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Graphical Abstract

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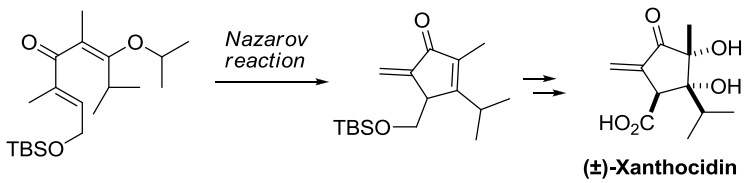

Total Synthesis of (±)-Xanthocidin using $FeCl_3$-Mediated Nazarov Reaction

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Abstract

The total synthesis of the antibiotic, (±)-xanthocidin (**1**), is described. The $FeCl_3$-promoted fast Nazarov reaction of the β-alkoxy divinyl ketone in the presence of *t*-BuOH provided the α-*exo*-methylene cyclopentenone, which is the core skeleton of this natural product. After methoxymethyl (MOM) esterification and protection of the reactive *exo*-methylene unit with a phenylseleno group, dihydroxylation, followed by oxidation, gave xanthocidin MOM ester. Finally, this ester was converted into (±)-xanthocidin (**1**) under mild conditions.

1. Introduction

A number of cyclopentenoid antibiotics, such as methylenomycin A/B,[1,2,3] sarkomycin,[4,5] and pentenomycin,[6,7] have been found in *Streptomyces* strains. Xanthocidin (**1**), structurally one of the most functionalized cyclopentenoids, was isolated from *Streptomyces xanthocidicus* by Asahi and co-workers in 1966, in Yamanashi, Japan (Figure 1). The compound exhibited *in vitro* antibacterial activity not only against *Escherichia coli* and *Bacillus agri* but also against *Xanthomonas oryzae* (MIC: 30 μg/mL), a pathogen of bacterial leaf blight, which is still one of the most serious diseases of rice.[8] Although xanthocidin (**1**) shows good promise of becoming a lead compound in agrochemicals, this molecule is unstable under basic or acidic conditions. Furthermore, the original strain has lost its ability to biosynthesize xanthocidin (**1**). Thus, structural conversion studies would require its total synthesis for the development of new agrochemicals based on this antibiotic.

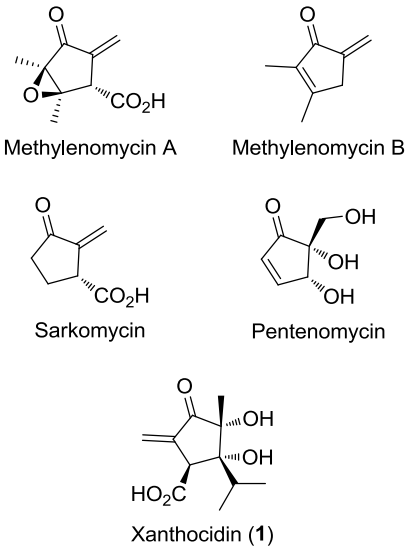
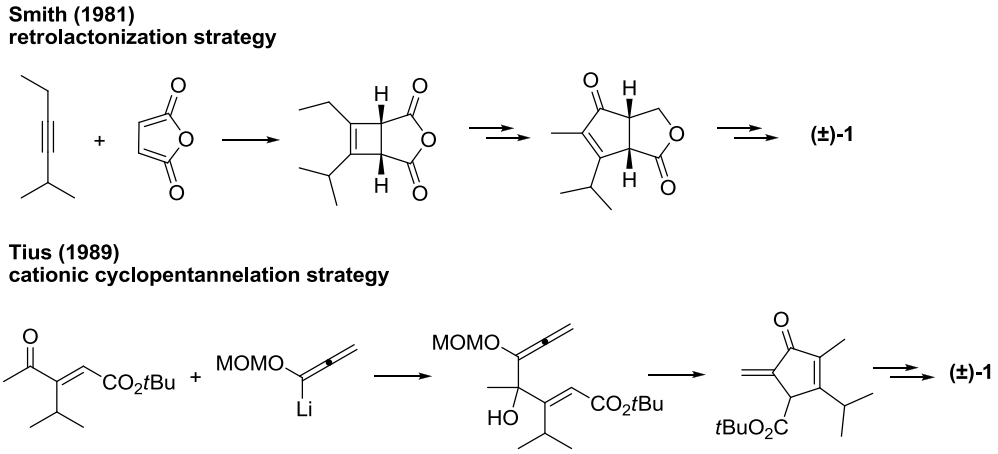


Figure 1 The cyclopentanoid antibiotics

Xanthocidin (**1**) has a highly oxidized five-membered ring, bearing contiguous *cis* vicinal diol, carboxylic acid, and conjugated *exo*-methylene group substituents. To date, Smith[9] and Tius[10] have reported syntheses of (±)-**1**[11] (Scheme 1), and Mori[12] has achieved the determination of its absolute configuration by the synthesis of non-racemic **1** using enzymatic resolution based on Smith's pioneering work. But there have been few reports on its bioactivity or structure activity relationship,[13] due to the limited supply of the compound. Herein we report the total synthesis of (±)-**1**, via our modified fast Nazarov reaction for the construction of the cyclopentenone core as the key step.

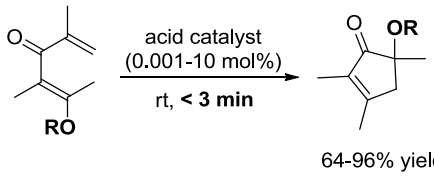


Scheme 1 Summary of syntheses by Smith and Tius

2. Results and discussion

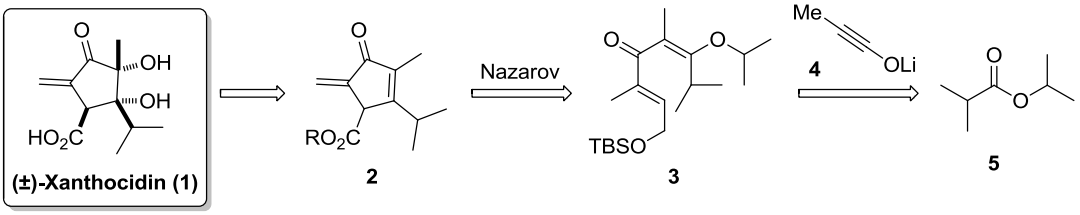
2.1. Synthetic strategy

We previously reported the acid-catalyzed fast Nazarov reaction using β-alkoxy divinyl ketones derived from torquoselective olefination via ynolates.[14] This electrocyclic reaction provides sterically congested multi-substituted cyclopentenones in good yield with high regioselectivity (Scheme 2).[15] More recently, we developed a new method for the generation of α-*exo*-methylene cyclopentadienones using the $FeCl_3$-mediated Nazarov reaction.[16]



Scheme 2 Acid-catalyzed fast Nazarov reaction of β-alkoxy divinyl ketones

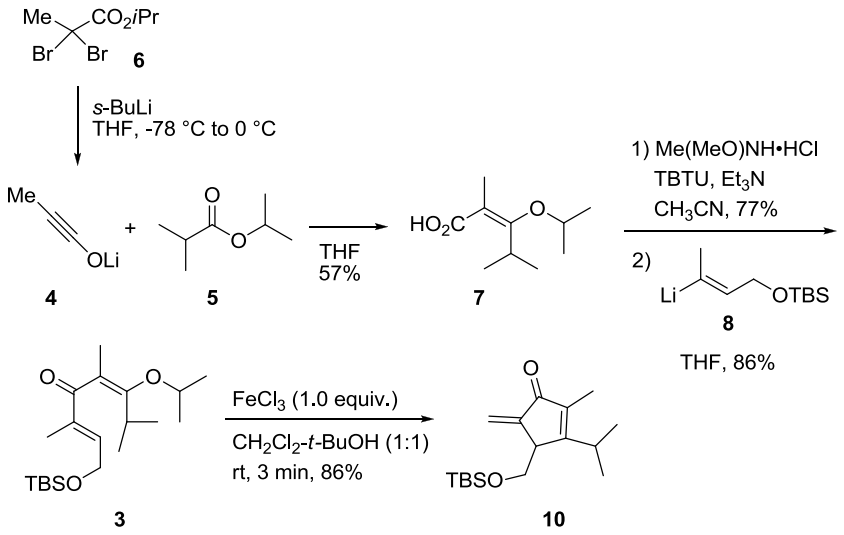
Our retrosynthetic analysis of (±)-xanthocidin (**1**) is illustrated in Scheme 3. (±)-Xanthocidin (**1)** would be prepared from the α-*exo*-methylene cyclopentadienone **2** bearing the requisite carbon skeleton. The cyclopentadienone **2** would be constructed by our modified Nazarov reaction, and its precursor, the β-alkoxy divinyl ketone **3**, would be prepared via the torquoselective olefination of the ester **5** with the ynolate **4**.



Scheme 3 Retrosynthetic strategy of (±)-**1**

2.2. Nazarov reaction[17]

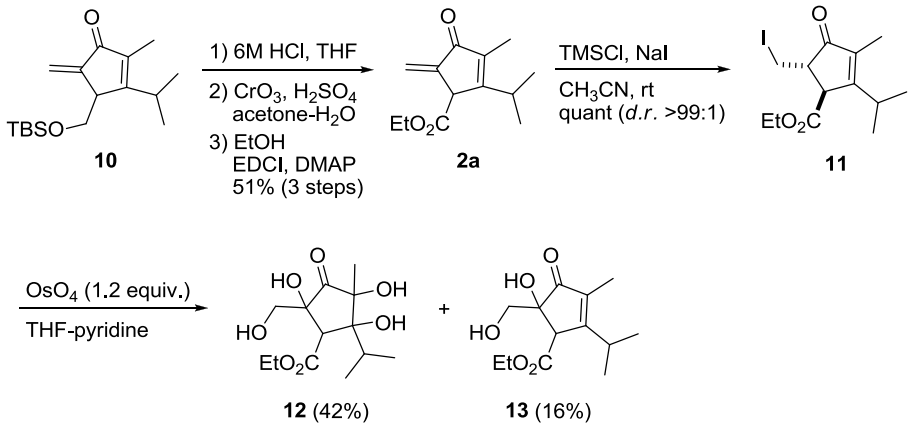
First, we attempted the preparation of the cyclopentadienone core intermediate (**10**) as shown in Scheme 4. The commercially available isobutyric acid isopropyl ester (**5**) reacted with the ynolate **4**,[18] prepared from the α,α-dibromo ester **6** and *s*-BuLi, at room temperature to give the tetrasubstituted olefin **7** with excellent *E*-selectivity.[19] The carboxylic acid in **7** was converted into the Weinreb amide,[20] followed by alkenylation with the alkenyllithium **8**,[21] prepared from the corresponding bromide and *t*-BuLi, to afford the β-alkoxy divinyl ketone **3** in 86% yield. We then tried the modified Nazarov reaction of the divinyl ketone **3** by treatment of 1.0 equivalent of $FeCl_3$ in CH_2Cl_2/*t*-BuOH (1:1) at room temperature, which smoothly gave the desired cyclization followed by β-elimination, to provide the α-*exo*-methylene cyclopentadienone **10** in 86% yield.



Scheme 4 Preparation of the cyclopentenone core (**10**) via the Nazarov reaction

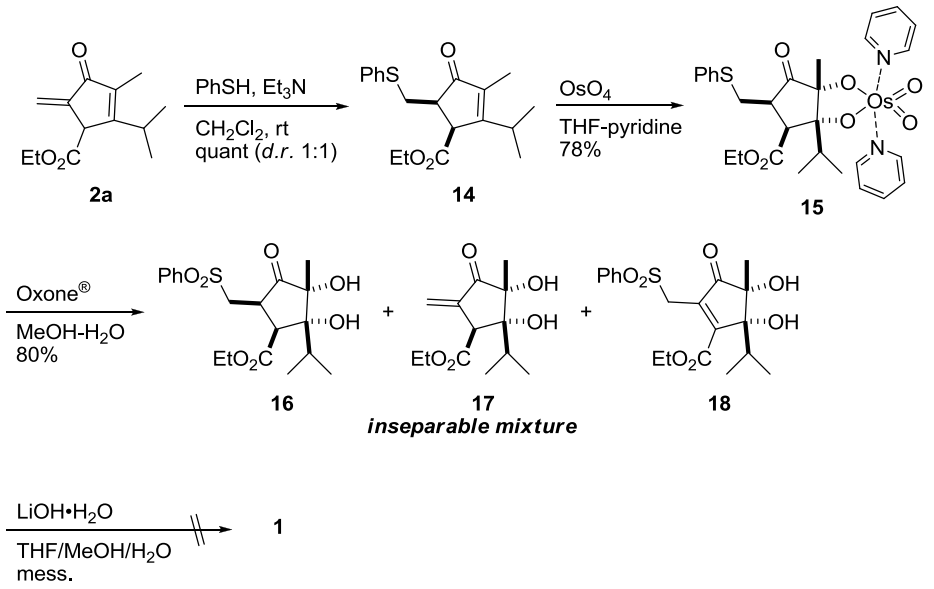
2.3. Total synthesis

With the core skeleton in hand, we next set out to synthesize (±)-xanthocidin (**1**). In order to achieve a total synthesis, the regioselective dihydroxylation of the *endo*-olefin first had to be considered. Accordingly, protection of the more reactive *exo*-methylene group by conversion to β-iodoketone was attempted, as in Tius' synthesis (Scheme 5). Desilylation of **10**, Jones oxidation, and esterification gave the ethyl ester **2a**, which was treated with TMSI, prepared by the *in situ* reaction of TMSCl and NaI in acetonitrile, to afford the *trans*-β-iodoketone **11** as a single isomer, because the initial product would be isomerized to the *trans*-product at room temperature, while Tius obtained the *cis*-product preferentially under kinetically controlled reaction conditions. The *endo*-olefin of **11** was subjected to dihydroxylation with OsO_4 resulting in formation of **12** and **13** *via* an undesired oxidation of the "protected" *exo*-methylene unit, probably due to the elimination of hydroiodic acid by the pyridine regenerating the *exo*-methylene *in situ*.



Scheme 5

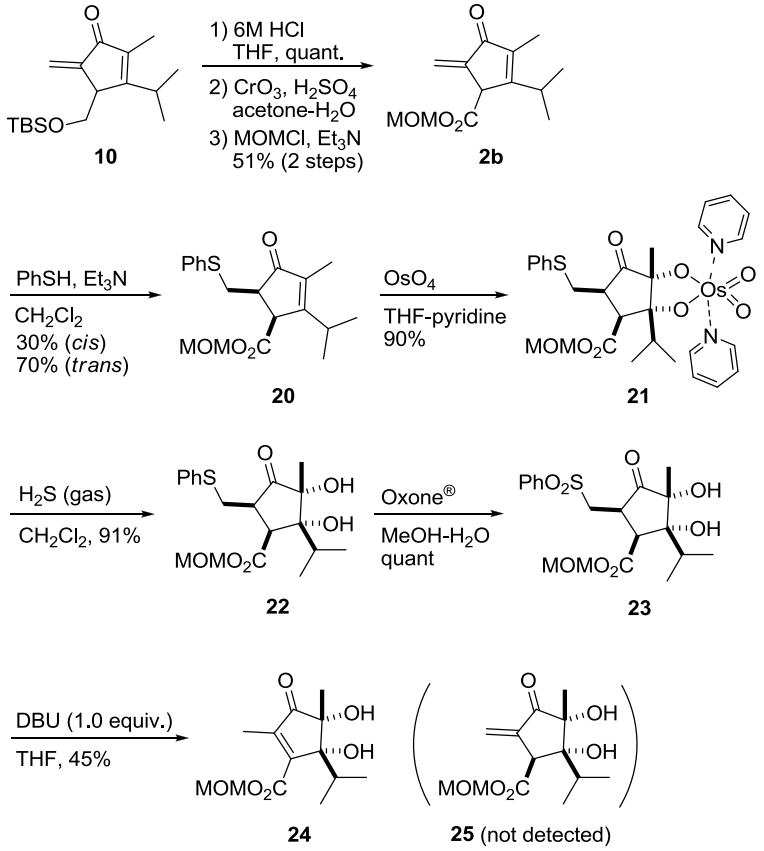
We next tried a phenylthio group as a more stable protecting group of the α-*exo*-methylene unit (Scheme 6). Conjugate addition of thiophenol to the enone **2a** was carried out to give the β-phenyl thioketone **14** as a 1:1 diastereomeric mixture. After separation of these isomers, the *cis*-isomer was *syn*-dihydroxylated with OsO_4 in THF/pyridine to afford the stable osmate-pyridine complex **15** with the desired stereochemistry. Oxidative deosmylation of **15** was performed with Oxone® in MeOH/H_2O to give an inseparable mixture containing the sulfone **16**, the sulfone-removed *exo*-methylene compound **17**, and the *endo*-olefin **18**, which would be generated by dehydrogenation of **16**. The mixture was subjected to the basic hydrolysis of the ethyl ester moiety, but a complex mixture was obtained. From these results, it can be concluded that the phenylthio group is a suitable protecting group for the *exo*-methylene, but xanthocidin (**1**) and its precursor ester are highly labile under basic conditions. To achieve the synthesis of **1**, the final conversion of the ester to carboxylic acid must be carried out under neutral or mild acidic conditions.



Scheme 6

In the Tius synthesis, the *tert*-butyl ester, the protecting group of the carboxylic acid, was deprotected by treatment of TBSOTf, followed by HCl in moderate yield. We chose the MOM ester, which was expected to be cleanly and conveniently deprotected under mild conditions (Scheme 7). The MOM ester **2b** was prepared in three steps from **10** in a manner similar to that described above. Conjugate addition of thiophenol to **2b** afforded the β-thioketone in a *cis/trans* ratio of 3:7. After separation, the *cis*-isomer **20** was oxidized with OsO_4 to afford the osmate complex **21** in good yield with high stereoselectivity. To avoid basic conditions in the following steps, deosmylation was

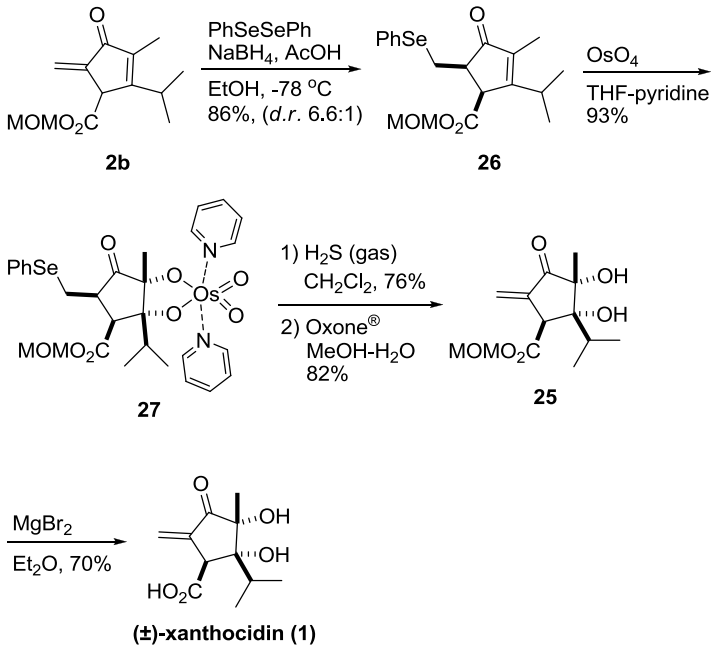
performed with H_2S gas,[22] prepared *in situ* from sodium hydrosulfide and aq. HCl, to furnish the diol **22** in excellent yield without any isomerization. The sulfide was oxidized by Oxone® to give quantitatively the sulfone **23**, which was subjected to the sulfone elimination under neutral conditions, but it did not proceed. When the sulfone **23** was treated with DBU, the *endo*-olefin product **24** was obtained. The desired *exo*-methylene cyclopentenone **25** would be generated initially, but spontaneously isomerized into **24** via deprotonation of the acidic proton at the α-position of the MOM ester by base.



Scheme 7

We then decided to select a phenylseleno (PhSe-) group for the protection of the α-*exo*-methylene group of **2b**, because it can be deprotected by oxidative elimination without using base (Scheme 8). Benzeneselenol, generated *in situ* from the reaction of diphenyl diselenide with $NaBH_4$,[23] was treated with **2b** at -78 °C to give the phenylselenide **26** as a 6.6:1 mixture of *cis*/*trans* diastereomers. After separation of the diastereomers by silica gel column chromatography, the major *cis*-isomer was subjected to diastereoselective *syn*-dihydroxylation with OsO_4 to afford the stable bis-pyridinium osmate **27** as a brown amorphous mass. Deosmylation of **27** was accomplished by reduction with hydrogen sulfide gas to afford the diol in 76% yield. Final deprotection leading to the synthesis of

(±)-xanthocidin (**1**) was achieved in two steps as follows: When the phenylselenide was treated with Oxone® in MeOH-H_2O, oxidative *syn*-elimination proceeded smoothly to regenerate the α-*exo*-methylene function. Investigation of the stereochemistry of the MOM ester **25** by NOE experiments revealed the desired *trans*-relationship between the MOM ester and the diol as shown in Figure 2. Finally, deprotection of the MOM ester **25** with $MgBr_2$ in Et_2O successfully afforded (±)-xanthocidin (**1**) as an oil.[24] Although this synthetic product was not stable enough to purify completely, the spectral properties of the synthetic **1** were identical in all respects to the values reported by Tius.[6b]



Scheme 8 Total synthesis of (±)-xanthocidin (**1**)

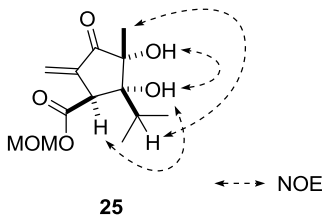


Figure 2 NOE experiments of MOM ester **25**

3. Conclusion

In summary, we have completed the total synthesis of (±)-xanthocidin (**1**) using the $FeCl_3$-mediated Nazarov reaction and the highly *E*-selective torquoselective olefination via the ynolate **4** as the key reaction steps.

4. Experimental

4.1. General Procedure

Reactions were monitored by thin-layer chromatography (TLC) carried out on precoated plates (0.25 mm, silica gel Merck Kieselgel 60 F_{254}) using UV light as the visualizing agent and an ethanolic solution of *p*-anisaldehyde, acetic acid, sulfuric acid, and heat as developing agents. Column chromatography was performed on silica gel (Kanto Chemical Co., Inc.). Commercial reagents and solvents were analytical grade or were purified by standard procedures, prior to use. *tert*-Butyllithium and *sec*-butyllithium, purchased from Kanto Chemical Co., Inc., were titrated with diphenylacetic acid. The α,α-dibromoester was prepared according to the literature reference.[25] Anhydrous dichloromethane (CH_2Cl_2), diethyl ether (Et_2O) and THF were purchased from Kanto Chemical Co., Inc. ^{1}H NMR, and ^{13}C NMR were measured in a $CDCl_3$ solution using a JEOL JNM-ECA600 spectrometer (^{1}H NMR at 600 MHz, ^{13}C NMR at 150 MHz) or a JEOL JNM-ECA400 (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) spectrometer using the normal standards (^{1}H NMR at 0.00 ppm (TMS), ^{13}C NMR at 77.0 ppm ($CDCl_3$)). Chemical shifts are reported in ppm (from TMS). When peak multiplicities are reported, the following abbreviations are used: s = singlet; d = doublet; t = triplet; q = quartet, m = multiplet, quin = quintuplet, sext = sextet, sept = septet, br = broad. IR spectra were recorded on Shimazu FTIP-8300 spectrometers. Mass spectra and high-resolution mass spectra were obtained on JMS-K9, Mstation JEOL JMS-700, or LCMS-2010EV mass spectrometers. Elemental analyses were performed with a Yanaco MT-5, MT-6 CHN-Corder.

4.2. Procedure

4.2.1. (*E*)-3-Isopropoxy-2,4-dimethyl-2-pentenoic acid (**7**). To a solution of isopropyl 2,2-dibromopropionate (7.76 g, 28.3 mmol) in 120 mL of dry THF, cooled to -78 °C under argon, was added dropwise a solution of *sec*-butyllithium (110 mL, 113.3 mmol in *n*-hexane/cyclohexane (1.03 M)). The yellow solution was stirred for 1 h at -78 °C and allowed to warm to 0 °C. After 30 min, the resulting reaction mixture was allowed to warm to room temperature, and a solution of isopropyl isobutyrate (2.46 g, 18.9 mmol) in dry THF (20 mL) was added dropwise. After 2 h, H_2O and hexane were added, and the mixture was extracted with 1M NaOH aq. The aqueous layer was acidified with a 3M HCl solution, followed by extraction with CH_2Cl_2. The organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo* to afford a crude carboxylic acid, which was purified by column chromatography over silica gel (20% EtOAc/Hex) to give **7** (1.99 g, 57% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.13 (d, *J* = 7.2 Hz, 6H), 1.26 (d, *J* = 6.0 Hz, 6H), 1.87 (s, 3H), 3.76 (sept, *J* = 7.2 Hz, 1H), 4.49 (sept, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 20.3, 22.6, 31.2, 73.2, 110.4, 174.0, 175.9; IR (neat) 2978, 1674,

1593, 1288, 1132, 1071, 472 cm^{-1}. MS (FAB) *m/z* 187 (M^++H); HRMS (FAB) *m/z* calcd for $C_{10}H_{19}O_3$ (M^++H): 187.1334. found: 187.1329.

4.2.2. (2*E*,5*E*)-1-*tert*-Butyldimethylsilyloxy-6-isopropoxy-3,5,7-trimethyl-2,5-octadien-4-one (**3**). To a solution of the carboxylic acid **7** (2.99 g, 16.0 mmol) in 64 mL of CH_3CN was added triethylamine (5.8 mL, 41.7 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (2.82 g, 28.9 mmol) at room temperature and the mixture was stirred for 30 min. To the stirred solution, *O*-benzotriazolyl-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TBTU, 9.27 g, 28.9 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, brine was added and the mixture was extracted with EtOAc. The organic extracts were washed with aqueous 1 M HCl, H_2O, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in *vacuo* to afford a crude residue, which was purified by column chromatography over silica gel (20~30% EtOAc/Hex) to give the Weinreb amide as a colorless oil (2.82 g, 77 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.11 (d, *J* = 7.2 Hz, 6H), 1.26 (d, *J* = 6.4 Hz, 6H), 1.82 (s, 3H), 2.59 (sept, *J* = 7.2 Hz, 1H), 3.23 (s, 3H), 3.68 (bs, 3H), 4.33 (sept, *J* = 6.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.2, 20.5, 22.4, 31.7, 60.8, 71.9, 113.6, 156.8; IR (neat) 2972, 1645, 1371, 1111, 1067, 486.1 cm^{-1}; MS (FAB) *m/z* 230 (M^++H); HRMS (FAB) *m/z* calcd for $C_{12}H_{24}NO_3$ (M^++H): 230.1756. found: 230.1750.

To a solution of 2-bromo-4-*tert*-butyldimethylsiloxy-2-butene (4.66 g, 17.56 mmol) in 40 mL of dry THF, cooled to -78 °C under argon, was added dropwise a solution of *tert*-butyllithium (23.4 mL, 35.1 mmol in *n*-pentane (1.50 M)). The mixture was stirred for 10 min, then allowed to warm to 0 °C. After 20 min, the mixture was cooled to -78 °C. A solution of the Weinreb amide (1.68 g, 7.32 mmol) in 20 mL of dry THF was added dropwise, and after 10 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc and the organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude divinyl ketone, which was quickly purified by column chromatography over silica gel (5% EtOAc/Hex) to give **3** (2.23 g, 86% yield) as a yellow oil. Due to its instability, the product was immediately subjected to the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.03 (d, *J* = 6.8 Hz, 6H), 1.28 (d, *J* = 6.0 Hz, 6H), 1.78 (m, 3H), 1.80 (m, 3H), 2.39 (sept, *J* = 6.8 Hz, 1H), 4.37 (sept, *J* = 6.0 Hz, 1H), 4.40 (dd, *J* = 1.2 Hz, 6.8 Hz, 2H), 6.55 (dt, *J* = 1.2 Hz, 6.8 Hz, 1H).

4.2.3. 4-((*tert*-Butyldimethylsilyloxy)methyl)-3-isopropyl-2-methyl-5-methylene-2-cyclopentenone (**10**). To a solution of **3** (1 g, 2.82 mmol) in 14 mL of CH_2Cl_2/*t*-BuOH (1:1) under argon was added anhydrous $FeCl_3$ (457 mg, 2.82 mmol). The resulting mixture was stirred for 3 min at room temperature and quenched by addition of saturated aqueous $NaHCO_3$. The resulting mixture was filtered through a pad of Celite®. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine,

and dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude mixture, which was purified by column chromatography over silica gel (5% EtOAc/Hex) to give **10** (717.1 mg, 86% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: -0.01 (s, 3H), 0.01 (s, 3H), 0.84 (s, 9H), 1.20 (d, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 7.6 Hz, 3H), 1.83 (s, 3H), 2.98 (sept, *J* = 7.2 Hz, 1H), 3.36 (bs, 1H) 3.68 (dd, *J* = 6.0 Hz, 9.6 Hz, 1H), 3.94 (dd, *J* = 4.0 Hz, 10.2 Hz, 1H), 5.42 (d, *J* = 1.2 Hz, 1H), 6.04 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: -5.73, -5.59, 8.63, 18.1, 19.4, 20.7, 25.7, 29.4, 47.3, 64.2, 114.8, 138.6, 144.8, 172.1, 196.4; IR (neat) 2959, 2930, 2361, 1697, 1622, 1256, 1111, 837.1, 777.3, 486.1 cm^{-1}; MS (FAB) *m/z* 295 (M^++H); HRMS (FAB) *m/z* calcd for $C_{17}H_{31}O_2Si$ (M^++H):295.2093. found: 295.2091.

4.2.4. Methoxymethyl 2-isopropyl-3-methyl-5-methylene-4-oxo-2-cyclopentenecarboxylate (**2b**). To a solution of **10** (717.1 mg, 2.43 mmol) in 11 mL of THF under nitrogen was added dropwise 6 M HCl (3.25 mL, 19.5 mmol). The resulting mixture was stirred for 1 h at room temperature, and quenched by addition of saturated aqueous $NaHCO_3$. The resulting mixture was extracted with $CHCl_3$. The organic extracts were washed with brine, and dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude residue, which was purified by column chromatography over silica gel (7% MeOH/$CHCl_3$) to give the alcohol (438.8 mg, quant) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (d, *J* = 7.2 Hz, 3H), 1.26 (d, *J* = 7.2 Hz, 3H), 1.39 (t, *J* = 6.4 Hz, 1H), 1.86 (s, 3H), 3.00 (sept, *J* = 7.2 Hz, 1H), 3.44 (bs, 1H), 3.74-3.80 (m, 1H), 4.04-4.09 (m, 1H), 5.47 (s, 1H), 6.13 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.27, 19.0, 20.3, 29.1, 47.0, 62.9, 115.3, 138.2, 143.8, 173.1, 196.5; IR (neat) 3445, 2932, 2876, 1682, 1616, 1323, 1051, 802.4 cm^{-1}; MS (FAB) *m/z* 181 (M^++H); HRMS (FAB) *m/z* calcd for $C_{11}H_{17}O_2$ (M^++H):181.1229. found: 181.1226.
A solution of the alcohol (500 mg, 2.77 mmol) in 18.5 mL of acetone was treated at 0 °C with freshly prepared Jones reagent (1.94 M) until a persistent orange color was observed. The progress of the reaction was also monitored by thin layer chromatography. After nearly 2 h, 2-propanol was added, and after addition of H_2O, the dark green solution was extracted with $CHCl_3$. The organic extracts were washed with brine, and dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude carboxylic acid. To a solution of the carboxylic acid (542 mg) in 28 mL of dry CH_2Cl_2 cooled to 0 °C under nitrogen were successively added triethylamine (1.17 mL, 8.37 mmol) and MOMCl (636 μL, 8.37 mmol), and the mixture was allowed to warm to room temperature. The resulting mixture was stirred for 2 h, and quenched by addition of H_2O. The mixture was extracted with CH_2Cl_2 and the organic extracts were washed with brine, and dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude residue, which was purified by column chromatography over silica gel (10% EtOAc/Hexane) to give **2b** (336.2 mg, 51% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (d, *J* = 7.6 Hz, 3H), 1.21 (d, *J* = 7.6 Hz, 3H), 1.90 (s, 3H), 3.05 (sept, *J* = 7.6 Hz, 1H), 3.43 (s, 3H), 4.24 (bs, 1H), 5.19 (d, *J* = 5.6 Hz, 1H), 5.28 (d, *J* = 6.4 Hz, 1H), 5.54 (s, 1H),

6.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.71, 19.9, 20.1, 29.5, 49.8, 57.8, 91.0, 116.3, 140.0, 141.1, 168.6, 170.5, 194.7; IR (neat) 2966, 1740, 1697, 1622, 1319, 1138, 1092, 962.5, 929.7, 480.3 cm^{-1}; MS (FAB) *m/z* 239 (M^++H); HRMS (FAB) *m/z* calcd for $C_{13}H_{19}O_4$ (M^++H): 239.1283, found: 239.1283.

4.2.5. Methoxymethyl 2-isopropyl-3-methyl-4-oxo-5-(phenylselenylmethyl)-2-cyclopentene carboxylate (**26**). To a stirred solution of diphenyl diselenide (475 mg, 1.52 mmol) in EtOH (20 mL), was added sodium borohydride (115 mg, 3.04 mmol) at 0 °C under argon. When the solution became colorless and clear (in ca. 5 min), the solution of sodium benzeneselenolate obtained was cooled to -78 °C, then glacial acetic acid (308 μL, 5.38 mmol) was added. After 5 min, a solution of **2b** in THF (10 mL) was added and the resulting mixture was stirred at -78 °C. After 1 h, the reaction was quenched with H_2O. The mixture was extracted with Et_2O and the organic extracts were washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude selenide, which was purified by column chromatography over silica gel (10%~20% EtOAc/Hexane) to give a separable diastereomeric mixture of **26** (*cis*-form, 688.7 mg, *trans*-form 104.6 mg, 86% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.10 (d, *J* = 6.8 Hz, 3H), 1.20 (d, *J* = 7.2 Hz, 3H), 2.70-2.76 (m, 1H), 2.79 (q, *J* = 11.6 Hz, 1H), 3.01 (sept, *J* = 6.8 Hz, 1H), 3.51 (s, 3H), 3.58 (dd, *J* = 4.0 Hz, 16 Hz, 1H), 3.99 (d, *J* = 6.0 Hz, 1H), 5.20 (d, *J* = 5.6 Hz, 1H), 5.28 (d, *J* = 6.4 Hz, 1H), 7.26-7.27 (m, 3H), 7.51-7.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.50, 19.7, 20.2, 23.5, 29.6, 49.3, 49.7, 58.1, 91.5, 127.1, 129.08, 129.13, 132.6, 137.0, 171.0, 171.1, 206.3; IR (neat) 2967, 1740, 1705, 1331, 1140, 1090, 924.0, 738.8, 480.3 cm^{-1}; MS (FAB) *m/z* 396 (M^+); HRMS (FAB) *m/z* calcd for $C_{19}H_{24}O_4Se$ (M^+): 396.0840, found: 396.0839.

4.2.6. Osmate bis(pyridino) complex (**27**). To a solution of **26** (30 mg, 0.076 mmol) in 0.7 mL of THF under argon was added OsO_4 (29 mg, 0.114 mmol) and pyridine (0.7 mL) in one portion. The resulting mixture was stirred for 1.5 h at room temperature, and quenched by addition of saturated aqueous sodium bisulfate. The resulting mixture was stirred for 15 min, and the mixture was extracted with $CHCl_3$. The organic extracts were washed with brine, and dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude osmate, which was purified by column chromatography over silica gel (3% MeOH/$CHCl_3$) to give **27** (57.4 mg, 93% yield) as a brownish black amorphous mass. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (d, *J* = 6.0 Hz, 3H), 1.34 (d, *J* = 6.4 Hz, 3H), 1.89 (s, 3H), 2.50 (sept, *J* = 6.8 Hz, 1H), 2.74 (dd, *J* = 11.2 Hz, 12.0 Hz, 1H), 3.48 (s, 3H), 3.48-3.54 (m, 1H), 3.61(dd, *J* = 4.8 Hz, 12.2 Hz, 1H), 3.91 (d, *J* = 8.0 Hz, 1H), 5.09 (d, *J* = 6.0 Hz, 1H), 5.29 (d, *J* = 6.0 Hz, 1H), 7.10-7.20 (m, 2H), 7.20-7.30 (m, 1H), 7.40-7.46 (m, 6H), 7.77-7.95 (m, 2H), 8.71 (bs, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.9, 19.6, 20.7, 23.2, 34.4, 50.2, 55.7, 57.9, 76.8, 90.6, 97.2, 98.0, 125.2, 126.5, 128.8, 130.0, 132.1, 140.5, 149.2, 172.6, 216.7; IR (neat) 2942,

1746, 1451, 1088, 941.3, 835.2, 692.5, 486.1 cm^{-1}; MS (FAB) *m/z* 808 (M^+); HRMS (FAB) *m/z* calcd for $C_{29}H_{34}O_8N_2OsSe$ (M^+): 810.1095, found: 808.1094. ($C_{29}H_{34}O_8N_2$ $^{80}Os^{190}Se$, $C_{29}H_{34}O_8N_2$ $^{78}Os^{192}Se$).

4.2.7. Methoxymethyl 2,3-dihydroxy-2-isopropyl-3-methyl-5-methylene-4-oxocyclopentane carboxylate (**25**). Hydrogen sulfide was bubbled through a solution of **27** (57.4 mg, 0.071 mmol) in 10 mL CH_2Cl_2 for 10 min. A black precipitate settled out, 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 the crude diol, which was quickly purified by column chromatography over silica gel (2% MeOH/$CHCl_3$) to give the diol (23.2 mg, 76% yield) as a colorless oil. Due to its instability, this product was immediately subjected to the next reaction. To a solution of the diol (23.2 mg, 0.054 mmol) in 1 mL of MeOH/H_2O (1:1), under nitrogen, was added oxone® (199.3 mg, 0.324 mmol). The resulting mixture was stirred at room temperature. After 15 min, the reaction was quenched with H_2O, and extracted with CH_3Cl. The organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude residue, which was purified by column chromatography over silica gel (2% MeOH/$CHCl_3$) to give **25** (12.0 mg, 82% yield) as a yellowish white amorphous mass. ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.0 Hz, 3H), 1.50 (s, 3H), 2.42 (sept, *J* = 6.8 Hz, 1H), 3.00 (s, 1H), 3.12 (s, 1H), 3.51 (s, 3H), 3.86 (s, 1H), 5.29 (dd, *J* = 6.4 Hz, 10.4 Hz, 2H), 5.79 (s, 1H), 6.43 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.4, 16.8, 20.3, 28.8, 53.8, 58.0, 80.9, 81.9, 91.0, 124.8, 139.4, 170.3, 206.5 ; IR (neat) 3476, 3431, 2949, 1746, 1728, 1456, 1331, 1094, 1017 cm^{-1}; MS (FAB) *m/z* 273 (M^++H); HRMS (FAB) *m/z* calcd for $C_{13}H_{21}O_6$ (M^++H): 273.1338, found: 273.1331.

4.2.8. (±)-Xanthocidin (**1**). To a solution of **25** (5.0 mg, 0.018 mmol) in 0.72 mL of Et_2O under argon was added $MgBr_2$ (27 mg, 0.147 mmol). The resulting mixture was stirred at room temperature. After 30 min, the reaction was quenched with a few drops of H_2O. Then the resulting mixture was acidified with 10% HCl, saturated with sodium chloride and extracted with Et_2O. The organic extract was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude residue, which was purified by column chromatography over silica gel ($CHCl_3$ to 7% MeOH/$CHCl_3$) to give (±)-xanthocidin **(1)** (2.9 mg, 70% yield) as a yellowish white oily solid. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.02 (d, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 7.2 Hz, 3H), 1.48 (s, 3H), 2.43 (sept, *J* = 6.6 Hz, 1H), 3.02-3.18 (brm, 2H), 3.87 (t, *J* = 2.4 Hz, 1H), 5.84 (d, *J* = 2.4 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 16.5, 16.9, 20.4, 29.0, 53.2, 80.9, 81.9, 125.3, 139.1, 173.8, 206.4; IR (neat) 3418, 2963, 2926, 1732, 1715, 1651, 1456, 1377, 1269, 1125, 1028 cm^{-1};MS (ESI) *m/z* 251 (M^++Na).

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