These functionalizations are free-radical chain processes, involving CCl_3 radical[7] or C_6H_5ICl radicals[8] as the hydrogen abstractors. Both of these species are known[7,8] to be highly selective for tertiary hydrogens; they also are clearly both rather bulky radicals. Under the circumstances, it is not surprising that they tend to attack on the less hindered α side of a steroid such as **6**, and that they attack tertiary axial hydrogens which are at the same time the most reactive and the most accessible.[9] Only hydrogens at positions 5, 9, and 14 are at the same time tertiary, α, and axial to a cyclohexane ring; in compounds such as **4** or **6** the hydrogen at C-5 may have decreased reactivity because of polar effects in the hydrogen abstraction transition state. Thus, it does seem that only[10] normal chemical factors are involved in the selectivity of this process, in contrast to the orientation factors involved in our remote oxidation methods. However, these highly selective reactions, in particular the reaction with $C_6H_5ICl_2$, may prove to be useful in steroid functionalization and related practical processes.[11]

(7) G. A. Russell and C. DeBoer, *J. Amer. Chem. Soc.*, **85**, 3136 (1963).

(8) D. D. Tanner and P. B. van Bostelen, *J. Org. Chem.*, **32**, 1517 (1967).

(9) *Reversible* free-radical abstraction of the hydrogen at C-14 had been observed previously by M. Grorodetsky and Y. Mazur, *J. Amer. Chem. Soc.*, **90**, 6540 (1968), and at C-5 by M. Gorodetsky, D. Kogan, and Y. Mazur, *ibid.*, **92**, 1094 (1970). The synthetically significant reaction at C-9 which we have observed could not have been detected in their epimerization studies.

(10) Although the ability of a *flat* reagent to pack on the *flat* side of the steroid so as to produce an activated complex with minimum volume may also be involved here.

(11) Support of this work by the National Institutes of Health is gratefully acknowledged.

Ronald Breslow,* James A. Dale, Paul Kalicky
Sophia Y. Liu, William N. Washburn

Department of Chemistry, Columbia University
New York, New York 10027

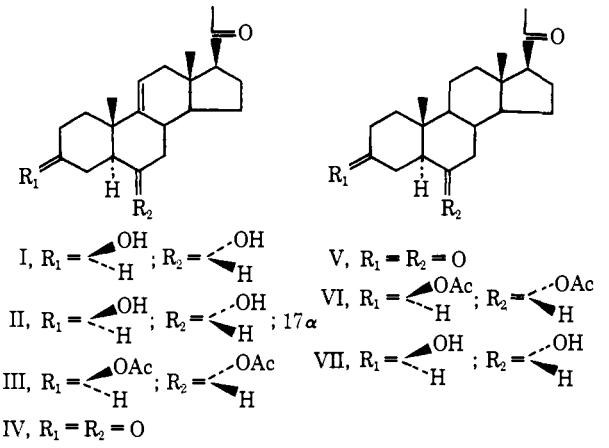
Received February 17, 1972

5α-Pregn-9(11)-ene-3β,6α-diol-20-one and 5α-Cholesta-9(11),20(22)-diene-3β,6α-diol-23-one. Two Novel Steroids from the Starfish *Acanthaster planci*

Sir:

In continuation of our work[1] on novel steroids from marine sources, we report the isolation of the hitherto unknown 5α-pregn-9(11)-ene-3β,6α-diol-20-one (I) and 5α-cholesta-9(11),20(22)-diene-3β,6α-diol-23-one (VIII) from the sapogenin portion (0.15% on dry basis) of *Acanthaster planci* Linn., a starfish threatening many of the Pacific coral reefs. The existence of the rare $\Delta^{9(11)}$ double bond, notably in the pregnene I, makes these compounds potentially interesting marine sources for corticosteroid syntheses.

Genin I [mp 162–163°, M^+ 332.23510, $C_{21}H_{32}O_3$ (required 332.23513); di-*p*-bromobenzoate, mp 198–200°] depicted a single positive Cotton effect [ORD, $\phi_{305} = +5199$, $\phi_{265} = -3812$; CD, $\theta_{287} = +7380$].



Its nmr spectrum (100 MHz, $CDCl_3$) depicted two quaternary methyl (δ 0.57, 0.95, s, 3 H each), an acetyl (2.11, s, 3 H), an acetyl methine (3.09, t, J = 9.5 Hz, 1 H, C-17α H), two secondary carbinol methine (3.57, m, 2 H, which are shifted in the noncrystalline diacetate III to 4.80 (m, 2 H)), and an olefinic proton (5.37, dt (distorted triplet), 1 H, J = 5.5 Hz) signal.

The skeleton and position of all three oxygens were established by hydrogenation of I followed by oxidation to the known triketone V[2] (identified by mixture melting point and comparison of ir, CD, and mass spectrum). Oxidation of I led to the triketone IV [mp 182–184°; M^+ 328; nmr ($CDCl_3$, benzene-d_6) C-18 CH_3 (0.63; 0.45, s, 3 H), C-19 CH_3 (1.01; 0.61, s, 3 H), CH_3CO (2.13; 1.75, s, 3 H), >C=C*H*CH_2 (5.60; 5.10, dt, 1 H)], which was essentially transparent in the uv (neutral or basic solution) and hence could not be an α,β- or β,γ-unsaturated ketone. Of the two possible alternative locations for the double bond (Δ^{14} or $\Delta^{9(11)}$), the former was excluded by the mass spectrum of IV which exhibited an important peak at *m/e* 243 (ring D cleavage)[3] thus indicating the presence of two oxygen atoms and the double bond in rings A, B, and C.

The stereochemistry of the two hydroxyl groups at positions 3 and 6 in I was established by hydrogenation of III followed by reoxidation (at C-20) to VI [$\theta_{292.5} = +5857$] and saponification to the known[4] 5α-pregnane-3β,6α-diol-20-one (VII) [mp 201–204°[4] (acetone–ether), 171–172° (acetone–hexane), M^+ 334].

In addition to I, there was isolated also a small amount of its 17α isomer 5α,17α-pregn-9(11)-ene-3β,6α-diol-20-one (II) [CD[5] of diacetate $\theta_{290} = -1541$, nmr and mass spectra very similar to that of I], but it is likely that it is an artifact produced during the acid hydrolysis of the glycoside rather than naturally occurring.

Genin VIII was isolated as a noncrystalline diacetate IX [λ_{max} (MeOH) 246.5 nm (ε 13,000); $\lambda_{max}(CHCl_3)$ 1735, 1685 cm^{-1}); CD(MeOH) $\theta_{247.5} = -12{,}000$; all spectral properties consistent with an α,β-unsaturated ketone]. The mass spectrum of IX showed the loss of two molecules of acetic acid (*m/e* 438, 378) and significant peaks at *m/e* 441 ($M^+ - C_4H_9$), 311 (438$^+$ –

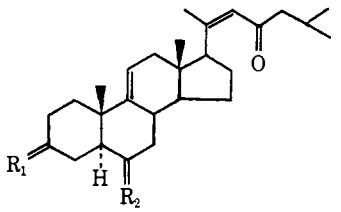
(1) R. L. Hale, J. Leclercq, B. Tursch, C. Djerassi, R. A. Gross, Jr., A. J. Weinheimer, K. Gupta, and P. J. Scheuer, *J. Amer. Chem. Soc.*, **92**, 2179 (1970); N. C. Ling, R. L. Hale, and C. Djerassi, *ibid.*, **92**, 5281 (1970); Y. M. Sheikh, C. Djerassi, and B. Tursch, *Chem. Connun.*, 217, 600 (1971).

(2) A. Schubert and R. Zepter, *J. Prakt. Chem.*, **26**, 159 (1964).

(3) L. Tökes, G. Jones, and C. Djerassi, *J. Amer. Chem. Soc.*, **90**, 5465 (1968).

(4) O. Mancera, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, **16**, 192 (1951).

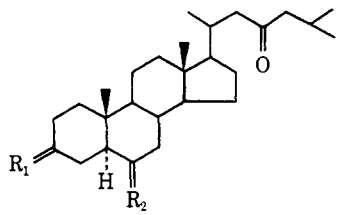
(5) G. Snatzke, G. Pieper, and R. Tschesche, *Tetrahedron*, 20, 107 (1964); C. Djerassi, *Bull. Soc. Chim. Fr.*, 741 (1957).



VIII, R_1 = 3α-OH, H; R_2 = 6β-OH, H

IX, R_1 = 3α-OAc, H; R_2 = 6β-OAc, H

X, $R_1 = R_2 = O$

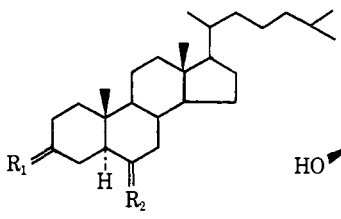


XI, R_1 = 3α-OAc, H; R_2 = 6β-OAc, H

XIa, R_1 = 3α-OAc, H; R_2 = 6β-OAc, H, 20 epimer

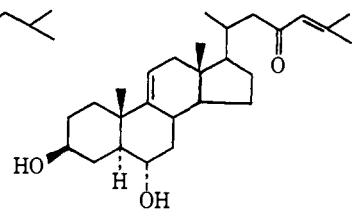
XII, R_1 = 3α-OH, H; R_2 = 6β-OH, H

XIIa, R_1 = 3α-OH, H; R_2 = 6β-OH, H, 20 epimer



XIII, R_1 = 3α-OH, H; R_2 = 6α-OH, H

XIV, $R_1 = R_2 = O$



XV

side chain + 2 H),[6] and 211 (ring D cleavage + $2CH_3COOH$). The nmr spectrum (100 MHz, $CDCl_3$) of IX depicted the presence of four methyl (δ 0.5–1.2, c, 12 H), two acetate, and a potential olefinic methyl mounted on a complex signal around δ 2.0, two broad acetate methine (δ 4.80, m, 2 H), and two olefinic protons [5.30 dt, 1 H (C=C*H*CH_2), and 6.06, s, 1 H (C=C*H*CO)]. Saponification of IX furnished the parent diol VIII [mp 117–119°;[7] M^+ 414.3213; $C_{27}H_{42}O_3$ (calcd 414.3134); λ_{max}(MeOH) 247.5 (ε 14,750); λ_{max}(KBr) 1690, 1680 cm^{-1} (C=CCO)] whose mass spectrum displayed diagnostic peaks[8] at *m/e* 357.2439, $C_{23}H_{33}O_3$ (calcd 357.2430, $M^+ - C_4H_9$), 329.2490, $C_{22}H_{33}O$ (calcd329.2480, 357 − CO, therefore C=CCO-C_4H_9), 287 (M^+ − side chain + 2 H), and 95.08612 (C_7H_{11}, calcd 95.08607; therefore one hydroxyl in ring A and the other at position 6).[9] Hydrolysis of IX with 5% potassium hydroxide in methanol under reflux (2 hr) led to considerable loss of uv absorption (nmr depicted loss of signal at δ 6.06) presumably due to partial conversion to β,γ-unsaturated ketone. The incorporation of only one methyl and a single proton in the α,β-unsaturated ketone grouping (therefore $\Delta^{20(22)}$, 23-oxo) was firmly established by the downfield shift of nmr[10] (60 MHz, $CDCl_3$) signals at 2.20 ± 0.05 and δ 6.05–2.40 and 6.16 (in benzene-d_6). Oxidation of VIII furnished the triketone X [mp 143–150°;[7] M^+ 410; λ_{max}(MeOH) 245 nm (ε 13,000, no change of ε in basic solution); λ_{max}($CHCl_3$) 1685, 1725 cm^{-1}; nmr (60 MHz, $CDCl_3$; benzene-d_6) C-18 CH_3 (0.51; 0.37, s), C-19 CH_3 (1.10; 0.68, s), $(CH_3)_2C$ (0.97, d, J = 6.5 Hz), C*H*$_3$C=CHCO (2.17; 2.24, s), C=C*H*CH_2 (5.60; 5.10, dt), C=C*H*CO (6.10; 6.0, s)]. The mass spectrum of X exhibited diagnostic peaks at *m/e* 353 ($M^+ - C_4H_9$, 100%), 325 (353 − CO), 283 (M^+ − side chain + 2 H). Identical chemical shifts for the nuclear olefinic hydrogen (in $CDCl_3$ and benzene-d_6) in VIII *vs.* I and X *vs.* IV, in addition to the lack of change of uv extinction of X in base, established the $\Delta^{9(11)}$ position of the second double bond in genin VIII.

Hydrogenation (10% Pd/C, EtOAc, 24–48 hr) of IX furnished two tetrahydro derivatives XI [λ_{max}($CHCl_3$) 1720 cm^{-1}; CD(MeOH) θ_{290} = −2367] and XIa [λ_{max}($CHCl_3$) 1720 cm^{-1}; CD(MeOH) θ_{290} = +1732] in a ratio of 2:8. Hydrolysis of XI and XIa furnished XII [mp 178–183°;[7] M^+ 418; λ_{max}($CHCl_3$) 1700 cm^{-1}; CD (MeOH) θ_{289} = −2042] and XIIa [mp 155°; M^+ 418; λ_{max}($CHCl_3$) 1700 cm^{-1}; CD(MeOH) $\theta_{287.5}$ = +1693]. The inversion in sign[11] of the Cotton effects of XI and XII *vs.* XIa and XIIa substantiates the epimeric nature at C-20. The base peak in the mass spectra of XII and XIIa occurred at *m/e* 318.25195, $C_{21}H_{34}O_2$ [calcd 318.2559, M^+ − CH_2=C(OH)C_4H_9], due to a McLafferty rearrangement associated with the 23-oxo function.

Wolff–Kishner reduction of XII furnished 5α-cholestane-3β,6α-diol (XIII)[12] [mp 216–218°; M^+ 404] which upon subsequent oxidation gave the known[12] diketone XIV (identical gc, nmr, mass spectra with synthetic 5α-cholestane-3,6-dione).

Genin I appears to be the first fully characterized pregnane from marine sources. Although it occurs as a glycoside (toxic to guppies), its biological role is as yet unknown. The presence of 17β-estradiol and progesterone[13] in the starfish *Pisaster ochraceus* has been suggested but more pertinent is the work of Schildknecht, *et al.*,[14] on the characterization of pregnane derivatives from defensive secretions of water beetles.

The side chain of genin VIII is highly unusual for a cholestane derivative. The only related sterol is marthasterone from the starfish *Marthasteria glacialis* for which Mackie, *et al.*,[15] proposed structure XV.

(6) S. G. Wyllie and C. Djerassi, *J. Org. Chem.*, **33**, 305 (1968).
(7) Melting point was determined after one crystallization.
(8) For a study of mass spectra of α,β-unsaturated aliphatic ketones, see Y. M. Sheikh, A. M. Duffield, and C. Djerassi, *Org. Mass Spectrom.*, **4**, 273 (1970).
(9) Y. M. Sheikh and C. Djerassi, unpublished results on mass spectrometry of steroidal diols.
(10) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 89 and 176–191.
(11) E. J. Eisenbraun, J. Osiecki, and C. Djerassi, *J. Amer. Chem. Soc.*, **80**, 1261 (1958).
(12) S. Wolf, M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **24**, 1034 (1959).
(13) C. R. Boticelli, F. L. Hisaw, Jr., and H. H. Wotiz, *Proc. Soc. Exp. Biol. Med.*, **103**, 875 (1960).
(14) For a review see H. Schildknecht, *Angew. Chem., Int. Ed. Engl.*, **9**, 1 (1970).
(15) A. B. Turner, D. S. H. Smith, and A. M. Mackie, *Nature (London)*, **233**, 209 (1971).

Marthasterone diacetate[16] and our diacetate IX show distinct differences in their nmr (δ 0.50–2.0 region) and mass spectra [characteristic *m/e* 98 peak ($(CH_3)_2C{=}CH\text{-}COHCH_2$) of marthasterone diacetate is relatively unimportant in IX].

The presence of the $\Delta^{20(22)}$ double bond in VIII suggests that it could be a precursor (either by hydration or through an intermediate epoxide) to (20*S*,22*R*)-monohydroxy or (20*S*,22*R*)-dihydroxy derivatives, believed to be involved[17] in the oxidative cleavage to pregnenolones (in the present case to genin I), or that the double bond arose from biodehydration of a 20*S* or 22*R* monohydroxy 23-ketone. Although labeling work is required to prove the bioorigin of the unique 23-oxo function in VIII and XV,[15] it can be speculated that it arises from the 22,23-olefinic linkage, so prevalent[18] in marine sterols, *via* an epoxide intermediate.

Work on other constituents of *A. planci* and a search for pregnanes from other echinoderms is currently in progress in our laboratory.

Acknowledgment. Financial assistance from the National Institutes of Health (Grant No. GM-06840) is gratefully acknowledged. Thanks are due to Dr. L. J. Durham, Dr. A. M. Duffield, and Mr. R. Ross for the spectral measurements.

(16) A. M. Mackie and A. B. Turner, *Biochem. J.*, **117**, 543 (1970).
(17) See S. Burstein and M. Gut, *Steroids*, **14**, 207 (1969), for experiments with adrenocortical preparations.
(18) J. Austin in "Advances in Steroid Biochemistry and Pharmacology," Vol. I, M. H. Briggs, Ed., Academic Press, New York, N. Y., 1970, pp 73–87.
(19) Faculté des Sciences, Université Libre de Bruxelles, Brussels, Belgium.

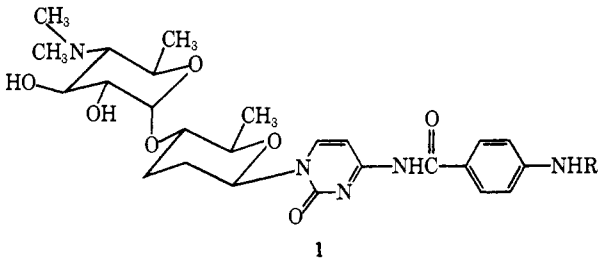
Younus M. Sheikh, Bernard M. Tursch,[19] Carl Djerassi*
Department of Chemistry, Stanford University
Stanford, California 94305
Received February 7, 1972

Total Synthesis of the Amino Sugar Nucleoside Antibiotic, Plicacetin

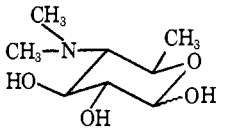
Sir:

Amicetin, bamicetin, and plicacetin are three structurally similar amino sugar nucleoside antibiotics isolated from the filtrates of an actinomycete designated *Streptomyces plicatus*.[1,2] Members of this group of antibiotics are potent inhibitors of *in vitro* protein synthesis,[3] and are reported to inhibit the KB strain of human epidermoid carcinoma cells[4] and increase the survival time of mice[5] with leukemia-82. They also inhibit Gram positive and Gram negative bacteria as well as mycobacteria broth both *in vitro* and *in vivo*.[2])

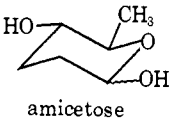
We wish to report here the total synthesis of plicacetin (**1**). To our knowledge this is the first total synthesis of a disaccharide pyrimidine nucleoside antibiotic.



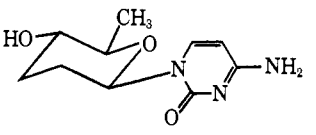
1
plicacetin, R = H
amicetin, R = L-α-methyl seryl



amosamine
2



amicetose
3



4

The gross structure and stereochemistry of amicetin and plicacetin have been determined[6–12] and several important fragments have been synthesized. Amosamine (**2**) has been shown to have the D-gluco configuration[13] and amicetose (**3**) is shown to have the 2,3,6-trideoxy-D-erythro structure[14] by synthesis.

The most difficult synthetic problem in the total synthesis of plicacetin was the stereospecific formation of the α-disaccharide linkage. The solution to this problem involved the synthesis of the stable crystalline β-chloro azido sugar derivative, **5**, which coupled without participation of the neighboring benzyloxy group to give excellent yields of derivatives with the required α configuration. The β-nucleoside linkage, in many cases easy to establish with the aid of a neighboring group, also represented a synthetic problem because of the lack of such groups. This problem had previously been solved during the synthesis[11] of the nucleosidic alcohol degradation fragment **4** of the antibiotic.

The chloro azido sugar **5** was prepared from the known α-methyl glycoside[15] **6** by the following series of reactions.

The methyl glycoside **6** was treated at 0° with acetic acid–acetic anhydride containing 0.5% sulfuric acid

(1) T. H. Haskell, *J. Amer. Chem. Soc.*, **80**, 747 (1958), and references cited therein.
(2) Amicetin was first isolated without bamicetin or plicacetin by C. DeBoer, E. L. Caron, and J. W. Hinman, *ibid.*, **75**, 499, 5864 (1953).
(3) T. D. Brock, *J. Bacteriol.*, **85**, 527 (1963).
(4) C. G. Smith, W. L. Lummis, and J. E. Grady, *Cancer Res.*, **19**, 847 (1959).
(5) J. H. Burchenal, M. Yuceloglu, M. K. Dagg, and C. C. Stock, *Proc. Soc. Exp. Biol. Med.*, **86**, 891 (1954).
(6) E. H. Flynn, J. W. Hinman, E. L. Caron, and D. O. Woolf, *J. Amer. Chem. Soc.*, **75**, 5867 (1953).
(7) P. Sensi, A. M. Grecco, G. G. Gallo, and G. Rolland, *Antibiot. Chemother.*, **7**, 645 (1957).
(8) C. L. Stevens, R. J. Gasser, T. M. Mukherjee, and T. H. Haskell, *J. Amer. Chem. Soc.*, **78**, 6212 (1956).
(9) S. Hanessian and T. H. Haskell, *Tetrahedron Lett.*, 2451 (1964).
(10) C. L. Stevens, N. A. Nielsen, and P. Blumbergs, *J. Amer. Chem. Soc.*, **86**, 1894 (1964).
(11) C. L. Stevens, N. A. Nielsen, P. Blumbergs, and K. G. Taylor, *ibid.*, **86**, 5695 (1964).
(12) N. Takamura, S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.*, **15**, 1776 (1967).
(13) C. L. Stevens, P. Blumbergs, and F. A. Daniher, *J. Amer. Chem. Soc.*, **85**, 1552 (1963).
(14) C. L. Stevens, P. Blumbergs, and D. L. Wood, *ibid.*, **86**, 3592 (1964).
(15) C. L. Stevens, P. Blumbergs, F. A. Daniher, D. H. Otterbach, and K. Grant Taylor, *J. Org. Chem.*, **31**, 2822 (1966).