two resonances at δ 129.9 and 137.6 in the ^{13}C NMR, leading to the conclusion that the molecule must also contain one ring. The striking correspondence between the carbon resonances in **1** and those assigned to terminal ring carbons in zeaxanthin (**8**, Figure 1) strongly suggest that the 1,3-butadione group in **1** must be attached to a 2,6,6-trimethyl-4-hydroxycyclohexenyl substituent. Examination of the ^1H NMR (Figure 2) confirms this structural hypothesis and provides evidence concerning the conformation of the cyclohexene ring. Thus the geminal methyl groups at C6 appear as two singlets at δ 1.08 (3 H) and 1.19 (3 H) while the olefinic methyl attached to C2 is a sharp singlet at δ 1.69 (3 H). All four methylene protons on C3 and C5 are clearly resolved at 400 MHz. A 2-Hz W coupling between H_a and H_d and an observed J_{bc} = 10 Hz and J_{ce} = 12 Hz suggest that the hydroxyl group on C4 must be pseudoequatorial as shown (Figure 2).

Acetylation of **1** (Ac_2O, pyridine, room temperature, 24 h) gave the monoacetoxy derivative **2** (60% yield):[9] mass spectrum, m/z 266.1521 (M^+), calcd for $C_{15}H_{22}O_4$ m/z 266.1518; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.03 (s, 3 H, CH_3CO_2), 5.07 (m, 1 H, AcOCH<).[10] Reaction of β-diketone **1** with NH_2OH·HCl (refluxing EtOH, NaOAc, 3 h) gave a quantitative yield of a single isoxazole derivative which is one of the two regioisomers **3** or **4**: mass spectrum, m/z 221.1414 (M^+), calcd for $C_{13}H_{19}NO_2$ m/z 221.1415; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.95 (s, 3 H), 1.12 (s, 3 H), 1.57 (s, 3 H), 2.31 (s, 3 H), 1.51 (m, unresolved, 1 H), 1.84 (ddd, J = 12, 2, 3 Hz, 1 H), 2.09 (dd, J = 17.5, 10 Hz, 1 H), 2.44 (ddd, J = 17.5, 6, 2 Hz, 1 H), 3.58 (br, 1 H), 4.10 (m, 1 H), 5.84 (s, 1 H).

The β-diketone **1** is related to 3-hydroxy-β-ionone (**5**)[11] and 3-hydroxy-β-damascone (**6**),[12] flavoring constituents of Burley tobacco. It is generally believed that metabolites containing this carbon skeleton are degradation products of carotenoids.[13] Zeaxanthin or a related algal carotenoid could conceivably lead to **1**.

The β-diketone **1** shows in vitro antibiotic activity against *Staphylococcus aureus*, and it has the potential of being an excellent trace-metal chelator. We are currently exploring the biological significance of these properties.

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Registry No. (-)-**1**, 72726-22-8; **2**, 72726-23-9.

(9) The other products were an inseparable mixture of the isomeric diacetates.

(10) The remainder of the ^1H NMR of **2** is complicated by the existence of all three tautomeric forms.

(11) Fujimori, T.; Kasuga, R.; Naguchi, M.; Kaneko, H. *Agric. Biol. Chem.* **1974**, *38*, 891. 3-Hydroxy-β-ionone is numbered according to the carotenoid convention which differs from the IUPAC nomenclature for cyclohexenes.

(12) Kaneko, H.; Harada, M. *Agric. Biol. Chem.* **1972**, *36*, 168.

(13) Isoe, S.; Hyeon, S. B.; Sakan, T. *Tetrahedron Lett.* **1969**, 279.

(14) All signals could be decoupled at 270 MHz.

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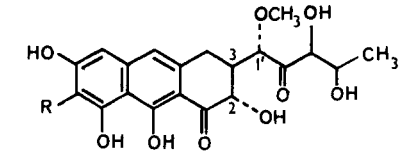
Stereocontrolled Synthesis of a Model Aureolic Acid Aglycone via Diels-Alder Reaction of an Unsaturated Sugar

Summary: The model aureolic acid aglycone **20** has been prepared in five steps from readily available starting materials. The first step, a Diels–Alder reaction between cyanobenzocyclobutene **3**, as its ring-opened *o*-quinone methide, and glucal derivative **8**, is both stereoselective and regioselective. The last step, a modified permanganate oxidation of an unsaturated nitrile to an aromatic acyloin, is also stereoselective.

Sir: The aureolic acid class of antitumor antibiotics is comprised of three subgroups. One group, the olivomycins, is a family of antibiotics isolated from *Actinomycetes olivoreticuli* with the polyoxygenated anthracene aglycone **1**, called olivin. The aglycone is linked to a disaccharide



1 R = H

2 R = CH_3

at C6 and a trisaccharide at C2.[1] Similarly, the chromomycins and the mithramycins are antibiotics from *Streptomyces* which have the aglycone **2** which is a 7-methylolivin.[2]

The only descriptions of synthetic studies in the aureolic acid series come from the Weinreb group.[3] Among several problems there remains open the question of establishing the correct stereochemical relationships at carbons 1′, 2, and 3, and it is our response to this aspect of the aureolic acid challenge that we now describe. Our retrosynthetic analysis suggested that a Diels–Alder addition of a naphthoquinone methide and an unsaturated sugar (as its cyclic enol ether) would afford a convergent synthesis of the aureolic acid group. The sugar would need to be derived from D-fucose (6-deoxygalactose) in order to correspond to the natural product configuration. For our initial studies we chose a readily available benzoquinone methide precursor.

Although precedents for the addition of an enol ether to a quinone methide and for the Diels–Alder reaction of sugars both existed, the regio- and stereoselectivity of our proposed reaction had to be tested.[4,5] Thus, thermolysis of cyanobenzocyclobutene **3** and dihydropyran **4** afforded a 4:1 mixture of tricyclics **5** and **6** in 70% yield. Each product could be ring opened to the same bicyclic **7**, thus demonstrating that they indeed were exo–endo epimers at the cyano group with the necessary regiochemistry for

(1) (a) Berlin, Y. A.; Esipov, S. E.; Kolosov, M. N.; Shemyakin, M. M.; *Tetrahedron Lett.* **1966**, 1431–6, 1643–7. (b) Bakhaeva, G. P.; Berlin, Y. A.; Chuprinova, O. A.; Kolosov, M. N.; Peck, G. Y.; Pietrovich, L. A.; Shemyakin, M. M.; Vasina, I. V. *Chem. Commun.* **1967**, 10–11. (c) Skarbek, J. O.; Brady, L. R. *Lloydia* **1975**, *38*, 369–77. (d) Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley: New York, 1979; pp 133–75. The last reference is a comprehensive review of the field.

(2) (a) Miyamoto, M.; Morita, K.; Kawamatsu, Y.; Noguchi, S.; Marumoto, R.; Tanaka, K.; Tatsuoka, S.; Nakanishi, K.; Nakadaira, Y.; Bhacca, N. S. *Tetrahedron Lett.* **1964**, 2355–65. (b) Bakhaeva, G. P.; Berlin, Y. A.; Boldyreva, E. F.; Chuprevna, O. A.; Kolosov, M. N.; Soifer, V. S.; Vasiljova, T. E.; Yartseva, I. V. *Ibid.* **1968**, 3595–8. (c) Berlin, Y. A.; Kolosov, M. N.; Pietrovich, L. A. *Ibid.* **1970**, 1329–31.

(3) (a) Hatch, R. P.; Shringapure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172–4177. (b) Dodd, J. H.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, 3593–3596.

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(5) Jurczak, J.; Tkacz, M. *Synthesis* **1979**, 42–4.

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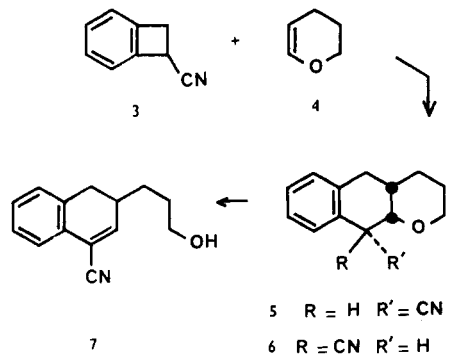
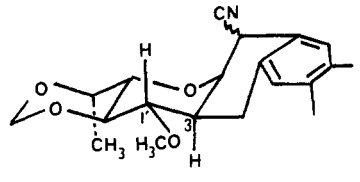
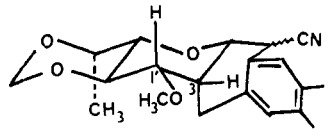


our project. The stereochemical problem can be summarized in the following way. The crucial chiral center to be established in the Diels–Alder reaction with our chiral alkene can be formed in two ways. Approach of the quinone methide, in either an exo or endo manner, toward the alkene face above the allylic methoxyl will afford the desired stereochemistry shown in A. Approach of the



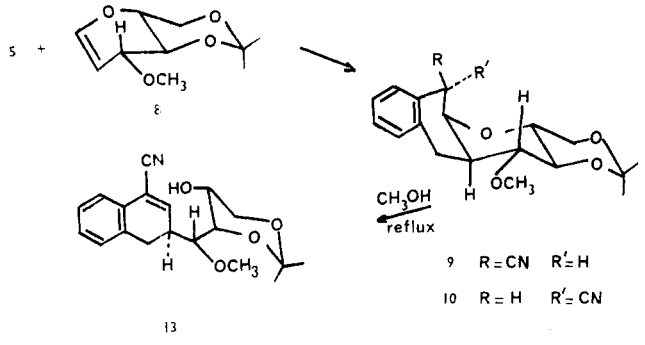
A



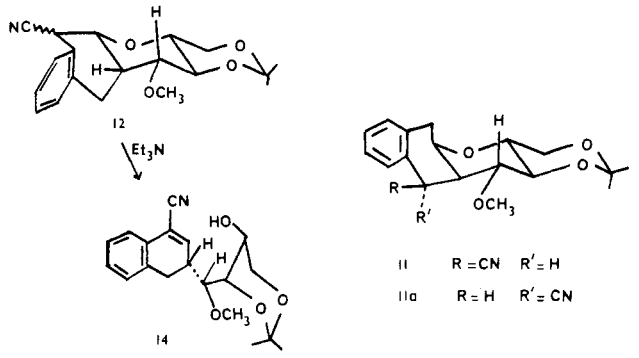
A′

quinone methide toward the face below the methoxyl will afford the unnatural stereochemistry of A′. Our examination of models and a precedent from the cytochalasin work of Vedejs[6] led us to predict that the natural stereochemistry would predominate in our reaction.

For our feasibility study, we chose the glucose derivative **8** which is enantiomeric at the methoxyl carbon to our proposed fucose dienophile; thus the stereochemical analysis simply becomes enantiomeric. In the event of reaction of cyanobenzocyclobutene **3** with sugar **8**, there was isolated by PLC adducts **9**–**12** and some ring-opened material **13**, contaminated with a trace of **14**, in addition

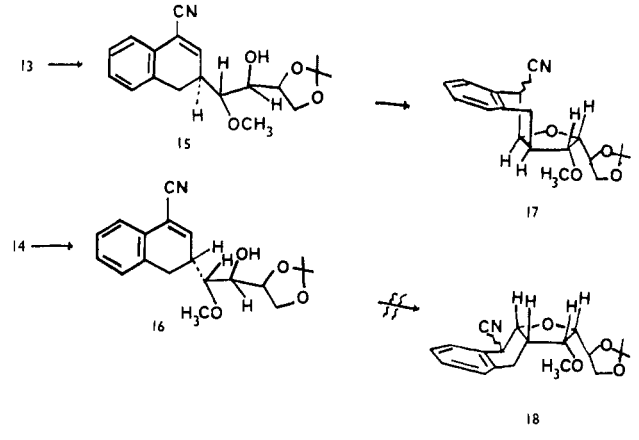


to two quinone methide dimers.[7] After correction for the 33% of cyanobenzocyclobutene consumed as dimer, the yields were 20% for **9** (mp 165–167 °C), 45% for **10**, 9% for **11**, 14% for **12** (mp 142–144 °C), and 4% for **13** (mp 122–124 °C). There is a 9:1 regioselectivity and, in the correct regioisomers, a 5:1 stereoselectivity for the predicted natural series. It was demonstrated that the major adducts **9** and **10** belonged to the same stereochemical series because **9** could be converted to **10** on alumina, and both adducts were converted to **13** (vide infra). One minor adduct was assigned the regioisomeric structure **11**. Upon



treatment with Et_3N, it did not ring open, but simply epimerized to **11a**.[8] Minor adduct **12** belonged to the correct regioisomeric series but to the unnatural stereochemical family. It could be ring opened to **14** (NMR δ 6.92, vinyl H), an epimer of **13** (NMR δ 6.80). Epimers **13** and **14** gave essentially equal and opposite ORD spectra, suggestive of compounds that differ only in the configuration of the center adjacent to the chromophoric system. That the major adducts **9** and **10** had the desired stereochemistry at the new center at C3 was inferred from the clean diaxial coupling constants discerned for the protons at C1′ and C2′.

Quantitative ring opening of **9** and **10** to nitrile **13** occurred in refluxing methanol. When triethylamine was used as a basic catalyst, some epimerization at C3 was detected. Nitrile **13** was treated with acetone and *p*-TosH and was quantitatively converted to isomeric acetonide **15**. This desirable outcome was predicted on the basis of precedents in the carbohydrate literature.[9] Nitrile **14** in a like manner was also converted to isomeric acetonide **16**.



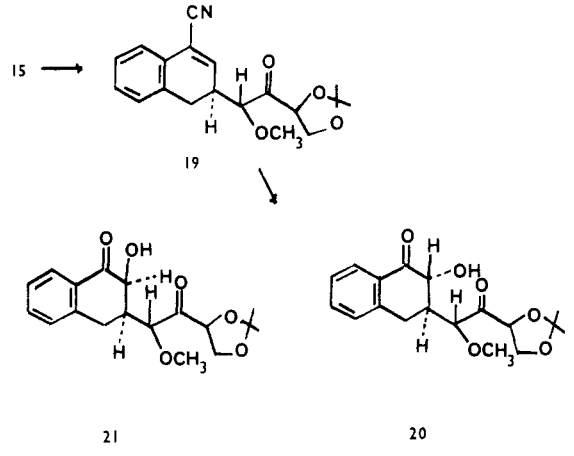
The chemical proof of the stereochemistry at the critical center, C3, is derived from the behavior of **15** and **16**. When **15** is treated with a catalytic amount of pyridine and

(6) Vedejs, E.; Gadwood, R. C. *J. Org. Chem.* **1978**, *43*, 376–7.
(7) Jones, O. W.; Kneen, G. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1647–54.

(8) Deuterium-exchange experiments, analyzed by NMR, revealed that the proton α to the cyanide was coupled to the only shielded methine proton, thus our assignment of regioisomeric structure.
(9) (a) Barker, S. A.; Bourne, E. J. *Adv. Carbohydr. Chem.* **1952**, *7*, 137–207. There are more modern reviews of acetal and ketal formation, but these authors point out that cyclic ketals of acyclic sugar alcohols tend to form five-membered rings at the chain terminus. If that least-encumbered ketal is precluded because the terminal hydroxyl is blocked, then trans-substituted dioxolanes are the next preferred type. (b) Bonner, T. G.; Bourne, E. J.; Cole, R. F. J.; Lewis, O. *Carbohydr. Res.* **1972**, *21*, 29–35.

CuCl, it is cyclized to tetrahydrofuran **17** which has its pairs of cis substituents on opposite faces of the THF ring, a fairly uncrowded array. In contrast to the facile reaction of **15**, the cyclization of **16** to **18** did not take place even when subjected to identical experimental conditions for an extended time period. It is clear that **18** would have all four substituents on the same face of the THF ring and would thus be very congested. Hence we conclude that our major products from the Diels–Alder reaction do have the "natural" stereochemistry, and we can proceed with our synthetic scheme.

The Garegg modification of the Collins oxidation[10] of **15** afforded ketone **19** (25–89%, IR 1720 cm^{-1}) with the other product being a B-ring aromatized species due to uncontrollable overoxidation. A Me_2SO–TFAA method[11] produced ketone **19** in 90% yield reproducibly. Hydroxylation of the double bond of **19**, creating a hydroxy cyanohydrin which should become a hydroxy ketone,[12] was predicted to create the new hydroxyl at C2 with the correct stereochemistry since the sugar side chain at C3 should force attack from the opposite side. In the event, oxidation with triphenylmethylphosphonium permanganate at −78 °C yielded **20** (41%) and **21** (25%) easily separable by PLC.[13] The major product had an IR spectrum (1730, 1680 cm^{-1}) characteristic of the aglycone when its phenolic H bonding is blocked.[1] Its UV spectrum (247, 287 nm) is characteristic of an aromatic acyloin. The NMR of its acetate revealed, for the proton at C2, a $J_{2,3}$ of 12 Hz at δ 5.62 which is diagnostic for the trans diaxial stereochemistry of the protons in the natural product. Thus, we have in hand a compound that has the critical stereochemical features of the aureolic acids. There now remains the substantial task of constructing the correctly substituted precursors so as to complete the synthesis of the natural aglycone.[14,15]



(10) (a) Garegg, P. J.; Samuelsson, B. *Carbohydr. Res.* **1978**, *67*, 267–70. (b) When PDC alone was used, the oxidation was much slower, and byproduct **17** was obtained. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402.

(11) Yoshimura, J.; Sato, K.; Hashimoto, H. *Chem. Lett.* **1977**, 1327–30.

(12) Freerksen, R. W.; Raggio, M. L.; Thoms, C. A.; Watt, D. S. *J. Org. Chem.* **1979**, *44*, 702–10. The cited report describes a thorough examination of reagents for the hydroxylation of unsaturated nitriles for the purpose of converting them to acyloins.

(13) Reischl, W.; Zbiral, E. *Tetrahedron* **1979**, *35*, 1109–10.

(14) We are grateful to Professor S. M. Weinreb for his many insights on the aureolic acid problem which he shared in numerous discussions, to Dr. L. Foley of Hoffmann-La Roche for her invaluable assistance in pinpointing the appropriate carbohydrate methodologies for our work, and finally for the Biomedical Sciences Research Support Grant RR 7150 to Fordham University which gave partial support to this project.

(15) The major elements of this report were the subject of a paper delivered at the American Chemical Society meeting in Washington, DC, Sept 1979, CARBO 44.

Registry No. **3**, 6809-91-2; **4**, 25512-65-6; **5**, 72727-00-5; **6**, 72777-12-9; **7**, 72727-01-6; **8**, 72727-02-7; **9**, 72727-03-8; **10**, 72777-13-0; **11**, 72727-04-9; **11a**, 72777-14-1; **12**, 72777-15-2; **13**, 72727-05-0; **14**, 72777-16-3; **15**, 72727-06-1; **16**, 72777-17-4; **17**, 72727-07-2; **19**, 72727-08-3; **20**, 72727-09-4; **21**, 72777-18-5.

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Stereochemically Controlled Synthesis of Steroid Side Chains: Synthesis of Desmosterol

Summary: (20*R*)-Desmosterol, a versatile intermediate for the synthesis of vitamin D metabolites and numerous other steroids having a side chain modified at C-24 and/or C-25, can be synthesized stereospecifically and efficiently by starting from the readily available 16α,17α-epoxypregnenolone and employing the potassium-assisted oxy–Cope rearrangement as a key stereodirecting process at C-20.

Sir: The significant stereochemical dependence of the side chains on their activities of various physiologically active steroids, such as insect and crustacean molting hormones (ecdysones) and vitamin D metabolites, has been well documented.[1] Furthermore, recent isolations[2] of numerous sterols possessing unusual side-chain structures from marine sources have facilitated efforts toward the stereocontrolled synthesis of the steroid side chains, especially at C-20.[3,4] Unlike genuinely acyclic carbon chains,[5] steroid side chains have intrinsic advantages in their stereocontrolled synthesis, since the stereochemistry can be transmitted in their synthesis from the asymmetric and rigid steroid ring portions. Here we report a stereocontrolled, efficient steroid side-chain synthesis employing the concept of the stereochemical transmission via the oxy–Cope rearrangement (Scheme I).

The Wharton reaction,[6] with hydrazine hydrate in diethylene glycol and potassium hydroxide, of the tetrahydropyranyl (THP) ether derivative **2** (mp 123–124 °C) of the readily available 16α,17α-epoxypregnenolone[7] gave

(1) (a) Hikino, H.; Hikino, Y. *Fortschr. Chem. Org. Naturst.* **1970**, *28*, 256. (b) Nakanishi, K. *Pure Appl. Chem.* **1971**, *25*, 167. (c) DeLuca, H. F. *Handb. Physiol., Sect. 7: Endocrinol.* **1976**, *7*, 265.

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(3) (a) Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199. (b) Trost. B. M.; Bernstein, P. R.; Funfschilling, P. C. *J. Am. Chem. Soc.* **1979**, *101*, 4378. (c) Grieco, P. A.; Takigawa, T.; Moore, D. R. *Ibid.* **1979**, *101*, 4380.

(4) For a stereocontrolled synthesis of (20*S*)-20-isocholesterol, see: Koreeda, M.; Koizumi, N. *Tetrahedron Lett.* **1978**, 1641.

(5) See the following references and those cited therein for recent approaches to the synthesis of isoprenoid chains bearing chiral methyl centers which utilize chiral transmission via Claisen rearrangement: (a) Chan, K. K.; Cohen, N.; DeNoble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497. (b) Cohen, N.; Eichel, W. F.; Lopretsi, R. J.; Neukom, C.; Saucy, G. *Ibid.* **1976**, *41*, 3512. (c) Chan, K. K.; Saucy, G. *Ibid.* **1977**, *42*, 3828. (d) Chan, K. K.; Specian, A. C., Jr.; Saucy, G. *Ibid.* **1978**, *43*, 3435.

(6) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 2615.

(7) Purchased from Sigma Chemical Co., St. Louis, MO.

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