Stereocontrolled Total Synthesis of (±)-Xanthocidin, Two Diastereomers, (±)-Epixanthocidin and (±)-β-Isoxanthocidin, and (±)-Desdihydroxy-4,5-didehydroxanthocidin, a Likely Biosynthetic Precursor

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We record here the *first* total synthesis of the cyclopentanoid antibiotic (±)-xanthocidin (**8**), two of the three possible diastereomers, which we term (±)-epixanthocidin (**9**) and (±)-β-isoxanthocidin (**10**), and desdihydroxy-4,5-didehydroxanthocidin (**11**), a probable biosynthetic precursor of xanthocidin. All four compounds were prepared from a common intermediate, bicyclic enone **13**. In each case the ultimate transformation was retrolactonization of the corresponding γ-lactone employing 2-(trimethylsilyl)ethanol/acetyl chloride.

Introduction and Background

In recent years a major focus of this laboratory has been the total synthesis, in stereocontrolled fashion, of a group of antibiotics known as the cyclopentanoid class. This effort included the synthesis of (±)-methylenomycin A (**1a**, Chart I),[2] its epimer (**1b**),[2] (±)-desepoxy-4,5-didehydromethylenomycin A (**2**),[3] (±)-sarkomycin (**3**),[4] the pentenomycins I–III (**4a–c**),[5] their epimers (**5a–c**),[5] dehydropentenomycin I (**6**),[5] and (+)-kjellmanianone (**7**).[6] In this, a full account, we record the details of the *first* total synthesis of the closely related cyclopentanoid antibiotic, xanthocidin (**8**, Chart II),[7] as well as two of the three

Chart I

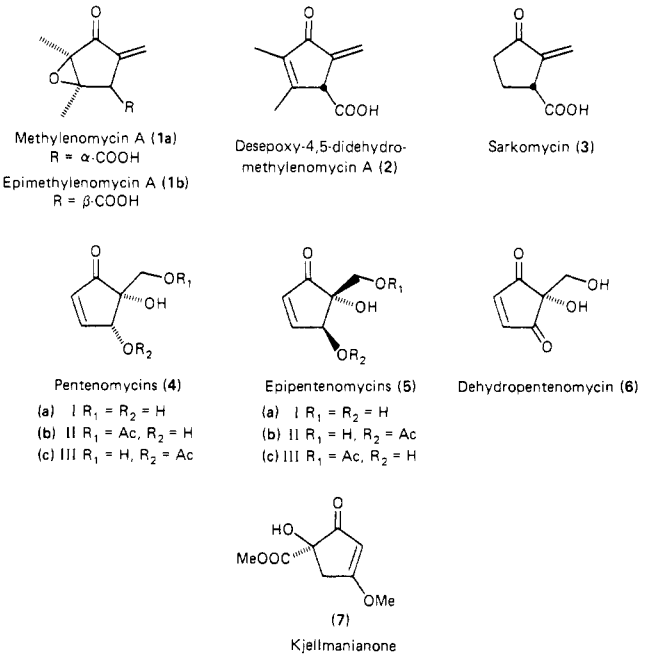
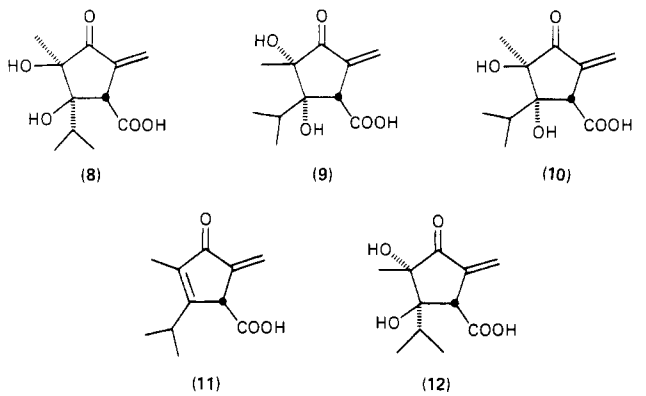


Chart II



(1) Camille and Henry Dreyfus Teacher–Scholar, 1978–1983; recipient of a National Institutes of Health (National Cancer Institute) Career Development Award, 1980–1985.

(2) (a) Haneishi, T.; Kitahara, N.; Takiguchi, Y.; Arai, M.; Sugawara, S. *J. Antibiot.* **1974**, *27*, 386. Haneishi, T.; Terahara, A.; Arai, M.; Hata, T.; Tamura, C. *Ibid.* **1974**, *27*, 393. (b) Haneishi, T.; Terahara, A.; Hamano, K.; Arai, M. *Ibid.* **1974**, *27*, 400. (c) For synthetic approaches to methylenomycin A see: Scarborough, R. M.; Smith, A. B., III *J. Am. Chem. Soc.* **1977**, *99*, 7085. Jernow, J.; Tautz, W.; Rosen, P.; Blount, J. *J. Org. Chem.* **1979**, *44*, 4210. Koreeda, M.; Liang Chen, Y. P.; Akagi, H., presented at the 178th National Meeting of the American Chemical Society, Washington, D.C., 1979. Scarborough, R. M., Jr.; Smith, A. B., III *J. Am. Chem. Soc.* **1980**, *102*, 3904. Takahashi, Y.; Isoke, K.; Hagiwara, H.; Kosugi, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1981**, 714.

(3) (a) Hornemann, U.; Hopwood, D. A. *Tetrahedron Lett.* **1978**, 2977; (b) For synthetic approaches to 4,5-desepoxy-4,5-didehydromethylenomycin A, see: Boschelli, D.; Scarborough, R. M., Jr.; Smith, A. B., III *Tetrahedron Lett.* **1981**, *22*, 19. Koreeda, M.; Liang Chen, Y.-P. *Ibid.* **1981**, *22*, 15.

(4) (a) Umezawa, H.; Takeu, T.; Nitta, K.; Yamamoto, T.; Yamaoka, S. *J. Antibiot., Ser. A.* **1953**, *6*, 101. Umezawa, H.; Takeuchi, T.; Nitta, K.; Okami, Y.; Yamamoto, Y.; Yamaoka, S. *Ibid.* **1953**, *6*, 153. Umezawa, H.; Yamamoto, T.; Yakeuchi, T.; Osato, T.; Okami, Y.; Yamaoka, S.; Okuda, T.; Nitta, K.; Yagishita, K.; Utahara, R.; Umezawa, S. *Antibiot. Chemother. (Washington, D.C.)* **1954**, *4*, 514 and references cited therein. (b) For synthetic approaches to Sarkomycin, see: Toki, K. *Bull. Chem. Soc. Jpn.* **1956**, *30*, 450. Toki, K. *Ibid.* **1958**, *31*, 333. Shemyakin, M. M.; Ravdel, G. A.; Chaman, Y. S.; Shvetsov, Y.; Vinogradova, T. J. *Chem. Ind. (London)* **1957**, *1320*. Marx, J. N.; Minaskanian, G. *Tetrahedron Lett.* **1980**, *21*, 4175. Boeckman, R. K., Jr.; Naegely, P. C.; Arthur, S. D. *J. Org. Chem.* **1980**, *45*, 752. Smith, A. B., III; Wexler, B., *J. Org. Chem.*, in press. Kobayashi, Y.; Tsuji, T. L. *Tetrahedron Lett.* **1981**, *22*, 4295.

(5) (a) Pentenomycin I–III: Umino, K.; Furumai, T.; Matsuzawa, N.; Awataguchi, Y.; Ito, Y.; Okuda, T. *J. Antibiot.* **1973**, *26*, 506; Umino, K.; Takeda, N.; Ito, Y.; Okuda, T. *Chem. Pharm. Bull.* **1974**, *22*, 1233. Data, T.; Aoe, K.; Kotera, K.; Umino, K. *Ibid.* **1974**, *22*, 1963. Shomura, T.; Hoshida, J.; Kondo, Y.; Watanabe, H.; Omoto, S.; Inouye, S.; Niida, T. *Kenkyu* Nempo **1976**, *16*, 1. Shomura, T.; et al. (Meiji Seka), Japanese Kokai, 19276-82, July 1976. Hatano, K.; Hasegawa, T.; Izawa, M.; Iwasaki, H. (Takeda Chemical Industries, Ltd.), Japanese Kokai 7570597, 1975; *Chem. Abstr.* **1976**, *84*, 3287. Hatano, K.; Izawa, M.; Hasegawa, T.; Tonida, S.; Asai, M.; Iwasaki, H.; Yamano, T. *J. Takeda Res. Lab.* **1979**, *38*, 22. (b) Dehydropentenomycin I: Noble, M.; Noble, D.; Fletton, R. A. *J. Antibiot.* **1978**, *31*, 15; (c) For synthetic approaches to pentenomycins I–III, their epimers, and dehydropentenomycin I, see: Branca, S. J.; Smith, A. B., III. *J. Am. Chem. Soc.* **1978**, *100*, 7767. Smith, A. B., III; Pilla, N. N. *Tetrahedron Lett.* **1980**, *21*, 4691. Smith, A. B., III; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855. (d) For an alternate synthesis of (−)-pentenomycin I, see: Verheyden, J. P. H.; Richardson, A. C.; Bhatt, R. S.; Grant, B. D.; Fitch, W. L.; Moffatt, J. G. *Pure Appl. Chem.* **1978**, *50*, 1363. Shono, T.; Matsumura, Y.; Yamane, S.; Suzuki, M. *Chem. Lett.* **1980**, 1619.

(6) (a) Nakayama, M.; Fukuoka, Y.; Nozaki, H.; Matsuo, A.; Hayashi, S. *Chem. Lett.* **1980**, 1243. For synthetic approaches to kjellmanianone see: Irie, H.; Katakawa, J.; Tomita, M.; Mizuno, Y. *Ibid.* **1981**, 637. Boschelli, D.; Smith, A. B., III; Stringer, O. D.; Jenkins, R. H., Jr.; Davis, F. A. *Tetrahedron Lett.* **1981**, *22*, 4385.

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possible diastereomers (9 and 10), and desdihydroxy-4,5-didehydroxanthocidin (11),[7] a possible (probable) biosynthetic precursor.

Xanthocidin (8), a *highly unstable* member of the cyclopentanoid class of antibiotics known to possess in vitro activity against *Escherichia coli* and *Stapholococcus aureus* 209P, was isolated in 1966 by Asahi et al. from *Streptomyces* sp. No. 51-4.[8] At that time chemical and spectral data permitted definition only of the carbon skeleton. Indeed, at the outset of this venture some 12 years later, the relative and absolute stereochemistry of xanthocidin remained undefined. In this regard we conjectured that of the four possible diastereomers for xanthocidin, structure 8 was most probable. We reasoned that as in the case of methylenomycin A (1a) wherein the desepoxy derivative (2) is known to serve as an advanced biosynthetic precursor,[3] desdihydroxy-4,5-didehydroxanthocidin (11) would be a likely precursor to xanthocidin. That is, in analogy with the epoxidation of desepoxy-4,5-didehydromethylenomycin A, cis hydroxylation of 11 trans to the carboxyl group would lead to xanthocidin (8) having the stereochemistry depicted. That this structural analysis proved correct was demonstrated in 1980 by the appearance of a single-crystal X-ray study.[9]

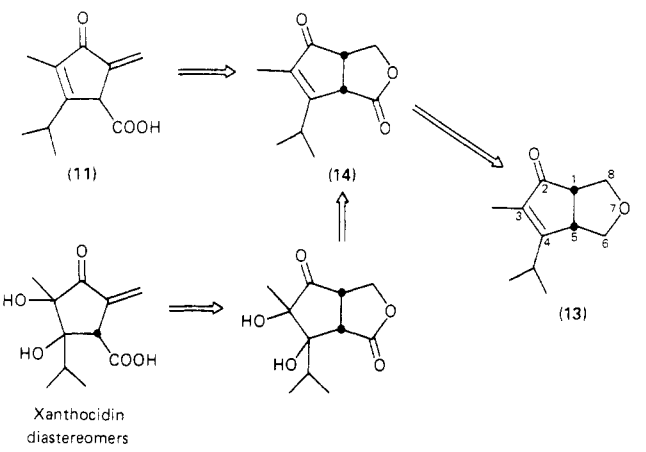
With the stereochemistry of xanthocidin defined, we termed the three related diastereomers epixanthocidin (9), β-isoxanthocidin (10), and α-isoxanthocidin (12).[10]

Our interest in xanthocidin as a synthetic target stemmed from its close structural similarity to methylenomycin A and sarkomycin, the former recently shown to be active against Lewis lung carcinoma in mice,[11a] the latter an antitumor agent used clinically in Russia and Japan.[11b] Furthermore, the opportunity to establish both the structure and relative stereochemistry of xanthocidin via total synthesis as well as devise an approach to desepoxy-4,5-didehydroxanthocidin, the probable biosynthetic precursor, was quite attractive.

Results and Discussion

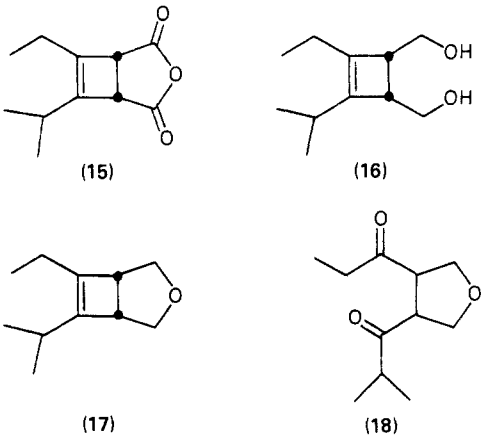
(i) A Common Synthetic Strategy for the Stereocontrolled Construction of the Xanthocidin Diastereomers. Armed only with the conjecture that stereostructure 8 was the principal synthetic target, our synthetic strategy, at least at the outset, had to be sufficiently versatile as to provide access to all four diastereomers of the xanthocidin skeleton as well as to the postulated biosynthetic precursor (11). The retrolactonization strategy employed to great advantage in the methylenomycin area[2] appeared ideal in this regard. Such a strategy here calls initially for construction of bicyclic ketone 13 (Scheme I), which in turn could serve as a *common* intermediate for desdihydroxy-4,5-didehydroxanthocidin as well as the xanthocidin diastereomers. For example, oxidation of the tetrahydrofuran ring of 13 at C(6) would

Scheme I



afford 14, which we have termed cyclodesdihydroxy-4,5-didehydroxanthocidin in analogy to the methylenomycin area.[2] Subsequent retrolactonization would then lead to desdihydroxy-4,5-didehydroxanthocidin (11). Alternatively, introduction of the vicinal hydroxyls in each of four possible relative configurations followed by oxidation at C(6) would lead to the diastereomers of cycloxanthocidin. Retrolactonization of each would in turn yield the diastereomers of xanthocidin. Central to this scenario, the concave–convex nature of enone 13 was anticipated to provide the geometric bias required to introduce the vicinal hydroxyl substituents in a stereocontrolled fashion. For the retrolactonization process, we planned to employ either the lithium thiomethoxide/HMPA[2] or 2-(trimethylsilyl)-ethanol/acetyl chloride[3] protocol developed previously in our laboratory.

(ii) Preparation of Common Intermediate 13: The Initial Synthetic Target. Our approach to bicyclic enone 13 parallels the earlier methylenomycin A work beginning with the preparation of cyclobutene 15. Irradiation of a



mixture of 2-methyl-3-hexyne (0.2 M) and maleic anhydride (0.15 M) in acetonitrile utilizing benzophenone (0.015 M) as a sensitizer afforded cyclobutene 15 in 58% yield as a light yellow solid (mp 60–61 °C).[12] This photochemical [2 + 2] cycloaddition was most conveniently carried out on a 30-g scale by employing the standard Hanovia 450-W mercury arc fitted with a Corex filter. Reduction of the anhydride functionality with 3 equiv of lithium aluminum hydride at the reflux point of tetrahydrofuran for 45 h gave diol 16, which in turn was

(7) For a preliminary account of this work see: Boschelli, D.; Smith, A. B., III *Tetrahedron Lett.* **1981**, *22*, 3733.

(8) Asahi, K.; Nagatsu, J.; Suzuki, S. *J. Antibiot.* **1966**, *A19*, 195. Asahi, K.; Suzuki, S. *Agric. Biol. Chem.* **1970**, *34*, 325.

(9) Asahi, K.; Sakurai, T.; Iimura, Y. *Agric. Biol. Chem.* **1980**, *44*, 2257.

(10) This nomenclature is based on retaining the configuration at the carbon bearing the carboxyl group. Epixanthocidin refers to that system wherein both the α and β centers are inverted. The Isoxanthocidins, in turn, are distinguished on the basis of inversion of either the α or β center, respectively.

(11) (a) Terahara, A.; Haneishi, T.; Arai, M. *Heterocycles* **1979**, 353. Also see ref 2. (b) Oboshi, S.; Aoki, K. *Chemother. (Tokyo)* **1956**, *4*, 91; *Chem. Abstr.* **1956**, *50*, 15939; Banyu Pharmaceutical Co., Ltd., Tokyo. Sung, S. C.; Quastel, J. H. *Cancer Res.* **1963**, *23*, 1549. Hooper, I. R.; Cheney, L. C.; Cron, M. J.; Fardig, O. B.; Johnson, D. A.; Johnson, D. L.; Palermiti, F. M.; Schmitz H.; Wheatley, W. B. *Antibiot. Chemother.* **1955**, *5*, 585. Also see ref 4.

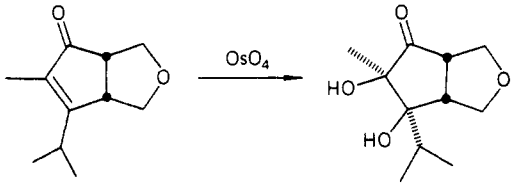
(12) For a recent review on the synthetic aspects of [2 + 2] photochemical cycloaddition to α,β-enones, see: Baldwin, S. W. In "Organic Photochemistry"; Padwa, A., Ed.; Marcel Dekker: New York, 1981; vol. 5, p 123.

transformed to tetrahydrofuran **17** via treatment with 1.1 equiv of *p*-toluenesulfonyl chloride in dry pyridine, first at 0 °C for 18 h and then at reflux for 2 h.[13] The yield for the two steps was 87%.[14]

To complete the preparation of **13**, cyclobutene **17** was subjected to ozonolysis in methanol at −78 °C followed by reduction of the ozonide with triphenylphosphine. Distillation afforded diketone **18** in 73% yield. Finally, intramolecular aldol condensation employing the conditions of McCurry and Singh[15] (2% NaOH/95% aqueous MeOH) led to a single cyclopentenone (**13**) in 74% yield after chromatography. The structure of **13** was secure based on its spectroscopic properties. In particular, the high-field (250 MHz) ^{1}H NMR spectrum revealed two doublets at δ 1.16 and 1.20 and a broad singlet at δ 1.72 indicative respectively of the vinyl isopropyl and methyl substituents, while the infrared spectrum displayed characteristic cyclopentenone absorptions[16] at 1695 (s) and 1635 (m) cm^{-1}. The overall yield of enone **13**, based on maleic anhydride, was 27%.

(iii) Cis Hydroxylation of Enone 13. With a viable approach to enone **13** secured, we turned to the introduction of the vicinal cis-hydroxyl substituents. Here we envisioned that osmium tetraoxide, a reagent known to approach from the least hindered side of a molecule,[17] would append the hydroxyls syn to the bridgehead hydrogens. The resultant stereochemistry would be that postulated (latter verified by X-ray analysis) for xanthocidin (**8**).

Toward this end, enone **13** was added to a solution of

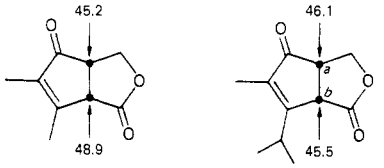


(13) (19)

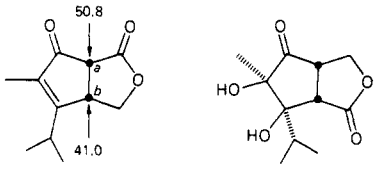
osmium tetraoxide in pyridine at 0 °C. After 4 h the osmate ester was cleaved via addition of aqueous sodium bisulfite.[18] Interestingly the osmate ester was extremely stable, requiring 19 h for hydrolysis. Workup and column chromatography gave a single crystalline diol (**19**, mp 75.0–76.0 °C) in 46% yield.[19]

With ample quantities of **19** in hand all that remained to complete a synthesis of xanthocidin was introduction of a C(6) carbonyl group (cf. ruthenium tetraoxide)[20] followed by retrolactonization. However, due to the known propensity of ruthenium tetraoxide to cleave cis diols,[21] it was imperative that this functionality be protected prior to oxidation of the tetrahydrofuran ring. Unfortunately, all attempts to provide such protection were thwarted, presumably due to the steric hindrance experienced by the tertiary hydroxyl groups. It was thus clear that oxidation of the C(6) carbon would have to be accomplished prior to hydroxylation.

(iv) Introduction of a Carbonyl Group at C(6): Synthesis of Cyclodesdihydroxy-4,5-didehydroxanthocidin (14). To achieve introduction of the requisite carbonyl group at C(6), we turned to the oxidation protocol developed earlier for the preparation of cyclodesepoxy-4,5-didehydromethylenomycin A (**20**).[3] Treatment of



(20) (14)



(21) (22)

enone **13** with 2.5 equiv of chromium trioxide (90% acetic acid/acetic anhydride, 2:1) at 100 °C for 1.5 h afforded two lactones (**14** and **21**) along with recovered starting enone **13**; the ratio was 2:1:1. Separation by flash chromatography[22] gave pure lactone **21** and a mixture of **14** and **13**. Preparative thin-layer chromatography of the latter afforded pure lactone **14** in low (ca. 15–25%) albeit useful yield. The formation of two lactones was in marked contrast to our experience in the methylenomycin A area wherein only a single lactone (**20**) was isolated.[2]

Lactones **14** and **21** could be differentiated on the basis of high-field ^{1}H and ^{13}C NMR data. In particular, it was a relatively easy matter to demonstrate the allylic disposition of H_b in **14** and **21** and the respective C(3) methyl substituents via double-resonance NMR techniques. That is, in both **14** and **21** the angular protons (H_a and H_b) displayed in the 250-MHz ^{1}H NMR spectra either as a doublet of doublets (J = 7 and 1.5 Hz) or as a broad multiplet. The observed collapse of the doublet of doublets at δ 3.76 (H_b) to a discrete doublet upon irradiation of the C(3) methyl resonance of **14** requires that H_b is coupled to only one vicinal proton and thereby must have the structure assigned. Conversely, only sharpening of the broad multiplet at δ 3.39 in **21** occurred upon irradiation of the C(3) methyl resonance. Furthermore the chemical shift values for the carbon resonances at C(1) and C(5) (δ 46.1 and 45.5, respectively) in **14** were found to be quite similar to the values observed for the corresponding car-

(13) Wolff, S.; Smith, A. B., III; Agosta, W. C. *J. Org. Chem.* **1974**, *36*, 1607.

(14) For the record all synthetic intermediates have been fully characterized; for those not discussed in detail, structural assignments rest on spectroscopic properties and elemental composition data recorded in the Experimental Section.

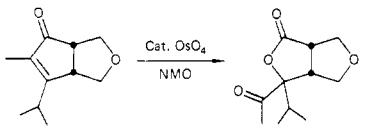
(15) McCurry, P. M., Jr.; Singh, R. K. *J. Org. Chem.* **1974**, *39*, 2316; 2317.

(16) Conley, R. T. "Infrared Spectroscopy"; Allyn and Bacon: Boston, 1970.

(17) For early observation on the steric requirements of OsO_4 see: Fieser, L. F.; Fieser, M. *Experientia* **1948**, *4*, 285.

(18) Baran, J. S. *J. Org. Chem.* **1960**, *25*, 257.

(19) Application of the VanRheenen catalytic osmium tetraoxide oxidation protocol (VanRheenen, V.; Kelly, R. C.; Cha, P. Y. *Tetrahedron Lett.* **1976**, 1973) to enone **13** employing *N*-methylmorpholine *N*-oxide as the secondary oxidant did not afford the expected diol **19**. Instead lactone **i** was formed in 50% yield. Studies demonstrating generality and utility of this transformation will be forthcoming in the near future; unpublished results of D. Boschelli of this laboratory.



(13) i

(20) Smith, A. B., III; Scarborough, R. M., Jr. *Synth. Commun.* **1980**, *205*. Also see ref 2.

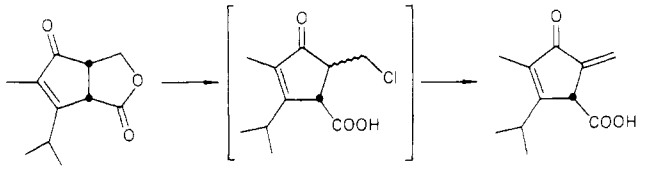
(21) Wolfe, S.; Hasan, S. K.; Campbell, J. R. *J. Chem. Soc., Chem. Commun.* **970**, 1420.

(22) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

bons in cyclodesepoxy-4,5-didehydromethylenomycin A (**20**; δ 45.2 and 48.9, respectively),[2] especially when compared to C(1) and C(5) in **21** (i.e., δ 50.8 and 41.0, respectively).

(v) Synthesis of Cycloxanthocidin (22). With a route to cyclodesdihydroxy-4,5-didehydroxanthocidin (**14**) secured, introduction of required vicinal hydroxyl groups on the least hindered or convex surface proved, as anticipated, straightforward. That is, addition of lactone **14** to 1.0 equiv of osmium tetraoxide in pyridine at 0 °C followed by hydrolysis with aqueous sodium bisulfite gave cycloxanthocidin **22** as a crystalline solid (mp 134–135 °C) in 65% yield after flash chromatography.

(vi) Retrolactonization: Synthesis of Xanthocidin (8) and Desdihydroxy-4,5-didehydroxanthocidin (11). With the synthesis of lactones **14** and **22** achieved, it now remained only to liberate the latent α-methylene-β-carbonyl functionality via retrolactonization to achieve a synthesis of desdihydroxy-4,5-didehydroxanthocidin (**11**) and xanthocidin (**8**), respectively. All attempts, however, to effect such a process with the powerful nucleophile lithium thiomethoxide failed; only recovered starting material or complex reaction mixtures resulted. Fortunately, we could call on the alternative retrolactonization procedure (i.e., 2-(trimethylsilyl)ethanol/acetyl chloride) developed in connection with the synthesis of desepoxy-4,5-didehydromethylenomycin A (**2**).[3] In this case, a 0.3 M solution of **14** in 2-(trimethylsilyl)ethanol was treated with 7.5 equiv of acetyl chloride at room temperature for 6 days. Removal of the solvent in vacuo followed by addition of 5% aqueous Na_2CO_3 and immediate acidification to pH 1 gave after extractive workup chloro acid **23**.

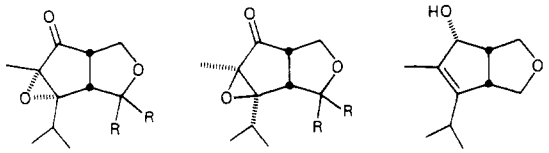


(14) (23) (11)

Alternatively, prolonged treatment with 5% Na_2CO_3 (ca. 1.5 h) converted the intermediate chloride to desdihydroxy-4,5-didehydroxanthocidin (**11**), the yield after purification via rapid flash chromatography[22] being 23%. Characteristic of the α-exomethylene ketone functionality of **11**, the methylene protons displayed as doublets (J = 2 Hz) at δ 5.60 and 6.18.

In a similar fashion, retrolactonization of **22** afforded (±)-xanthocidin (**8**) in 20–25% yield. That indeed racemic xanthocidin was in hand was confirmed by direct comparison of the 60-MHz ^{1}H NMR spectrum to the published spectrum[8] of natural (+)-xanthocidin.

(vii) The Xanthocidin Diastereomers: A Problem in Stereocontrolled Hydroxylation. Simultaneously with the now successful approach to xanthocidin (**8**), we also engaged in the synthesis of the related diastereomers. From the outset we envisioned preparation of epoxy lactones **24a** and **25a** followed by opening of the epoxide ring



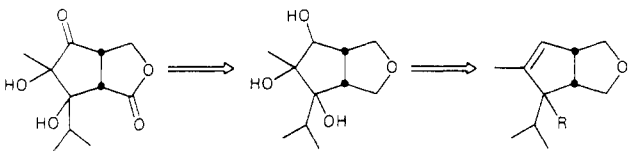
(24) (a) R, R = O (b) R = R = H (25) (a) R, R = O (b) R = R = H (26)

in stereocontrolled fashion to generate the desired vicinal hydroxyl substituents. As with xanthocidin, retrolactonization would then afford the respective diastereomers. We describe here the preparation of (±)-epixanthocidin (**9**) and (±)-β-isoxanthocidin (**10**) from common intermediate **13**; (±)-α-isoxanthocidin (**12**) remains elusive.

Reduction of enone **13** with sodium borohydride in the presence of cerium(III)[23] afforded endo-allylic alcohol **26** in 96% yield. Epoxidation with *m*-chloroperbenzoic acid, a reagent known to be directed by allylic hydroxyl groups,[24] followed by oxidation with Jones reagent[25] gave endo-epoxy ketone **24b** in 65% yield as a white crystalline solid (mp 70–71.5 °C). Alternatively, treatment of enone **13** with basic hydrogen peroxide according to the conditions of Corey and Ensley[26] afforded a mixture of two epoxides (**24b** and **25b**), as well as recovered starting material; the ratio was 1:4:1. Flash chromatography afforded pure exo-epoxy ketone **25b** in 34% yield. That the minor epoxy ketone obtained in this reaction was identical with **24b** was confirmed by spectral comparison. Ruthenium tetraoxide oxidation of the tetrahydrofuran ring of **24b** and **25b** then provided as anticipated **24a** and **25a**, respectively.

Unfortunately, all attempts to unveil the vicinal hydroxyls via the acid-catalyzed opening of the epoxide rings of **24a** and **25a** led either to recovered starting material or to complex mixtures.[27] Failure of this transformation is presumably a result of the tetrasubstituted nature of the epoxide rings magnified by the steric bulk of the isopropyl substituent.

Anticipating that opening of the epoxide ring of **24a** and **25a** might prove problematic, we simultaneously explored an alternate strategy. We conjectured in this regard that allylic alcohols **27a** and **27b**, available presumably via



Diastereomers of Xanthocidin (27) (a) R = α-OH (b) R = β-OH (c) R = α-OTMS

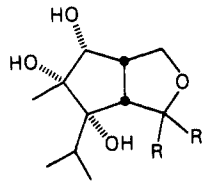
Wharton fragmentation[28] of epoxy ketones **24b** and **25b**, might serve as substrates for introduction of the requisite vicinal hydroxyl groups. Subsequent protection, followed by oxidation of the tetrahydrofuran ring at C(6), deprotection, and final mild oxidation of the derived secondary hydroxyl group could then be anticipated to afford the four diastereomers of xanthocidin.

To achieve the initial transformation of this strategy epoxy ketones **24b** and **25b** were each treated in methanol at 0 °C with hydrazine hydrate (85%). In the case of **24b** the desired allylic alcohol (**27a**) was obtained in 59% yield. Epoxy ketone **25b**, however, afforded an anomalous result; the instantaneous, albeit nonvigorous, release of gas upon

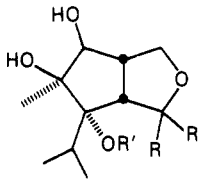
(23) Luché, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(24) Henbest, H. B. *Proc. Chem. Soc. London* **1963**, *75*, 159. Chamberlain, P.; Roberts, M. L.; Whitham, G. H. *J. Chem. Soc. B* **1970**, 1374. All see: Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159 and references cited therein.
(25) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548. Djerassi, C.; Engle, R. R.; Bowers, A. *J. Org. Chem.* **1956**, *21*, 1547.
(26) Corey, E. J.; Ensley, H. *J. Org. Chem.* **1973**, *38*, 3187.
(27) Even those protocols reported effective for the hydrolysis of sterically hindered epoxides failed in our case; see: Berti, G.; Macchia, B.; Macchia, F. *Tetrahedron Lett.* **1965**, 3421. Berti, G.; Macchia, B.; Macchia, F. *Tetrahedron* **1968**, 1755.
(28) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615.

addition of the hydrazine. Work up afforded enone **13** as the only isolable product. All variations (e.g., temperature, concentration, presence or absence of acid catalyst) led to the same result. Interestingly, the characteristic yellow color attributable to the intermediate diazine[29] was not observed. Although a definitive explanation of the disparity in reactivity between **24b** and **25b** is currently unavailable, we speculate that in the case of **25b** attack of hydrazine presumably occurs at either the epoxide or carbonyl oxygen. The result would be cleavage of the α-epoxide carbon–oxygen bond. Elimination of the elements of diimide and water then leads to the observed enone.[30]

Although the unavailability of **27b** via the Wharton fragmentation precluded further work on α-isoxanthocidin (**12**), the synthesis of epixanthocidin (**9**) and β-isoxanthocidin (**10**) from **27a** could now be anticipated. To this end, **27a** was treated with 1 equiv of osmium tetraoxide in pyridine at 0 °C. Here again we assumed that the convex–concave nature of the bicyclic[3.3.0] system would provide the stereochemical bias required to introduce the vicinal cis-hydroxyl substituents syn to the bridge hydrogens. After 4 h at room temperature the osmate ester was hydrolyzed with aqueous sodium bisulfite to give a 4:1 mixture of two triols. On the assumption that the above stereochemical rationale was correct, the major isomer was tentatively assigned structure **29a**, the result of exo attack. Such being the case, we conjectured that protection of the allylic alcohol functionality with a suitably bulky protecting group would increase the stereoselectivity of the attacking reagent. Toward this end, alcohol **27a** was converted to its trimethylsilyl derivative (**27c**) in 94% yield. Treatment of the latter with 1 equiv of OsO_4 afforded a *single* diol in 64% yield as a white crystalline solid. Interestingly, the hydroxylation process in this case (i.e., **27c**) proved to be much slower than that with **27a** (i.e., 22 h compared to 4 h). To our surprise removal of the silyl group with tetra-*n*-butylammonium fluoride[31] produced a triol (i.e., **29a**)



(28)
(a) R = R = H
(b) R, R = O



(29)
(a) R = R = H, R′ = H
(b) R = R = H, R′ = TMS
(c) R, R = O, R′ = H

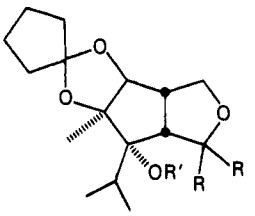
that was identical in all respects with the minor triol obtained from **27a**. In retrospect it was now evident that the major product derived from allylic alcohol **27a** was endotriol **28a**. That is, the relatively bulky exo-isopropyl substituent in **27a** blocks the approach of osmium tetraoxide, forcing hydroxylation to occur on the concave surface of the bicyclic system. Increasing the steric congestion of the concave face of **27a** by appending a trimethylsilyl group to the allylic hydroxyl forces OsO_4 to attack syn to the bridgehead hydrogens to afford **29b**.[32]

(29) Kosower, E. M. *Acc. Chem. Res.* **1971**, *4*, 193.

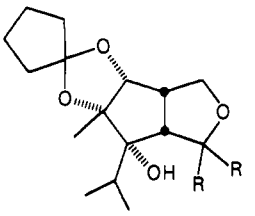
(30) To the best of our knowledge the hydrazine-induced deoxygenation of α,β-epoxy ketones is unprecedented.

(31) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

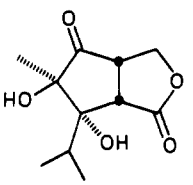
(viii) Synthesis of (±)-Epixanthocidin (9) and (±)-β-Isoxanthocidin (10). Greatly encouraged by our ability to direct cis hydroxylation to either the convex or concave face of **27a**, we focused attention next on completing the synthesis of β-isoxanthocidin (**10**). Introduction of a carbonyl group at C(6) of the tetrahydrofuran ring followed, after oxidation of the secondary hydroxyl group, by retrolactonization was all that remained. However, prior to such an oxidation the vicinal cis-hydroxyl groups required protection.[33] To this end, cyclopentylidene derivative **30a** was prepared in 80% yield from diol **29b** via



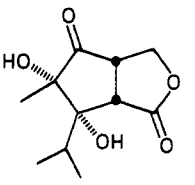
(30)
(a) R = R′ = H
(b) R, R = O; R′ = H
(c) R = R = H; R′ = TMS



(31)
(a) R = R = H
(b) R, R = O



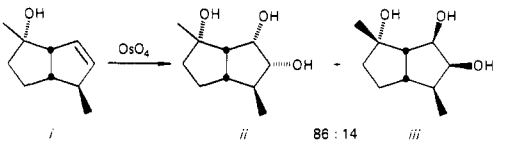
(32)



(33)

treatment with cyclopentanone (azeotropic removal of water),[34] followed by cleavage of the silyl group with tetra-*n*-butylammonium fluoride. Oxidation with ruthenium tetraoxide, employing sodium carbonate as a buffer to prevent hydrolysis of the acid-sensitive cyclopentylidene group,[35] then gave after chromatography a *single* lactone (**30b**) in 41% yield.[36] Hydrolysis of the cyclopentylidene group (trifluoroacetic acid/acetonitrile) generated unstable triol **29c** in 78% yield, which without purification was subjected to Swern oxidation[37] employing oxalyl chloride and dimethyl sulfoxide (CH_2Cl_2/−55 °C) to give after careful chromatography a 35% yield of cyclo-β-isoxanthocidin (**32**) as a white solid (mp 157–158 °C).

(32) A similar stereochemical result was recently reported by Kon and Isoe with the closely related bicyclo[3.3.0]octenol (i → ii and iii). These workers suggested that a complex between the hydroxyl and the OsO_4 directed the α or concave cis-hydroxylation; see: Kon, K., Isoe, S. *Tetrahedron Lett.* **1980**, *21*, 3399. A steric argument would also account for their observation.



(33) Initially the acetonide derivatives of **28a** and **29a** were prepared and oxidized to the corresponding lactones with RuO_4. However, deprotection proved quite problematic. Similar problems were not experienced with the corresponding cyclopentylidene derivatives; see ref 34.

(34) van Heeswijk, W. A. R.; Goedhart, J. B.; Vliegenthart, J. F. G. *Carbohydr. Res.* **197**, *58*, 337.

(35) Parikh, V. M.; Jones, J. K. N. *Can. J. Chem.* **1965**, *43*, 3452.

(36) Although only one lactone (**29b**) was isolated in this reaction, in view of our previous observations in the methylenomycin area there is no reason to believe, a priori, this reaction to be regiospecific. That is, since the yield was less then 50%, an equal amount of oxidation at C(8) is not unreasonable. This oxidation product, however, might experience further degradation (i.e., elimination of the β-ketal oxygen followed by oxidative cleavage of olefinic linkage); see ref 2b.

(37) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

Now in a position to exploit the retrolactonization protocol used to advantage in our synthesis of xanthocidin (8), we treated lactone **32** with acetyl chloride in 2-(trimethylsilyl)ethanol to afford (±)-β-isoxanthocidin (**10**) in 30% yield after chromatographic separation. That retrolactonization had occurred was immediately apparent by the appearance of the characteristic exo-methylene resonances in the high-field (250 MHz) ^{1}H NMR spectrum. For comparison purposes Table I lists the IR and ^{1}H NMR spectral data for xanthocidin (**8**), β-isoxanthocidin (**10**), epixanthocidin (**9**; vide infra), methylenomycin A (**1a**),[2] and epimethylenomycin A (**1b**).[2]

With a synthesis of β-isoxanthocidin (**10**) in hand we turned to complete a synthesis of epixanthocidin (**9**) by employing the 4:1 mixture of triols obtained from allylic alcohol **27a**. Protection of the cis-diol functionality again as the cyclopentylidene derivative afforded a mixture of **30a** and **31a** in 86% yield. The major isomer **31a** was obtained in pure form by chromatography. Ruthenium tetraoxide oxidation then led to the *single* lactone **31b** in 38% yield.

Removal of the cyclopentylidene protecting group via acid hydrolysis (10% HCl/acetone) gave the corresponding triol **28a** in 80% yield, which without purification was subjected to Swern oxidation.[37] Careful chromatography gave cycloepixanthocidin (**33**) in 25% yield from **31b** as a white solid (mp 124–126 °C). Once again retrolactonization was easily achieved via the 2-(trimethylsilyl)ethanol/acetyl chloride protocol. Chromatography then provided (±)-epixanthocidin (**10**) in 50% yield. That the desired conversion had taken place without event was verified via the spectral data (see Table I).

Experimental Section

Materials and Equipment. Melting points were obtained on a Thomas-Hoover instrument and are corrected. Boiling points are uncorrected. All solvents used were reagent grade. Ether and tetrahydrofuran were distilled from sodium and benzophenone; methylene chloride from phosphorous pentoxide; benzene, toluene, dimethylformamide, and dimethyl sulfoxide from calcium hydride; pyridine from potassium hydroxide; and methanol from magnesium sulfate. Unless otherwise specified solutions were dried over $MgSO_4$. Osmium tetraoxide was purchased from PolyScience Corp. in 1-g vials. 2-(Trimethylsilyl)ethanol was purchased from Fluka. Photochemical experiments were carried out with a Hanovia Model L mercury lamp (No. 679A-36) in a quartz immersion well with Corex 7740 as a filter. Precoated silica gel plates (250 μm) with a fluorescent indicator (Merck) were used for analytical thin-layer chromatography (TLC). Visualization was achieved via ultraviolet light or ethanolic 12-molybdophosphoric acid [7% (w/v)]. For preparative separations precoated silica gel GF (Analtech) plates (500 or 1000 μm) were used. Silica gel 60 (particle size 0.040–0.063 mm) supplied by Merck was used for flash chromatography. Proton NMR spectra were obtained for deuteriochloroform solutions on either a Varian T-60 A (60 MHz) or a Bruker WP-250 FT (250 MHz) spectrometer. Carbon NMR spectra were obtained on a JEOL PS-100 spectrometer. Chemical shifts are reported as δ values in relative to tetramethylsilane (δ_{Me_4Si} 0.00). All infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer for carbon tetrachloride or chloroform solutions. High-resolution mass spectra were obtained from the University of Pennsylvania Mass Spectrometry Service on a Hitachi Perkin-Elmer RMH-2 high-resolution double-focusing electron impact spectrometer interfaced with a Kratos DS-50-S data system. Microanalyses were determined by the Rockefeller Microanalytical Laboratories under the direction of S. T. Bella.

Preparation of Cyclobutene 15. A mixture of 5.25 g (53.57 mmol) of maleic anhydride, 6.09 g (63.45 mmol) of 2-methyl-3-hexyne, and 0.95 g (5.20 mmol) of benzophenone in 250 mL of acetonitrile was irradiated for 16 h. Removal of solvent and excess 2-methyl-3-hexyne in vacuo followed by distillation (bp 108 °C, 0.8 mmHg) afforded 5.88 g of **15** (57%) as a pale yellow solid (mp

Table I. High-Field ^{1}H NMR Data of (±)-Xanthocidin (8), (±)-Epixanthocidin (9), (±)-β-Isoxanthocidin (10), (±)-Desdihydroxy-4,5-didehydroxanthocidin (11), (±)-Methylenomycin A (1a), (±)-Epimethylenomycin A (1b), and (±)-Desepoxy-4,5-didehydromethylenomycin A (2)[a]

(±)-xanthocidin (8)[b]	1.46 (s, 3 H)	1.06 (d, J = 7 Hz, 3 H) 1.07 (d, J = 7 Hz, 3 H)	2.42 (st, J = 7 Hz, 4 H)	3.87 (t, J = 2 Hz, 1 H)	5.84 (d, J = 2 Hz, 4 H)		6.45 (d, J = 2 Hz, 1 H)
(±)-epixanthocidin (9)[b]	1.23 (s, 3 H)	1.05 (d, J = 7 Hz, 3 H) 1.07 (d, J = 7 Hz, 3 H)	2.05 (st, J = 7 Hz, 1 H)	3.62 (t, J = 3 Hz, 1 H)	5.82 (d, J = 3 Hz, 1 H)		6.44 (d, J = 3 Hz, 1 H)
(±)-β-isoxanthocidin (10)[b]	1.43 (s, 3 H)	0.97 (d, J = 7 Hz, 3 H) 1.07 (d, J = 7 Hz, 3 H)	2.31 (st, J = 7 Hz, 1 H)	3.92 (t, J = 3 Hz, 1 H)	5.66 (d, J = 3 Hz, 1 H)		6.37 (d, J = 3 Hz, 1 H)
(±)-desdihydroxy-4,5-didehydroxanthocidin[b] (11)	1.88 (d, J = 1 Hz, 3 H)	1.18 (d, J = 7 Hz, 3 H) 1.21 (d, J = 7 Hz, 3 H)	3.06 (st, J = 7 Hz, 1 H)	4.22 (br s, 1 H)	5.60 (d, J = 2 Hz, 1 H)		6.18 (d, J = 2 Hz, 1 H)
(±)-methylenomycin A[c] (1a)	1.48 (s, 3 H)	1.58 (s, 3 H)		3.82 (m, 1 H)	5.65 (d, J = 1.8 Hz, 1 H)		6.27 (d, J = 1.8 Hz, 1 H)
(±)-epimethylenomycin A[c] (1b)	1.44 (s, 3 H)	1.68 (s, 3 H)		3.77 (m, 1 H)	5.81 (d, J = 2.6 Hz, 1 H)		6.41 (d, J = 2.6 Hz, 1 H)
(±)-desepoxy-4,5-didehydromethylenomycin A[c] (2)	1.85 (d, J = 1 Hz, 3 H)	2.14 (d, J = 1 Hz, 3 H)		4.10 (br s, 1 H)	5.66 (d, J = 2 Hz, 1 H)		6.21 (d, J = 2 Hz, 1 H)

[a] s = singlet, d = doublet, t = triplet, st = septuplet, m = multiplet, br = broad. [b] 250-MHz ^{1}H NMR data. [c] 220-MHz ^{1}H NMR data.

60–61 °C). An analytical sample of **15** was obtained via flash chromatography, eluting with ether; IR 2960 (w), 1855 (w), 1780 (s), 1220 (w), 1066 (w), 897 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.04–1.20 (complex m, 9 H), 2.26 (m, J = 8 Hz, 2 H), 2.62 (st, J = 6 Hz, 1 H), 3.76 (br, s, 1 H), 3.80 (br, s, 1 H); mass spectrum, m/e 194.0939 (M^+, calcd for $C_{11}H_{14}O_3$, 194.0943).

Preparation of Diol 16. To a magnetically stirred suspension of lithium aluminum hydride (4.25 g, 111 mmol) in 80 mL of anhydrous tetrahydrofuran cooled to 0 °C was added dropwise a solution of anhydride **15** (7.24 g, 37.30 mmol) in 45 mL of tetrahydrofuran. After heating at reflux for 42 h, the mixture was cooled to 0 °C and the excess hydride destroyed by slow addition of 6 mL of water, 7 mL of 15% NaOH, and 14 mL of water. The aluminum salts were removed by filtration, and the organic layer was dried. Removal of solvents in vacuo gave 6.60 g (96%) of diol **16**. An analytical sample was obtained via flash chromatography eluting with ether; IR 3310 (br, s), 2960 (w), 2865 (s), 1465 (w), 1027 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.14–1.87 (complex m, 9 H), 2.01 (m, J = 8 Hz, 2 H), 2.43 (st, J = 7 Hz, 1 H), 3.02 (complex m, 2 H), 3.64 (t, J = 11 Hz, 2 H), 3.82–4.16 (complex m, 4 H; 2 H, D_2O ex); mass spectrum, m/e 184.1461 (M^+, calcd for $C_{11}H_{20}O_2$, 184.1464).

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.82; H, 10.96.

Preparation of Tetrahydrofuran 17. To a cold (0 °C) solution of 9.50 g (50.00 mmol) of *p*-toluenesulfonyl chloride in 100 mL of dry pyridine was added 7.70 g (41.83 mmol) of diol **16** in 50 mL of pyridine. The mixture was kept at 4 °C for 18.5 h, then warmed to room temperature, and heated at reflux for 1.5 h. Workup consisted of extraction into ether and washing with 10% HCl. Removal of solvent in vacuo afforded 5.71 g of **17** (82%). An analytical sample of ether **17** [bp 105 °C (33 torr)] was obtained via flash chromatography eluting with ether; IR 2965 (s), 2940 (s), 2840 (s), 1460 (w), 1077 (s), 910 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.90–1.15 (complex m, 9 H), 2.02 (m, J = 8 Hz, 1 H), 2.16 (m, J = 8 Hz, 1 H), 2.48 (st, J = 7 Hz, 1 H), 3.05–3.24 (complex m, 4' H), 3.78 (t, J = 9 Hz, 2 H); mass spectrum, m/e 166.1344 (M^+, calcd for $C_{11}H_{18}O$, 166.1358).

Preparation of Diketone 18. A solution of 3.32 g (24.08 mmol) of bicyclic ether **17** in 40 mL of dry methanol was cooled to −78 °C and treated with ozone, until the blue color of ozone persisted. This solution was then poured into 6.70 g (26.67 mmol) of triphenylphosphine in 50 mL of dry methanol at −78 °C. The mixture was allowed to warm to room temperature and stirred for an additional 2 h. Removal of solvents in vacuo and Kugelrohr distillation [bp 93 °C (0.5 torr)] afforded 3.26 g (80%) of diketone **18**. An analytical sample was obtained by flash chromatography eluting with ether; IR 2975 (w), 2940 (w), 2875 (w), 1715 (s), 1460 (w), 1380 (w), 1360 (w), 926 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.06 (t, J = 8 Hz, 3 H), 1.09 (d, J = 7 Hz, 3 H), 1.12 (d, J = 7 Hz, 3 H), 2.48 (q, J = 8 Hz, 2 H), 2.68 (st, J = 7 Hz, 1 H), 3.64 (q, J = 8 Hz, 1 H), 3.71–3.89 (complex m, 3 H), 4.12 (t, J = 8 Hz, 2 H); mass spectrum, m/e 198.1253 (M^+, calcd for $C_{11}H_{18}O_3$, 198.1256).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.75; H, 9.02.

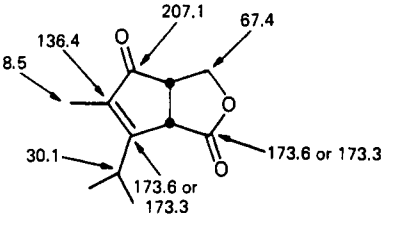
Preparation of Enone 13. A solution containing 3.41 g (17.22 mmol) of diketone **18** in 55 mL of 2% (w/v) methanolic sodium hydroxide (95% MeOH) was heated at reflux for 1.5 h. After cooling to room temperature, the solution was neutralized with 10% HCl, extracted into ether, washed with brine, and dried. Removal of solvent in vacuo followed by flash chromatography eluting with ether gave 2.30 g of (74%) enone **13** as a pale yellow oil. An analytical sample was obtained by flash chromatography eluting with ether; IR 2965 (s), 2920 (w), 2855 (w), 1695 (s), 1630 (w), 1460 (s), 1325 (w), 1206 (w), 1064 (s), 918 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.18 (d, J = 9 Hz, 3 H), 1.19 (d, J = 9 Hz, 3 H), 1.72 (d, J = 1 Hz, 3 H), 2.80 (td, J = 7, 2 Hz, 1 H), 2.95 (st, J = 9 Hz, 1 H), 3.44 (br, J = 7 Hz, 1 H), 3.63 (d, J = 8 Hz, 1 H), 3.71 (d, J = 8 Hz, 1 H), 3.87 (dd, J = 9, 2 Hz, 1 H), 4.10 (dd, J = 9, 2 Hz, 1 H); mass spectrum, m/e 180.1152 (M^+, calcd for $C_{11}H_{16}O_2$, 180.1151).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.29; H, 9.02.

Preparation of Diol 19. To a 0 °C solution of 879.0 mg (3.46 mmol) of osmium tetraoxide in 10 mL of pyridine was added 611.0 mg (3.40 mmol) of enone **13** in 7 mL of pyridine. The solution quickly changed from bright yellow to black. After this stirred at room temperature for 3.5 h, a solution of 2.1 g of $NaHSO_3$ in 10 mL of water was added to cleave the osmate ester. After an additional 24 h the solids were filtered off, and the filtrate was extracted with chloroform. The organic extract was then washed with brine, dried, and concentrated in vacuo to give 459.0 mg of a pale yellow solid. Column chromatography, eluting with 2:1 ethyl acetate/chloroform gave 337.0 mg (46%) of diol **19** as a colorless solid (mp 75.0–77.0 °C): IR 3540 (w), 2980 (s), 2285 (s), 1750 (s), 1475 (w), 1390 (s), 1250 (w), 1189 (w), 1118 (s), 1094 (s), 1072 (w), 1028 (s), 983 (s), 908 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.87 (d, J = 7 Hz, 3 H), 0.94 (d, J = 7 Hz, 3 H), 1.18 (s, 3 H), 2.02 (st, J = 7 Hz, 1 H), 2.89–3.02 (complex m, 2 H), 3.05 (s, 1 H, D_2O ex), 3.27 (s, 1 H, D_2O ex), 3.66 (dd, J = 9, 7 Hz, 1 H), 3.79 (t, J = 9 Hz, 1 H), 3.95 (dd, J = 11, 3 Hz, 1 H), 4.07 (d, J = 9 Hz, 1 H); mass spectrum, m/e 214.1191 (M^+, calcd for $C_{11}H_{18}O_4$, 214.1205).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.51; H, 8.26.

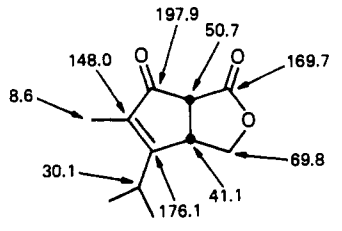
Oxidation of Enone 13 to Lactones 14 and 21. To a solution of 1.33 g (7.38 mmol) of enone **13** in 12 mL of acetic anhydride heated to 100 °C was added dropwise a solution containing 1.59 g (15.87 mmol) of CrO_3 in 24 mL of 90% glacial acetic acid. When addition was complete, the green solution was stirred at 100 °C for an additional 0.5 h. The mixture was cooled, extracted into ether, washed with water, and dried. Removal of solvent in vacuo yielded 1.23 g of a yellow oil containing starting enone **13** and two isomeric lactones, **14** and **21**. Flash chromatography eluting with ether separated 152.7 mg of **21** from 791.5 mg of a mixture of **14** and enone **13**. This mixture was placed on three 1000-μm silica gel preparative plates (CH_2Cl_2, two developments) to yield 144.0 mg of **14** and 446.0 mg of recovered starting material **13**. The yield of lactone **14** based on recovered starting material was 15%. Analytical samples were prepared by flash chromatography eluting with ether. Lactone **14**: IR 2975 (w), 2930 (w), 1775 (s), 1710 (s), 1630 (w), 1123 (w) cm^{-1}; ^1H NMR ($CDCl_3$ 250 MHz) δ 1.24 (d, J = 7.5 Hz, 3 H), 1.36 (d, J = 7.5 Hz, 3 H), 1.80 (d, J = 1.3 Hz, 3 H), 3.14 (st, 7.5 Hz, 1 H), 3.31 (complex m, 1 H), 3.88 (dd, J = 7.5, 1 Hz, 1 H), 4.41 (dd, J = 10, 4 Hz, 1 H), 4.50 (t, J = 10 Hz, 1 H); mass spectrum, m/e 194.0938 M^+, calcd for $C_{11}H_{14}O_3$, 194.0943). The natural abundance ^{13}C NMR spectrum is summarized in the following structure:



(14)

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.08; H, 7.16.

Lactone **21**: IR 2970 (w), 2930 (w), 2860 (w), 1780 (s), 1710 (s), 1645 (w), 1156 (w), 1120 (w), 1050 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.21 (dd, J = 7 Hz, 3 H), 1.22 (d, J = 7 Hz, 3 H), 1.78 (d, J = Hz, 3 H), 3.07, 7, J = 7 Hz, 1 H), 3.51 (d, J = 7 Hz, 1 H), 3.89 (complex m, 1 H), 4.28 (dd, J = 10, 4 Hz, 1 H), 4.62 (t, J = 10 Hz, 1 H); mass spectrum, m/e 194.0962 (M^+, calcd for $C_{11}H_{14}O_3$, 194.0943). The natural abundance ^{13}C NMR spectrum is summarized in the following structure:



(21)

Preparation of Cycloxanthocidin 22. To a 0 °C solution of 187.4 mg (0.739 mmol) of OsO_4 in 3 mL of pyridine was added 139.5 mg (0.718 mmol) of **14** in 4 mL of pyridine. The bright yellow solution immediately turned black, indicating the formation of the osmate ester. After this stirred at room temperature for 4 h, a solution of 1.36 g of $NaHSO_3$ in 5.6 mL of H_2O was added. After 18 h, the reaction mixture consisted of an orange solvent with tan solids, indicating that the osmate ester had cleaved. This mixture was thoroughly extracted with chloroform, and the organic extract was then washed with brine and dried. Removal of solvent in vacuo and flash chromatography eluting with ether resulted in 109.5 mg of **22** (65%) as a pale yellow solid. An analytical sample of **22** was obtained by flash chromatography eluting with distilled ether (mp 134–136 °C); IR 3540 (s), 2975 (s), 2935 (s), 1780 (s), 1755 (s), 1380 (w), 1173 (w), 1122 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.98 (d, J = 7 Hz, 3 H), 1.16 (s, 3 H), 1.18 (d, J = 7 Hz, 3 H), 2.42 (st, J = 7 Hz, 1 H), 3.09 (s, 2 H, D_2O ex), 3.44 (td, J = 9, 2 Hz, 1 H), 3.46 (d, J = 10 Hz, 1 H), 4.36 (dd, J = 10, 2 Hz, 1 H), 4.46 (dd, J = 10, 9 Hz, 1 H); mass spectrum, m/e 228.1001 (M^+, calcd for $C_{11}H_{16}O_5$, 228.0997).

Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.87; H, 7.07. Found: C, 57.73; H, 6.99.

Preparation of (±)-Xanthocidin (8). To a suspension of 64.0 mg (0.28 mmol) of lactone **22** in 1.05 mL of 2-(trimethylsilyl)-ethanol was slowly added 150 μL (2.1 mmol) of acetyl chloride. The lactone dissolved, and the resulting solution was stirred at room temperature under a nitrogen atmosphere for 7 days. At the end of this time a dark lower layer had formed. The solvent was removed in vacuo, and the residue was dissolved in ether. The acidic material was then extracted into 80 mL of 5% Na_2CO_3. After standing at room temperature for 1.7 h, the basic layer was acidified to pH 1 with 10% HCl and then extracted into ether followed by chloroform. The combined organic layers were dried and then concentrated in vacuo to give 55.0 mg of a dark yellow oil that consisted mainly of (±)-xanthocidin (**8**). Purification was achieved via rapid flash chromatography eluting with ether to give 12.6 mg (19%) of (±)-xanthocidin (**8**) as a pale yellow low-melting solid: IR 3520 (w), 3010 (s), 2970 (s), 1730 (s), 1710 (s), 1255 (s), 1107 (s), 1023 (s), 928 (w), 763 (s, br) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.06 (d, J = 7 Hz, 3 H), 1.07 (d, J = 7 Hz, 3 H), 1.46 (s, 3 H), 2.42 (st, J = 7 Hz, 1 H), 3.87 (t, J = 2 Hz, 1 H), 5.84 (d, J = 2 Hz, 1 H), 6.45 (d, J = 2 Hz, 1 H). This material exhibited a 60-MHz ^1H NMR spectrum identical with that published for natural (+)-xanthocidin.

Preparation of (±)-Desdihydroxy-4,5-didehydroxanthocidin (11). To a solution of 88.2 mg (0.45 mmol) of lactone **14** in 1.7 mL of 2-(trimethylsilyl)ethanol, was slowly added 240 μL (3.4 mmol) of acetyl chloride. This solution was stirred at room temperature under a nitrogen atmosphere for 6 days. The solvent was then removed in vacuo, and the residue was dissolved in ether. The acidic material was then extracted into 5% Na_2CO_3 and allowed to stand at room temperature for 1.5 h. This basic solution was then acidified to pH 1 with 10% HCl and extracted into ether. The organic layer was dried and then concentrated in vacuo to give 61.5 mg of a yellowish-orange oil. Purification was achieved by preparatory thin-layer chromatography (1000 μm plate) eluting with ether to give 20.5 mg (23%) of (±)-desdihydroxy-4,5-didehydroxanthocidin as a pale yellow oil: IR 3909 (s, br), 2960 (s), 1700 (s), 1680 (s), 1620 (s), 1465 (w), 1395 (w), 1310 (w), 1030 (w), 962 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.18 (d, J = 7 Hz, 3 H), 1.21 (d, J = 7 Hz, 3 H), 1.88 (d, J = 1 Hz, 3 H), 3.06 (st, J = 7 Hz, 1 H), 4.22 (br s, 1 H), 5.60 (d, J = 2 Hz, 1 H), 6.18 (d, J = 2 Hz, 1 H); mass spectrum, m/e 194.0937 (M^+, calcd for $C_{11}H_{14}O_3$, 194.0943).

Preparation of Allylic Alcohol 26. To a magnetically stirred solution of 6.18 g (34.3 mmol) of enone **13** in 88 mL of 0.4 M cerium(III) chloride in methanol at room temperature was slowly added 1.36 g (35.8 mmol) of sodium borohydride. After this stirred for 30 min, an additional 1.36 g of sodium borohydride was added. After 30 min, 80 mL of water was added, and the mixture was stirred for 20 min and then extracted into ether. Drying followed by removal of solvent in vacuo gave 6.04 g of **26** (96%) as a pale yellow oil. An analytical sample was prepared by flash chromatography eluting with ether; IR 3440 (br), 2960 (s), 2865 (s), 1470 (w), 1380 (w), 1117 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.94 (d, J = 4 Hz, 3 H), 0.97 (d, J = 4 Hz, 3 H), 1.62 (d, J = 2 Hz, 3 H) 1.95 (d, J = 10 Hz, 1 H, D_2O ex), 2.62 (st, J = 8 Hz, 1 H), 2.75 (ddd, J = 12, 8, 2 Hz, 1 H), 3.14 (br m, 1 H), 3.37 (dd, J = 9, 6 Hz, 1 H), 3.50 (t, J = 8 Hz, 1 H), 3.58 (dd, J = 9, 4 Hz, 1 H), 4.15 (dd, J = 9, 2 Hz, 1 H), 4.27 (dd, J = 9, 8 Hz, 1 H); mass spectrum, m/e 182.1294 (M^+, calcd for $C_{11}H_{18}O_2$, 182.1307).

Preparation of *endo*-Epoxy Ketone 24b. To a stirring solution of 6.04 g (33.21 mmol) of allylic alcohol **26** in 85 mL of dry methylene chloride, cooled to 0 °C, was slowly added 6.99 g (39.94 mmol) of *m*-chloroperbenzoic acid in 80 mL of methylene chloride. After refrigeration overnight, the mixture was extracted with methylene chloride, washed with saturated $NaHCO_3$ to remove acidic material, dried, and concentrated in vacuo to give 6.12 g (93%) of the endo epoxide as a yellow oil.

To this material dissolved in 110 mL of acetone, cooled on an ice bath, was added dropwise 13.5 mL of 2.79 M Jones reagent (37.66 mmol). After stirring at 0 °C for 20 min, 1 mL of 2-propanol was added to destroy excess Jones reagent. The green mixture was extracted into ether, washed with water, dried, and concentrated in vacuo. Flash chromatography eluting with ether gave 3.95 g (65%) of epoxy ketone **24b** as a white solid (mp 70.0–71.5 °C). An analytical sample was obtained by further chromatography, eluting with ether; IR 2960 (s), 2860 (s), 1740 (s), 1375 (w), 1260 (s), 1110 (s), 1048 (w), 910 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.04 (d, J = 7 Hz, 3 H), 1.08 (d, J = 7 Hz, 3 H), 1.39 (s, 3 H), 1.77 (st, J = 7 Hz, 1 H), 2.96–3.12 (complex m, 2 H), 3.65 (dd, J = 8, 6 Hz, 1 H), 3.89 (t, J = 9 Hz, 1 H), 3.98–4.06 (complex m, 2 H); mass spectrum, m/e 196.1088 (M^+, calcd for $C_{11}H_{16}O_3$, 196.1099).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.50; H, 8.28.

Preparation of Lactone 24a. A biphasic mixture of 3.75 g (17.6 mmol) of sodium periodate in 20 mL of water and 82.0 mg (0.062 mmol) of ruthenium dioxide in 10 mL of carbon tetrachloride was stirred vigorously until the bright yellow color of ruthenium tetraoxide persisted. A solution of 870.6 mg (4.44 mmol) of epoxy ketone **24b** in 10 mL of carbon tetrachloride was added. The yellow color faded and then reappeared, and the solution was stirred at room temperature for 6 days. The phases were separated, the aqueous layer was extracted with additional carbon tetrachloride, and 1.0 mL of 2-propanol was added to the organic layer to precipitate ruthenium dioxide. After drying, removal of solvent in vacuo followed by recrystallization from pentane gave 320.3 mg (42%) of white crystalline lactone **24a**. An analytical sample was obtained by flash chromatography eluting with ether (mp 78–80 °C); IR 2960 (s), 2920 (s), 1780 (s), 1750 (s), 1475 (w), 1380 (w), 1180 (w), 1050 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.15 (d, J = 7 Hz, 3 H), 1.33 (d, J = 7 Hz, 3 H), 1.46 (s, 3 H), 2.09 (st, J = 7 Hz, 1 H), 3.28–3.45 (complex m, 2 H), 4.20 (dd, J = 9, 6 Hz, 1 H), 4.42 (dd, J = 9, 8 Hz, 1 H); mass spectrum, m/e 210.0898 (M^+, calcd for $C_{11}H_{14}O_4$, 210.0892).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.86; H, 6.67. Found: C, 62.86; H, 6.71.

Preparation of *exo*-Epoxy Ketone 25b. To a 0 °C solution of 1.40 g (7.79 mmol) of enone **13** in 10 mL of dry methanol were added 0.93 mL of 3.0 N NaOH (2.79 mmol) and 3.6 mL of 30% hydrogen peroxide. The solution was kept at 0 °C with additional aliquots of 3.0 N NaOH (0.93 mL) added at 3.5 and 5 h. After an additional 22 h at 0 °C the reaction mixture was extracted into ether, washed twice with brine, dried over magnesium sulfate, and concentrated in vacuo to give 906.1 mg of 4:1:1 mixture of desired epoxy ketone **25b**, isomeric epoxy ketone **24b**, and starting enone **13**. Flash chromatography eluting with ether gave 480.0 mg of **25b** (34% based on recovered starting material) as a white solid. An analytical sample was obtained by additional flash chromatography eluting with ether (mp 50.0–51.0 °C); IR (2960 (s), 2920 (s), 2860 (s), 1745 (s), 1460 (w), 1220 (w), 1070 (s), 912 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.98 (d, J = 7 Hz, 3 H), 1.16 (d, J = 7 Hz, 3 H), 1.38 (s, 3 H), 1.87 (st, J = 7 Hz, 1 H), 2.87 (td, J = 8, 3 Hz, 1 H), 3.20 (dd, J = 12, 8 Hz, 1 H), 3.59 (dd, J = 12, 7 Hz, 1 H), 3.74 (t, J = 9 Hz, 1 H), 3.82 (t, J = 9 Hz, 1 H) 3.91 (dd, J = 9, 3 Hz, 1 H); mass spectrum, m/e 196.1094 (M^+, calcd for $C_{11}H_{16}O_3$, 196.1099).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.22; H, 8.27.

Preparation of Lactone 25a. A mixture consisting of 1.36 g (6.38 mmol) of sodium periodate in 18 mL of water and 29.0

mg (0.22 mmol) of ruthenium dioxide in 8 mL of carbon tetrachloride was vigorously stirred until generation of the deep yellow color of ruthenium tetraoxide. A solution containing 305.8 mg (1.56 mmol) of epoxy ketone **25b** in 10 mL of carbon tetrachloride was added dropwise to the two-phase system of ruthenium tetraoxide. The yellow color faded immediately and then reappeared in a few hours. Stirring was continued for an additional 5 days. After this time the phases were separated, and 250 μL of 2-propanol was added to the carbon tetrachloride layer to precipitate ruthenium dioxide. After drying, removal of solvent in vacuo followed by flash chromatography eluting with ether gave 131.0 mg (40.0%) of the desired lactone **25a** as a pale yellow oil. An analytical sample was obtained by additional chromatography eluting with ether; IR 2970 (s), 2930 (s), 1775 (s), 1750 (s), 1455 (w), 1255 (s), 1168 (w), 1087 (s), 1027 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.18 (d, *J* Hz, 3 H), 1.34 (d, *J* = 7 Hz, 3 H), 1.52 (s, 3 H), 2.28 (st, *J* = 7 Hz, 1 H), 3.13 (td, *J* = 9, 2 Hz, 1 H), 3.75 (d, *J* = 9 Hz, 1 H), 4.36 (dd, *J* = 9, 7 Hz, 1 H), 4.57 (dd, *J* = 9, 2 Hz, 1 H); mass spectrum, *m/e* 210.0871 (M^+, calcd for $C_{11}H_{14}O_4$, 210.0892).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.86; H, 6.67. Found: C, 62.66; H, 6.81.

Preparation of Allylic Alcohol 27a. To a solution of 5.5 mL of 95% hydrazine hydrate in 9 mL of dry methanol, cooled to 0 °C under a stream of nitrogen, was slowly added 1.36 g (6.90 mmol) of epoxy ketone **25a** in 12 mL of methanol. The bright yellow solution was stirred at 0 °C for an additional 25 min and then refrigerated at 4 °C for 5 days, at which time the yellow color had partially faded. After the addition of 30 mL of water, the rearrangement product was extracted into ether and dried, and the solvent was removed in vacuo. Flash chromatography eluting with ether gave 736.3 mg (59%) of allylic alcohol **27a** as a yellow oil. An analytical sample was prepared by flash chromatography eluting with ether; IR 3550 (w), 3430 (w), 2970 (s), 2860 (s), 1450 (w), 1360 (w), 1275 (w), 1063 (s), 1022 (s), 992 (s), 915 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.73 (d, *J* = 7 Hz, 3 H), 0.95 (d, *J* = 7 Hz, 3 H), 1.67 (s, 3 H), 1.9, (s, 1 H, D_2O ex), 2.00 (st, *J* = 7 Hz, 1 H), 2.68 (dd, *J* = 8, 7 Hz, 1 H), 3.11 (br m, 1 H), 3.41 (dd, *J* = 9, 6 Hz, 1 H), 3.49 (dd, *J* = 8, 8 Hz, 1 H), 3.61 (dd, *J* = 8, 2 Hz, 1 H), 4.23 (d, *J* = 9 Hz, 1 H), 5.42 (s, 1 H).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.53; H, 9.89. Found: C, 72.49; H, 9.91.

Preparation of Trimethylsilyl Ether 27c. To a solution of 250.0 mg (1.37 mmol) of **27a** in 12 mL of dimethylformamide was added 880 μL (6 equiv) of triethylamine followed by 525 μL of trimethylsilyl chloride (3 equiv). This mixture was heated at 30–35 °C on an oil bath for 26.5 h. Workup consisted of extracting into ice cold 1:1 ether/pentane and washing with cold water, saturated $NaHCO_3$, additional cold water, and brine. The organic layer was dried and the solvent removed in vacuo. Flash chromatography eluting with ether gave 94% yield of **27c** as a pale yellow oil: IR 2945 (s), 2865 (s), 1450 (w), 1380 (w), 1255 (s), 1052 (b), 908 (s), 824 (b) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.08 (s, 9 H), 0.66 (d, *J* = 7 Hz, 3 H), 0.88 (d, *J* = 7 Hz, 3 H), 1.65 (s, 3 H), 1.86 (st, *J* = 7 Hz, 1 H), 2.63 (td, *J* = 7, 3 Hz, 1 H), 2.98 (br m, 1 H), 3.46 (t, *J* = 9 Hz, 1 H), 3.57 (d, *J* = 5 Hz, 2 H), 4.03 (dd, *J* = 9, 3 Hz, 1 H), 5.35 (s, 1 H).

Preparation of Diol 29b. To a 0 °C solution of 566.0 mg (2.23 mmol) of osmium tetraoxide in 6 mL of pyridine was added 578.3 mg (2.27 mmol) of **27c** in 6 mL of pyridine. After this stirred at room temperature for 22 h, a solution of 4 g of $NaHSO_3$ in 12 mL of water was added. After 24.5 h the mixture was thoroughly extracted with chloroform, and the organic layer was then washed with brine. After drying, removal of solvent in vacuo followed by flash chromatography eluting with ether gave a 64% yield (411.9 mg) of **29b** as a white crystalline solid. An analytical sample was obtained by additional flash chromatography eluting with ether (mp 116.0–119.0 °C); IR 3400 (s br), 2960 (s), 2855 (s), 1375 (w), 1260 (s), 1185 (s), 1095 (b) 1010 (w), 908 (w), 880 (s), 820 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.14 (s, 9 H), 0.88 (d, *J* = 7 Hz, 3 H), 0.92 (d, *J* = 7 Hz, 3 H), 1.26 (s, 3 H), 2.04 (st, *J* = 7 Hz, 1 H), 2.16 (s, 1 H, D_2O ex), 2.28 (br s, 1 H, D_2O ex), 2.51 (m, 1 H), 2.83 (ddd, *J* = 10, 8, 4 Hz, 1 H), 3.49 (t, *J* = 9 Hz, 1 H), 3.53–3.82 (complex m, 3 H), 3.84 (dd, *J* = 9, 4 Hz, 1 H).

Anal. Calcd for $C_{14}H_{28}O_4Si$: C, 58.29; H, 9.78. Found: C, 58.37; H, 9.81.

Preparation of Diols 28a and 29a. To a 0 °C solution of 551 mg (2.16 mmol) of osmium tetraoxide in 20 mL of pyridine was added 384 mg (2.11 mmol) of allylic alcohol **27a** in 7 mL of pyridine. After this stirred at room temperature for 4 h, a solution of 4 g $NaHSO_3$ in 16 mL of water was added. After 19 h the mixture was thoroughly extracted with chloroform, and the organic layer was then washed with brine. After drying, removal of solvent in vacuo gave 341 mg of a mixture of 3:1 mixture of **28a** and **29a**, respectively, which was not purified but was converted into a mixture of cyclopentylidine derivatives **31a** and **30a**.

Preparation of *endo*-Cyclopentylidene Derivative 31a. To a solution of 133.0 mg (0.62 mmol) of a 3:1 mixture of the triols **28a** and **29a** in 25 mL of benzene was added 3 mL of cyclopentanone followed by 28.5 mg of *p*-toluenesulfonic acid. This solution was heated at reflux for 22.5 h, with removal of water via a Dean Stark trap. The solution was cooled, extracted into ether, and washed with a small volume of saturated $NaHCO_3$. The organic layer was dried, concentrated in vacuo, and purified by flash chromatography eluting with ether to give 149.7 mg (86%) of a mixture of the two isomers **31a** and **30a**. Additional chromatography (1:1:10, ether/pentane/methylene chloride) gave 65.0 mg (37%) of the desired isomer **31a** as a colorless oil: IR 3540 (w), 3010 (s), 2970 (s), 2880 (s), 1460 (w), 1390 (w), 1340 (s), 1210 (s), 1106 (s), 1072 (w), 970 (w), 902 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.79 (d, *J* = 7 Hz, 3 H), 0.83 (d, *J* = 7 Hz, 3 H), 1.32 (s, 3 H), 1.54–1.72 (complex m, 7 H), 1.90–2.02 (complex m, 2 H), 2.46 (s, 1 H, D_2O ex), 2.62–2.83 (complex m, 2 H), 3.65 (dd, *J* = 9, 7 Hz, 1 H), 3.69 (dd, *J* = 9, 6 Hz, 1 H), 4.02 (dd, *J* = 8, 7 Hz, 1 H), 4.09 (d, *J* = 8 Hz, 1 H), 4.17 (dd, *J* = 9, 3 Hz, 1 H); mass spectrum, *m/e* 282.1837 (M^+, calcd for $C_{16}H_{26}O_4$, 282.1832).

Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 67.87; H, 9.28.

Oxidation of *endo*-Cyclopentylidene Derivative 31a to Lactone 31b. To a solution of 477.0 mg (2.22 mmol) of sodium periodate in 12 mL of water was added 10% Na_2CO_3 until a pH of ~7 was reached; 12.0 mg (0.09 mmol) of ruthenium dioxide in 6 mL of carbon tetrachloride was added, and the biphasic mixture was stirred until the yellow color of ruthenium tetraoxide was achieved. At this point 164.0 mg (0.58 mmol) of tetrahydrofuran **31a** was added, and the mixture was stirred at rt for 3.5 days. Workup consisted of extraction into methylene chloride followed by addition of 0.5 mL of isopropyl alcohol to precipitate the ruthenium dioxide. The organic layer was dried over magnesium sulfate, and the solvent was removed in vacuo. Chromatography eluting with 10:1 methylene chloride/ether gave a 38% yield of lactone **31b** as a white solid. An analytical sample was obtained by flash chromatography eluting with ether (mp 94–96 °C); IR 3750 (w), 3560 (w), 3050 (s), 1750 (s), 1340 (w), 1220 (s), 1117 (w), 920 (w), 770 (s), 710 (s), 640 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.94 (d, *J* = 7 Hz, 3 H), 1.04 (d, *J* = 7 Hz, 3 H), 1.42 (s, 3 H), 1.54–1.79 (complex m, 4 H), 1.80–2.05 (complex m, 5 H), 2.86 (d, *J* = 9 Hz, 1 H), 2.93–3.08 (complex m, 1 H), 3.62 (s, 1 H, D_2O ex), 4.24 (t, *J* = 9 Hz, 1 H), 4.28 (d, *J* = 2 Hz, 1 H), 4.65 (dd, *J* = 9, 4 Hz, 1 H).

Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.74; H, 7.96.

Preparation of *exo*-Cyclopentylidene Derivative 30a. To a solution of 1.86 g (6.47 mmol) of diol **29a** in 120 mL of benzene was added 20 mL of cyclopentanone followed by 240.0 mg of *p*-toluenesulfonic acid. This solution was heated at reflux for 20.5 h with removal of water via a Dean Stark trap. The solution was cooled, poured into ether, and washed with a small volume of saturated $NaHCO_3$ solution. The organic layer was dried over magnesium sulfate and concentrated in vacuo. Flash chromatography eluting with ether gave 2.37 g of a 3:1 mixture of the protected alcohol **30c** and the alcohol **30a**; 2.22 g of this mixture was dissolved in 50 mL of tetrahydrofuran and treated with 7 mL of 1 M tetra-*n*-butylammonium fluoride for 10 min. The reaction mixture was extracted into ether and washed with brine. The organic layer was then dried over magnesium sulfate and concentrated in vacuo. Purification via flash chromatography eluting with ether gave 1.64 g of the alcohol **30a** (89% from diol **29**). An analytical sample was obtained by additional chromatography, eluting with ether (mp 75–76 °C): IR 3480 (w), 2950 (s), 2875 (s), 1475 (w), 1380 (s), 1340 (s), 1196 (s), 1098 (s), 1042 (s), 960 (s), 892 (w), 870 (w), 768 (s), 652 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250

MHz) δ 0.90 (d, J = 7 Hz, 3 H), 0.97 (d, J = 7 Hz, 3 H), 1.37 (s, 3 H), 1.58–1.69 (complex m, 4 H), 1.73–1.88 (complex m, 4 H), 2.05 (st, J = 7 Hz, 1 H), 2.53 (s, 1 H, D_2O ex), 2.62–2.75 (complex m, 1 H), 2.97 (dd, J = 9, 6 Hz, 1 H), 3.57 (dd, J = 9, 6 Hz, 1 H), 3.64 (dd, J = 9, 7 Hz, 1 H), 3.82 (t, J = 9 Hz, 1 H), 4.09 (d, J = 2 Hz, 1 H), 4.12 (d, J = 9 Hz, 1 H).

Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.03; H, 9.35.

Oxidation of *exo*-Cyclopentylidene Derivative 30a to Lactone 30b. Following a procedure identical with that given for the isomeric material, 253.0 mg (0.89 mmol) of **30a** was converted to 108.8 mg (41% yield) of the lactone **30b**. An analytical sample was obtained by chromatography eluting with ether (mp 126.0–128.0 °C; IR 3610 (w), 2795 (s), 1760 (s), 1460 (w), 1380 (w), 1340 (s), 1250 (w), 1185 (s), 1120 (s), 1062 (s), 1025 (s), 870 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.07 (d, J = 7 Hz, 3 H), 1.13 (d, J = 7 Hz, 3 H), 1.37 (s, 3 H), 1.55–1.70 (complex m, 4 H), 1.73–1.87 (complex m, 4 H), 2.21 (st, J = 7 Hz, 1 H), 2.28 (s, 1 H, D_2O ex), 2.98 (app qd, J = 9, 2 Hz, 1 H), 3.35 (d, J = 9 Hz, 1 H), 4.05 (t, J = 9 Hz, 1 H), 4.18 (d, J = 2 Hz, 1 H), 4.46 (dd, J = 9, 8 Hz, 1 H).

Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.84; H, 8.23.

Preparation of Cyclo-β-isoxanthocidin (32). To a room-temperature solution of 208.5 mg (0.70 mmol) of lactone **30b** in 15 mL of acetonitrile and 15 mL of water was added 4.0 mL of trifluoroacetic acid. After 22 h an additional 2.0 mL of trifluoroacetic acid was added, and the mixture was then stirred at 60 °C for 4 h. At this time a final 1.0 mL of trifluoroacetic acid was added. After stirring for an additional 1 h at 60 °C, the reaction mixture was extracted into ether and washed with 10% Na_2CO_3. The organic layer was dried, and the solvent was removed in vacuo to give 210.0 mg of a light yellow oil. Flash chromatography eluting with ether gave 39.5 mg of recovered starting material **30b** and 114.1 mg (78%) of triol **29c**.

To 50 μL (0.55 mmol) of oxalyl chloride in 1 mL of methylene chloride at −55 °C was added 80 μL (1.04 mmol) of dimethyl sulfoxide. After this stirred at −55 °C for 3 min, a solution of 105.7 mg (0.46 mmol) of triol **29c** in 1 mL of methylene chloride, 50 μL of methylene chloride, and 50 μL of dimethyl sulfoxide was added. This mixture was stirred at −55 °C for 15 min and then at room temperature for 5 min. After cooling to −55 °C, 300 μL of triethylamine was added and the reaction mixture extracted into methylene chloride. The organic layer was washed with 2% HCl and then 5% Na_2CO_3 and dried. Removal of solvent in vacuo gave 72.8 mg of a yellow oil. Flash chromatography eluting with ether gave 36.7 mg (35%) of **32** as a white solid (mp 157–158 °C): IR 3485 (w, br), 2945 (s), 1770 (s), 1750 (s), 1455 (w), 1385 (w), 1172 (w), 1095 (w), 1028 (w); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.03 (d, J = 7 Hz, 3 H), 1.13 (d, J = 7 Hz, 3 H), 1.33 (s, 3 H), 1.62 (s, br, 1 H, D_2O ex), 2.37 (st, J = 7 Hz, 1 H), 2.93 (s, br, 1 H, D_2O ex), 3.44 (d, J = 12 Hz, 1 H), 3.52 (complex m, 1 H), 4.35 (dd, J = 10, 4 Hz, 1 H), 4.51 (t, J = 10 Hz, 1 H); mass spectrum, *m/e* 228.0982 (M^+, calcd for $C_{11}H_{16}O_5$, 228.0997).

Preparation of (±)-β-Isoxanthocidin (10). To a suspension of 26.0 mg (0.11 mmol) of lactone **32** in 2.2 mL of 2-(trimethylsilyl)ethanol was slowly added 265 μL (3.7 mmol) of acetyl chloride. The flask was equipped with a drying tube, and the reaction mixture was stirred at room temperature for 4 days. At this point an additional 200 μL (2.8 mmol) of acetyl chloride was added, and stirring was continued for 3 days. The solvent was removed in vacuo, and the residue was dissolved in ether. The acidic material was extracted into 5% Na_2CO_3 and allowed to stand for 1 h at room temperature. Acidification to pH 1 with 10% HCl followed by extraction into ether, drying, and removal of solvent in vacuo gave 21.0 mg of a bright yellow oil. Purification by thin-layer chromatography (10 × 10 cm, 250-μm analytical plate) eluting with ether gave 10.2 mg of a yellow oil that consisted mainly of β-isoxanthocidin B (**10**). A second chromatographic separation under identical conditions yielded 8.0 mg (30%) of (±)-β-isoxanthocidin (**10**) as a pale yellow low-melting solid: IR 3670 (w), 3400 (br), 2975 (s), 2870 (s), 1735 (s), 1710 (s), 1640 (w), 1390 (s), 1115 (s), 916 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.97 (d, J = 7 Hz, 3 H), 1.07 (d, J = 7 Hz, 3 H), 1.43 (s, 3 H), 2.31 (st, J = 7 Hz, 1 H), 3.92 (t, J = 3 Hz, 1 H), 5.66 (d, J = 3 Hz, 1 H), 6.37 (d, J = 3 Hz, 1 H).

Preparation of Cycloepixanthocidin (33). To 47.0 mg (0.16 mmol) of lactone **31b** in 6 mL of acetone was added 2 mL of 5% HCl. Additional 2-mL aliquots of 10% HCl were added after 20 and 29 h. After a total reaction time of 41 h the reaction mixture was extracted into methylene chloride and washed with a saturated $NaHCO_3$ solution. The organic layer was dried and the solvent removed in vacuo to give 29.0 mg (80%) of triol **28b** as a colorless oil.

With the Swern oxidation conditions reported for the isomeric triol **29c**, 61.5 mg (0.27 mmol) of triol **28b** was converted to 63.0 mg of **33**. Purification of this material was achieved via two chromatographic separations; first eluting with ethyl acetate and second eluting with ether to obtain 15 mg (25%) of **33** as a white solid (mp 124–126 °C): IR 3524 (br), 2980 (s), 1780 (s), 1755 (s), 1450 (w), 1380 (s), 1180 (s), 1119 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.06 (d, J = 7 Hz, 3 H), 1.17 (d, J = 7 Hz, 3 H), 1.31 (s, 3 H), 2.13 (st, J = 7 Hz, 1 H), 3.05 (s, 1 H, D_2O ex), 3.13 (s, 1 H, D_2O ex), 3.27 (d, J = 11 Hz, 1 H), 3.50 (td, J = 11, 5 Hz, 1 H), 4.31 (dd, J = 10, 5 Hz, 1 H), 4.47 (t, J = 10 Hz, 1 H); mass spectrum, *m/e* 228.0986 (M^+, calcd for $C_{11}H_{16}O_5$, 228.0997).

Preparation of (±)-Epixanthocidin (9). To a suspension of 12.0 mg (0.052 mmol) of lactone **33** in 1 mL of 2-(trimethylsilyl)ethanol was slowly added 120 μL (1.68 mmol) of acetyl chloride. The flask was equipped with a drying tube, and the reaction mixture was stirred at room temperature for 5 days. The solvent was removed in vacuo and the residue dissolved in ether. The acidic material was extracted into 5% Na_2CO_3 and allowed to stand at room temperature for 1 h. Acidification to pH 1 with 10% HCl followed by extraction into ether, drying, and removal of solvent in vacuo gave 14.7 mg of a dark yellow solid. Purification was achieved by thin-layer chromatography (10 × 11 cm, 250-μm analytical plate) eluting with ether to yield 6.0 mg (50%) of (±)-epixanthocidin (**9**) as a pale yellow low-melting solid: IR 3660 (w), 3380 (br), 2980 (s), 2870 (s), 1725 (s, br), 1640 (w), 1385 (s), 1265 (s), 1100 (s), 904 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.05 (d, J = 7 Hz, 3 H), 1.07 (d, J = 7 Hz, 3 H), 1.23 (s, 3 H), 2.05 (st, J = 7 Hz, 1 H), 3.62 (t, J = 3 Hz, 1 H), 5.82 (d, J = 3 Hz, 1 H), 6.44 (d, J = 3 Hz, 1 H).

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Registry No. (±)-**8**, 80952-58-5; (±)-**9**, 84142-80-3; (±)-**10**, 84142-81-4; (±)-**11**, 80927-72-6; (±)-**13**, 80927-77-1; (±)-**14**, 80927-80-6; (±)-**15**, 80927-73-7; (±)-**16**, 80927-74-8; (±)-**17**, 80927-75-9; (±)-**18**, 80927-76-0; (±)-**19**, 84370-64-9; (±)-**21**, 80927-81-7; (±)-**22**, 80927-79-3; (±)-**24a**, 84370-68-3; (±)-**24b**, 84370-67-2; (±)-**25a**, 84415-17-8; (±)-**25b**, 84415-16-7; (±)-**26**, 84370-65-0; (±)-**26** (*endo*-epoxide), 84370-66-1; (±)-**27a**, 84370-69-4; (±)-**27c**, 84370-70-7; (±)-**28a**, 84370-72-9; (±)-**28b**, 84415-21-4; (±)-**29a**, 84415-18-9; (±)-**29b**, 84370-71-8; (±)-**29c**, 84370-76-3; (±)-**30a**, 84415-19-0; (±)-**30b**, 84471-48-7; (±)-**30c**, 84370-75-2; (±)-**31a**, 84370-73-0; (±)-**31b**, 84370-74-1; (±)-**32**, 84415-20-3; (±)-**33**, 84415-22-5; maleic anhydride, 108-31-6; 2-methyl-3-hexyne, 36566-80-0; cyclopentanone, 120-92-3; 1-acetyl-1-isopropyl-3-oxotetrahydro-1*H*,3*H*-furo[3,4-*c*]furan, 84370-77-4.