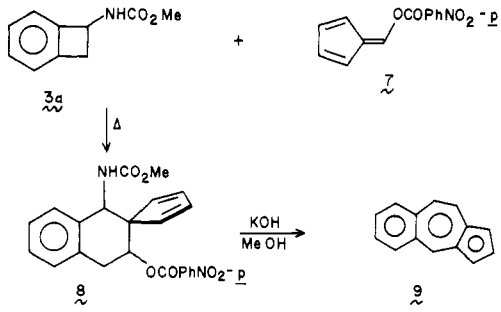

two steps find analogy in the Hafner–Ziegler azulene synthesis.[18]

The subtle factors that control the competition between spiro [4 + 2] and [6 + 4] cycloadditions are currently under investigation.

Acknowledgment. We are grateful to the National Science Foundation and the National Institutes of Health for financial support of this research. The 300-MHz spectrometer (Pittsburgh) and X-ray diffractometer (LSU) were acquired with funds from the National Science Foundation, to whom we are triply grateful.

Supplementary Material Available: ORTEP drawing of **5a**, crystallographic data for **5a**, and table of positional and thermal parameters (6 pages). Ordering information is given on any current masthead page.

(18) Ziegler, K.; Hafner, K. *Angew. Chem.* **1955**, *67*, 301. Hafner, K. *Justus Liebigs Ann. Chem.* **1957**, *606*, 79.

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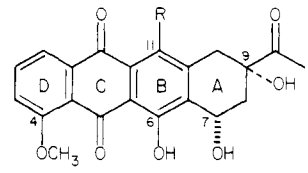
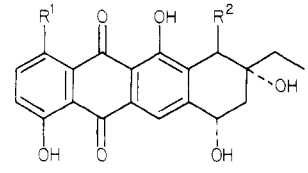
Regiospecific Total Synthesis of 6-Deoxyanthracyclines: 4-Demethoxy-6-deoxydaunorubicin

Summary: A regiospecific approach to 6-deoxyanthracyclinones, which has resulted in the synthesis of the novel anthracycline 4-demethoxy-6-deoxydaunorubicin, is reported. The construction of aglycone entails the coupling of the metalated 1,4-dimethoxynaphthalene with 2-carbomethoxy-4-acetylcyclohexanal. The new aldehyde was prepared from cis tetrahydrophthalic monoester via a regioselective acylation followed by conversion of the carboxylic group to a formyl group. The daunosaminyl glycoside showed on HeLa cells the same cytotoxicity as daunorubicin.

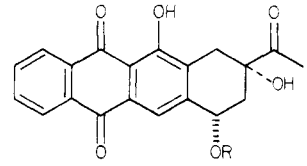
Sir: Recent advances in the regiospecific synthesis of anthracyclines have provided several new routes to aglycones with ring B as in daunomycinone (**1**)[1] or in its 11-deoxy analogue (**2**).[2] Little attention has been focused on the synthesis of 6-deoxyanthracyclinones represented hitherto by naturally occurring pigments δ-rhodomycinone (**3**),[3] α_2-rhodomycinone (**4**), α-citromycinone (**5**), and γ-citromycinone (**6**).[4] In this communication we report the synthesis of the novel anthracycline 4-demethoxy-6-deoxydaunorubicin (**7**).



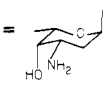
1, R = OH
2, R = H



3, R^1 = OH; R^2 = CO_2CH_3
4, R^1 = R^2 = OH
5, R^1 = H; R^2 = OH
6, R^1 = R^2 = H

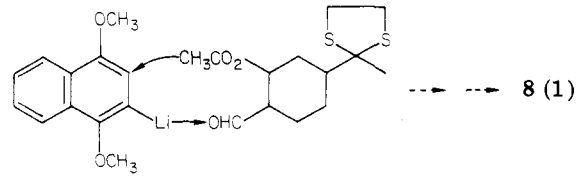


7, R =

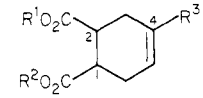


8, R = H

Our original synthetic approach for the construction of the aglycone **8** entails the coupling of the metalated 1,4-dimethoxynaphthalene (**9**), which formally represents the CD rings, with the new aldehyde **10**, the ring A precursor, followed by cyclization affording ring B as illustrated in eq 1.



9 **10**



11, R^1 = CH_3; R^2 = R^3 = H
12, R^1 = CH_3; R^2 = H; R^3 = $COCH_3$
13, R^1 = R^2 = CH_3; R^3 = $COCH_3$

The substrate **11**[5] was chosen as inexpensive starting material for the preparation of **10**. The reaction of **11** with CH_3COCl (i, $CHCl_3$, 3 equiv of $AlCl_3$, −5 °C, 8 h; ii, K_2CO_3, room temperature, 5 h) gave regioselectively **12**[6] (mp 117–121 °C) in 65% overall yield after crystallization. The regioselectivity of this reaction, affording only **12**, is probably due to the polarization induced on the double bond of **11** by an intermediate aluminum carboxylate. The structure of **12** was supported by spectroscopic[7] and chemical[8] evidence. Compound **12** was readily transformed into **10**, obtained as an oil in 45% overall yield (i, EtOH,

(1) For a comprehensive review, see: Arcamone, F. *Med. Chem. (Academic)* **1981**, *17*.

(2) (a) Kimball, S. D.; Walt, D. R.; Johnson, F. *J. Am. Chem. Soc.* **1981**, *103*, 1561. (b) Kende, A. S.; Boettger, S. D. *J. Org. Chem.* **1981**, *46*, 2799.

(3) Brockmann, H.; Brockmann, H., Jr. *Chem. Ber.* **1963**, *96*, 1771.

(4) (a) Brockmann, H.; Niemeyer, J. *Chem. Ber.* **1968**, *101*, 1341. (b) Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett.* **1981**, 1337. (c) Kende, A. S.; Gesson, J. P.; Demuth, T. P. *Ibid.* **1981**, 1667.

(5) Yadav, J.; Corey, P.; Hsu, C. T.; Perlman, K.; Sih, C. J. *Tetrahedron Lett.* **1981**, 811.

(6) All products showed ^1H and ^{13}C NMR, IR, and mass spectra consistent with the assigned structures. Melting points are uncorrected; the yields are unoptimized.

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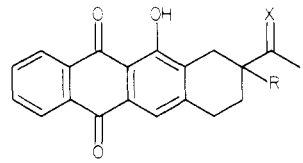
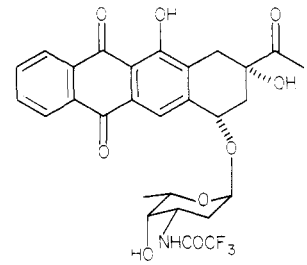
Pd/C, H_2; ii, $HS(CH_2)_2SH$, *p*-TSA; iii, $ClCO_2Et$, Et_3N; iv, THF, $NaBH_4$, −75 °C; v, CH_2Cl_2, PCC, room temperature). The generation of the nucleophile **9** by reaction of 1,4-dimethoxy-2-bromonaphthalene[9] with 1.0 equiv of *n*-BuLi (Et_2O, −70 °C) and the subsequent addition of aldehyde **10** (Et_2O, from −70 °C to room temperature) followed by the usual workup gave a crude reaction mixture,[10] which was treated directly with concentrated H_2SO_4 (room temperature, 30 min) to afford the tetracyclic target **14** (mp 174–176 °C) isolated in 10% overall yield (based on **10**) after chromatography. The introduction of the tertiary hydroxyl group to give **15** (mp 201–202 °C) was performed according to a known procedure[11] (i, Ac_2O, *p*-TSA, 120 °C, 12 h; ii, CH_2Cl_2, *m*-chloroperbenzoic acid; iii, OH^-; iv, H^+) in 60% overall yield. The final step to achieve **8** was the introduction of the hydroxyl group at C-7 in **16** (mp 211–212 °C) via homolytic bromination (Br_2, AIBN, CCl_4, 45 °C, 6 h) followed by alkaline treatment (0.1 N aqueous NaOH).[12] Finally, acid hydrolysis of the ketal group gave **8** (mp 206–208 °C) (26% overall yield from **15**): IR (KBr) 1705, 1665, 1625 cm^{-1}; UV (MeOH) λ_{max} 248, 256, 330, 406 nm; ^1H NMR (200 MHz, $CDCl_3$) δ 2.2–2.04 (m, H-8), 2.41 (s, $COCH_3$), 2.94 (d, J = 18 Hz, H_{ax}-10), 3.07 (d, J = 18 Hz, H_e-10), 4.08 (d, J = 10 Hz, OH-7), 4.45 (s, OH-9), 4.91 (br d, H_e-7, J = 10 Hz; after D_2O addition W_H = 8 Hz), 7.82 (m, H-2, H-3), 8.00 (s, H-6), 8.32 (m, H-1, H-4), 13.10 (s, OH-11).

Glycosidation of **8** with 1-chloro-*N*,*O*-(trifluoroacetyl)-daunosamine[13] was performed according to a stereoselective procedure[14] with $AgSO_3CF_3$ to yield the mixture of the two α diastereoisomers **17** [mp 155–160 °C dec); ^1H NMR (270 MHz, $CDCl_3$) δ 1.34 (d, J = 7 Hz, CH_3-5′), 2.42 (s, $COCH_3$), 3.09 (d, J = 15 Hz, H_{ax}-10), 3.17 (d, J = 15 Hz, H_e-10), 5.01 (m, W_H = 7 Hz, H-7), 5.20 (m, W_H = 5.0 Hz, H-1′), 6.76 (br d, J = 8 Hz, NH), 7.82 (s, H-6)] and **18** [mp 135–140 °C dec; ^1H NMR (270 MHz, $CDCl_3$) δ 1.45 (d, J = 7 Hz, CH_3-5′), 2.41 (s, $COCH_3$), 3.00 (d, J = 15 Hz, H_{ax}-10), 3.30 (d, J = 15 Hz, H_e-10), 5.07 (m, W_H = 7 Hz, H-7), 5.26 (m, W_H = 5 Hz, H-1′), 6.73 (br d, J = 8 Hz, NH), 7.75 (s, H-6)], separated by silica gel chromatography. In 6-deoxy glycosides a discrimination between natural[15] 7(*S*),9(*S*) and unnatural 7(*R*),9(*R*) configuration was not possible on the basis of NMR data, which were instead determinant in the case of 4-demethoxydaunorubicins. In the latter case the relative shieldings[16] of H-7 and H-1′ changed significantly for the diastereoisomers, possibly due to different associations of OH-6 and the oxygen of the sugar ring, as proposed by Nakata.[17] The natural configuration was assigned to **17** on the basis of the similarity of its CD curve with that of daunorubicin.[18] Compound **7**, obtained from **17** after hydrolysis of the N-protecting group, showed the same cytotoxicity[19] on HeLa cells (ID_{50} = 17 ng/mL) as daunorubicin, while the free amino glycoside obtained from **18** was practically inactive (ID_{50} > 1000 ng/mL).



14, R = H; X = O
15, R = OH; X = O
16, R = OH; X = O O



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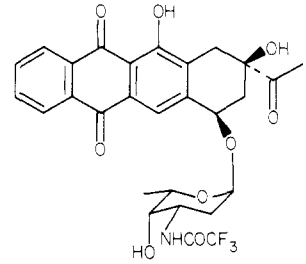

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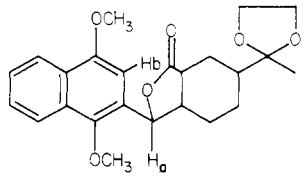
Acknowledgment. We are grateful to Dr. B. Gioia and A. Vigevani for mass and CD spectra and to A. M. Casazza for cytotoxic activity data.

(7) ^{13}C NMR of **12** ($CDCl_3$) 24.1 (C-6), 25.1 (CH_3CO), 26.2 (C-3), 38.9 (C-1), 39.3 (C-2), 52.0 (OCH_3), 137.4 (C-4), 138.0 (C-5), 173.0 ($COOCH_3$), 178.0 (COOH), 198.3 ppm ($COCH_3$). ^{13}C NMR of **13** (mp 58–60 °C) ($CDCl_3$) 24.1 (C-6), 25.1 (CH_3CO), 26.3 (C-3), 39.1 (C-2), 39.4 (C-1), 51.8 (2 OCH_3), 137.7 (C-4), 137.8 (C-5), 172.6, 172.9 ppm (2 $COOCH_3$). Carbons α to carboxylic groups are somewhat less deshielded than carbons α to carbomethoxy groups (Δδ = 1 ppm; see Wehrli, F. W.; Wirthlin, T. "Interpretation of ^{13}C-NMR Spectra"; Heyden: London, 1978; p 37). The best agreement between the calculated and experimental values of **12**, considering the difference in shielding at C-1 and C-2 and the values of **13**, was found for the structure with the carboxylic group at C-1.

(8) Conversion of the carboxylic group of **12** to an hydroxyl group (Denny, D. B.; Sherman, N. *J. Org. Chem.* **1965**, *30*, 3760) followed by alkaline aromatization afforded methyl 3-acetylbenzoate.

(9) Ungnade, H. E.; Hein, H. *J. Org. Chem.* **1949**, *14*, 911.

(10) At least three products were detected by TLC. In a different run, in which the 2,2-(ethylenedioxy) derivative of **10** was used, a major product was isolated by chromatography and characterized as the lactone **19**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.23 (s, CH_3), 5.83 (br s, H_a), 6.59 (s, H_b).



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(11) Suzuki, F.; Trembeath, S.; Gleim, R. D.; Sih, C. J. *J. Org. Chem.* **1978**, *43*, 4159.

(12) Our results are not in agreement with the activating effect of the *peri*-hydroxyl group on radical bromination, as suggested by Kende in citromycinone synthesis. The steric hindrance due to the ketalized side chain apparently directs the reaction to C-7, whereas in Kende's substrate, possessing an ethyl group at C-9, the position C-10 seems to be more easily attacked by the reagent. The stereoselectivity of hydroxylation is probably due to the assistance of the 9-OH [see for instance: (a) Kende, A. S.; Rizzi, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 4247. (b) Confalone, P. N.; Pizzolato, G. *Ibid.* **1981**, *103*, 4251].

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(14) Arcamone, F.; Penco, S.; Redaelli, S.; Hanessian, S. *J. Med. Chem.* **1976**, *19*, 1424.

(15) Natural stereochemistry as in daunomycinone.

(16) In the natural configuration H-7, and H-1′ are at δ 5.13 and 5.43, respectively; in the unnatural configuration, H-7 and H-1′ are at 5.33 and 5.22 (unpublished results from our laboratory). [See also: Habilitationschrift Fachbereich Chemie der Universität Hamburg vorgelegt von Dr. rer. nat. Karsten Khron, Hamburg, Germany, 1979.]

(17) Nakata, Y.; Hopfinger, A. J. *FEBS Lett.* **1980**, *117*, 259.

(18) (a) Marsh, J. P.; Iwamoto, R. H.; Goodman, L. *Chem. Commun.* **1968**, 589. (b) Arcamone, F.; Cassinelli, G.; Franceschi, G.; Penco, S.; Pol, C.; Redaelli, S.; Selva, A. International Symposium on Adriamycin, Springer-Verlag: Berlin, 1972.

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