J* = 2.25, 1H), 3.14 (br s, 1H), 3.08 (br s, 1H), 2.42 (sept, *J* = 6.75 Hz, 1H), 1.47 (s, 3H), 1.03 (d, *J* = 6.75 Hz, 3H), 1.02 (d, *J* = 6.75 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 175.0, 139.0, 125.4, 81.9, 80.9, 53.4, 29.0, 20.3, 16.9, 16.4; IR (neat) 3450 br, 2980, 2940, 1730, 1715, 1640, 1370, 1170, 1035, 990 cm^{-1}; m/e (FAB) 267 (M+K$^+$), 249 (M+K$^+$-H_2O), 231 (M+K$^+$-2H_2O), 221 (M+K$^+$-H_2O-CO), 205 (M+K$^+$-H_2O-CO_2), 193, 177.

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