DBH and the design of novel neurotransmitter analogues are currently under investigation.

Acknowledgments. Partial support of this work by the Biomedical Research Support Program of NIH is gratefully acknowledged.

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(23) Abushanab, E.; Reed, D.; Suzuki, F.; Sih, C. J. *Tetrahedron Lett.* **1978**, *37*, 3415-3418.

(24) Alfred P. Sloan Foundation Research Fellow, 1977-1979.

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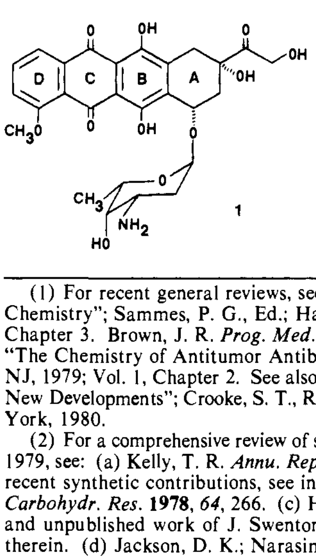
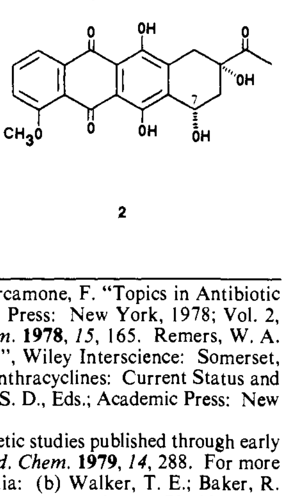
An Efficient, Regiospecific Synthesis of (±)-Daunomycinone

Sir:

The efficacy of adriamycin (**1**) as an agent for the treatment of a broad spectrum of human cancers has precipitated a deluge of activity directed toward anthracycline total synthesis.[1,2] Central to the synthetic[2] problem has been the challenge posed by aglycones such as daunomycinone (**2**).[3] Numerous aglycone syntheses have been achieved.[2] Nonetheless, the goal of developing an efficient, regiospecific route that is potentially amenable to large-scale operation and sufficiently flexible to provide at least putative access to a diversity of analogues has been elusive.

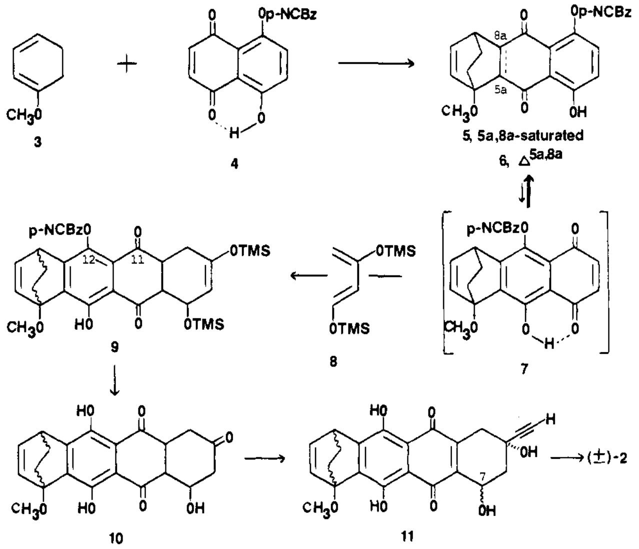


1



2

Scheme I[4]



We now report a ten-step regiospecific synthesis of (±)-**2** from commercially available starting materials which proceeds in 36% overall yield (Scheme I).

Thus, Diels–Alder reaction between *p*-nitrocarbobenzoxy (*p*-NCBz) naphthazarin[5] (**4**, prepared from naphthazarin[6] by treatment with *p*-NCBzCl[6] and CaH_2 in THF)[7] and **3**[8] (20 °C, CH_2Cl_2) gives **5** regiospecifically, as anticipated[9] on the basis of earlier studies. Oxidation of **5** ($\leq$1 equiv of KH, excess PbO_2, THF) affords **6**. Although NMR data indicate that **6** exists almost

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(1) For recent general reviews, see: Arcamone, F. "Topics in Antibiotic Chemistry"; Sammes, P. G., Ed.; Halsted Press: New York, 1978; Vol. 2, Chapter 3. Brown, J. R. *Prog. Med. Chem.* **1978**, *15*, 165. Remers, W. A. "The Chemistry of Antitumor Antibiotics", Wiley Interscience: Somerset, NJ, 1979; Vol. 1, Chapter 2. See also: "Anthracyclines: Current Status and New Developments"; Crooke, S. T., Reich, S. D., Eds.; Academic Press: New York, 1980.

(2) For a comprehensive review of synthetic studies published through early 1979, see: (a) Kelly, T. R. *Annu. Rep. Med. Chem.* **1979**, *14*, 288. For more recent synthetic contributions, see inter alia: (b) Walker, T. E.; Baker, R. *Carbohydr. Res.* **1978**, *64*, 266. (c) Horton, D. *J. Antibiot.* **1979**, *32*, S-145; and unpublished work of J. Swenton, D. Jackson, and W. Weckerle cited therein. (d) Jackson, D. K.; Narasimhan, L.; Swenton, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 3989. (e) Braun, M. *Tetrahedron Lett.* **1979**, 2885. (f) Savard, J.; Brassard, P. *Ibid.* **1979**, 4911. (g) Krohn, K.; Rösner, A. *Liebigs Ann. Chem.* **1979**, 2018. (h) Krohn, K.; Behnke, B. *Ibid.* **1979**, 2011. (i) Krohn, K.; Ostermeyer, H.-H.; Tolkiehn, K. *Chem. Ber.* **1979**, *112*, 2640. (j) Krohn, K.; Tolkiehn, K. *Ibid.* **1979**, *112*, 3453. (k) Iwataki, I.; Nakamura, Y.; Takahashi, K.; Matsumoto, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2731. (l) Hauser, F. M.; Prasanna, S. *J. Org. Chem.* **1979**, *44*, 2596. (m) Carrupt, P.-A.; Vogel, P. *Tetrahedron Lett.* **1979**, 4533. (n) Sih, C. J.; Massuda, D.; Corey, P.; Gleim, R. D.; Suzuki, F. *Ibid.* **1979**, 1285. (o) Oda, N.; Nagai, S.-I.; Ito, I. *Chem. Pharm. Bull.* **1979**, *27*, 2229. (p) Boeckman, R. K., Jr.; Delton, M. H.; Dolak, T. M.; Watanabe, T.; Glick, M. D. *J. Org. Chem.* **1979**, *44*, 4396. (q) Wiseman, J. R.; Pendery, J. J.; Otto, C. A.; Chiong, K. G. *Ibid.* **1980**, *45*, 516. (r) Chandler, M.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1007. (s) Parker, K. A.; Iqbal, T. *J. Org. Chem.* **1980**, *45*, 1149. (t) Barton, D. H. R.; Dawes, C. C.; Franceschi, G.; Foglio, M.; Ley, S. V.; Magnus, P. D.; Mitchell, W. L.; Temperelli, A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 643. (u) de Silva, S. O.; Watanabe, M.; Snieckus, V. *J. Org. Chem.* **1979**, *44*, 4802. (v) Whitlock, B. J.; Whitlock, H. W. *J. Org. Chem.* **1980**, *45*, 12. (w) Parker, K. A.; Kallmerten, J. *Ibid.* **1980**, *45*, 2614, 2620. (x) Rama Rao, A. V.; Deshpande, V. H.; Reddy, N. L. *Tetrahedron Lett.* **1980**, *21*, 2661. (y) Gesson, J.-P.; Jacquesy, J.-C.; Mondon, M. *Ibid.* **1980**, *21*, 2509. (z) Terashima, S.; Tanno, N.; Koga, K. *Ibid.* **1980**, *21*, 2749, 2753. (aa) Penco, F.; Angelucci, F.; Ballabio, M.; Vigevani, A.; Arcamone, F. *Ibid.* **1980**, *21*, 2253. (bb) Bridson, J. N.; Bennett, S. M.; Butler, G. *J. Chem. Soc., Chem. Commun.* **1980**, 413. (cc) Fronza, G.; Fuganti, C.; Grasselli *Ibid.* **1980**, 442. (dd) *Tetrahedron Lett.* **1980**, *21*, 2999. (ee) Tolkiehn, K.; Krohn, K. *Chem. Ber.* **1980**, *113*, 1575. (ff) Fariña, F.; Primo, J.; Torres, T. *Chem. Lett.* **1980**, 77. (gg) Amarco, A.; Carreno, M. C.; Fariña, F. *Tetrahedron Lett.* **1979**, 3983. (hh) Jew, S.-s.; Terashima, S.; Koga, K. *Chem. Pharm. Bull.* **1979**, *27*, 2351. See also ref 9g-l.

(3) The conversion of (±)-**2** into the natural antipode of **1** has been achieved.[1,2a,c]

(4) The structures of all single compounds in Scheme I are supported by spectral data and combustion analyses. In the case of most mixtures of stereoisomers (e.g., **10**), the individual isomers have been isolated and characterized by spectral and analytical data. Full experimental details are available upon request.

(5) The choice of the *p*-NCBz group arose from the finding that the Grignard reaction (**10** → **11**) fails completely when the C-12 oxygen in **10** is "protected" as an ester or carbonate (we believe that the C-11 carbonyl in such compounds is preferentially attacked by HC≡CMgBr and that deprotonation of the C-11 OH, as well as that at C-6, in **10** suppresses Grignard addition at the neighboring carbonyl). Due to the *pronounced* tendency for **9** and **10** to suffer A-ring aromatization, severe constraints are imposed on the reaction conditions employable for deprotection. "Directing" groups other than *p*-NCBz which were examined and found wanting, for one or more reasons, include pivaloyl, acetyl, CBz, *t*-BOC, *tert*-butyldimethylsilyl, chloroacetyl, and *o*-nitrobenzoyl.

(6) Available from Fluka/Tridom.

(7) On the basis of unrecoverable naphthazarin, the yield is quantitative; conversion is 62%.

(8) The technical grade of **3** available from Aldrich is satisfactory. We thank Dr. Max Brinkman of Heico for a generous sample of 1-methoxycyclohexa-1,4-diene.

(9) (a) Kelly, T. R.; Gillard, J. W.; Goerner, R. N., Jr.; Lyding, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 5513. For related studies from this laboratory, see: (b) Kelly, T. R.; Goerner, R. N., Jr.; Gillard, J. W.; Prazak, B. K. *Tetrahedron Lett.* **1976**, 3869. (c) Kelly, T. R.; Gillard, J. W.; Goerner, R. N., Jr. *Ibid.* **1976**, 3873. (d) Kelly, T. R. *Ibid.* **1978**, 1387. (e) Kelly, T. R.; Tsang, W.-G. *Ibid.* **1978**, 4457. (f) Kelly, T. R.; Montury, M. *Ibid.* **1978**, 4309, 4311. (g) Kelly, T. R.; Magee, J. A.; Weibel, F. R. *J. Am. Chem. Soc.* **1980**, *102*, 798. For recent relevant papers from other laboratories, see: (h) Manning, W. B. *Tetrahedron Lett.* **1979**, 1661. (i) Russell, R. A.; Collin, G. J.; Sterns, M.; Warrener, R. N. *Ibid.* **1979**, 4229. (j) Takano, S.; Hatakeyama, S.; Ogasawara, K.; Kametani, T. *Heterocycles* **1979**, *12*, 1163. (k) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3548, 3554. (l) Boeckman, R. K.; Jr.; Dolak, T. M.; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098. We do not entirely concur with the generalizations put forward in the last cited paper.

exclusively as the tautomer depicted,[10] a facile, albeit unfavorable, equilibrium between **6** and its more dienophilic tautomer **7** exists.[11] This equilibrium, and the attendant intramolecular transfer of the directing groups,[9,12] provides a vehicle for the regiospecific annelation of **6** to **9** upon reaction (25 °C, 48 h in CH_2Cl_2) with **8**.[13,14] Cleavage of the TMS (3 N HCl, 30% H_2O_2 in THF)[15] and *p*-NCBz (Zn, HOAc, THF, 0 °C) groupings yields **10**.

The sequence from **4** to **10** is best effected without purification of intermediates and affords **10** in 89% overall yield; it is conveniently conducted on a multigram scale and requires no chromatographies [**10** (>95% pure) is isolated by trituration].

Treatment of **10** with excess $HC\equiv CMgBr$[13,16] and oxidation (O_2, aqueous $NaHCO_3$ in THF) of the crude product generate **11** (74%) as a mixture of stereoisomers. Thermolysis of this mixture (*o*-xylene, 145 °C, 30 min, 89%) and hydration of the resulting crude product (40% H_2SO_4, $HgSO_4$, THF) afford (75%) a separable 83:17 mixture of (±)-**2** and its 7-epimer.[17] The (±)-**2** so obtained exhibits spectral and solubility properties identical with those previously[18] reported for (±)-**2**; TLC and HPLC[17] comparison of (±)-2 with authentic, naturally-derived (+)-**2** confirms the identity. In no instance was the regioisomer of **2** detected.[18]

Acknowledgments. Support from the National Cancer Institute (Grants CA00040 and CA17631) is gratefully acknowledged. The contributions[9,14] made by Drs. J. W. Gillard, R. N. Goerner, Jr., J. M. Lyding, K. Borah, M. Montury, and W.-G. Tsang to the ultimate completion of this protracted enterprise cannot be overstated. We thank Andree Fortin and Richard Rogers for technical assistance.

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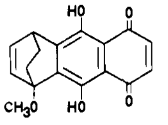
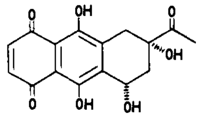
(10) The NMR spectrum of **6** exhibits peaks at δ 7.29 (2 H, s, aromatic H's) and δ 12.75 (1 H, s, OH); for a relevant discussion, see ref 9a, footnote 8.

(11) The rate and associated thermodynamic parameters for the (degenerate) tautomerization of naphthazarin monoacetate have been determined: Calder, I. C.; Cameron, D. W.; Sidell, M. D. *J. Chem. Soc. D* **1971**, 360. We thank Professor Cameron for bringing this paper to our attention.

(12) It is noteworthy that in related cases (e.g., i[9c] and ii[2j]) where no analogous means of controlling regiochemistry are available Diels–Alder reactions afford predominantly the *wrong* regioisomer.



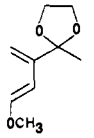
i



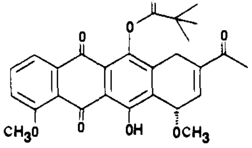
ii

(13) For a previous demonstration of the utility of **8** as an A-ring synthon, see: Krohn, K.; Tolkiehn, K. *Tetrahedron Lett.* **1978**, 4023, and ref 2j. For related studies, see: Fariña, F.; Prados, P. *Ibid.* **1979**, 477.

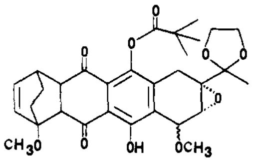
(14) The use of iii[9c] as an A-ring synthon in either ABC → ABCD or BCD → ABCD approaches was abandoned after *extensive* investigation because of our inability to achieve a productive elaboration of compounds such as iv and v (unpublished work of J. W. Gillard, R. N. Goerner, Jr., J. M. Lyding, K. Borah, and M. Montury). The regiochemistry of iv and v was not rigorously established.



iii



iv



v

(15) Use of conventional methods (e.g., KF/MeOH or H_3O^+) for cleaving the TMS groups led to extensive A-ring aromatization.[5] The potential utility of H_2O_2 in this context was first noted in the course of an unsuccessful attempt to deacetylate the corresponding acetate (**9**, Ac instead of *p*-NCBz) by using aqueous hydrogen peroxide; see: Jencks, W. P. *J. Am. Chem. Soc.* **1958**, *80*, 4585.

(16) Kende, A. S.; Tsay, Y.-g.; Mills, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 1967. For experimental details, see: Kende, A. S.; Mills, J. E.; Tsay, Y.-g. U.S. Patents 4021457, 1977, and 4070382, 1978.

(17) This ratio was determined on a Varian 5000 chromatograph equipped with a 30 cm × 4 mm CH-10 Micro Pak column and a UV detector (λ_{max} and ϵ values of (±)-**2** and (±)-epi-**2** are identical) by using a 40:60 acetonitrile/water solvent mixture [flow rate, 1 mL/min; retention times for (±)-**2** and (±)-epi-**2**, 12 and 6 min, respectively]. We thank Dr. Wm. Pegg for suggesting the solvent system.

(18) Daunomycinone (**2**) and its regiomer are easily distinguishable by NMR;[2j] NMR spectra of crude reaction mixtures contained no resonances attributable to the regiomer.

(19) Recipient of NIH Research Career Development Award, 1975–1980.

Book Reviews[*]

Transmethylation. Edited by E. Usdin, R. J. Borchardt, and C. R. Creveling. Elsevier-North Holland, New York. 1979. xxii + 631 pp. $55.00.

A conference held at Bethesda in 1978 provided the proceedings that constitute this volume. It contains the texts of 64 papers reproduced from the authors' typescripts, with figures, tables, references, and limited experimental detail. The papers are grouped in four subdivisions: S-Adenosylmethionine; Small-molecule N-, O-, and C-Methyltransferases; Nucleic Acid Methyltransferases; and Protein Methyltransferases. There is an author index and a 26-page subject index, and a glossary of abbreviations. The last is actually a list of acronyms, without which biochemists seem to be virtually inarticulate, and with which, the ordinary chemist is frequently mystified. Some of them, such as PCA for perchloric acid, are hard to justify for use in formal publications.

Enzyme Nomenclature 1978. Recommendations of the Nomenclature Committee of the International Union of Biochemistry. Prepared by the Nomenclature Committee of the International Union of Biochemistry. Academic Press, New York. 1979. 606 pp. $20.00.

This edition is a revision of the 1972 Recommendation of the IUPAC-IUB Commission on Biochemical Nomenclature. The book contains a brief introductory chapter followed by a chapter on principles, rules, and guidelines used for categorizing enzymes. The enzyme list itself is extensive and presents the following data for each enzyme: (i) the enzyme number, (ii) the recommended name, (iii) the catalyzed reaction, (iv) other names for the enzyme, (v) the systematic name, (vi) comments, and (vii) references. There are a total of 3859 references to the enzyme list. The list is indexed on an alphabetical basis using both recommended names and other commonly employed names. The book also contains an appendix on the nomenclature of electron-transport proteins.

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[*] Unsigned book reviews are by the Book Review Editor.