CYCLOADDITIONS OF BENZOPYRONES: RAPID ACCESS TO BICYCLIC
# AB-RING ANALOGUES OF ANTHRACYCLINES

Michael E. Jung,*[1] Richard W. Brown, Jeffrey A. Hagenah, and Charles E. Strouse*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024

Summary: Cycloaddition of the benzopyrone 10b with 1,1-disubstituted alkenes 12, 14, and 16 produces fair yields of the lactones 13, 15, and 17, AB-ring analogues of the anthracyclines.

A large amount of synthetic work has been directed recently[2] at the total synthesis of aklavinone 1, the aglycone of the clinically important antitumor antibiotic aclacinomycin A, 2, which has resulted in six total syntheses.[3] Also of synthetic interest are the C10-epimers of the aclacinomycins, namely compounds such as mimimycin 4 and other compounds of the bohemic acid complex[4] (e.g., collinemycin) which are derived from the aglycone, 10-epi-ε-pyrromycinone 3. Compounds of the two general types are interconvertible by base-catalyzed epimerization at C10 in the respective aglycones.[2b,4] We now report a new method for the rapid production of bicyclic A,B-ring analogues of these compounds from readily available starting materials in only a few steps.
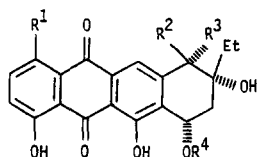

|	R^1	R^2	R^3	R^4
1	H	CO_2Me	H	H
2	H	CO_2Me	H	Rh—DF—Cin
3	OH	H	CO_2Me	H
4	OH	H	CO_2Me	Rh—DF—DF

Rh = α-rhodosamine   DF = 2-deoxy-L-fucose
Cin = cinerulose A

For several years we have been working on approaches to the anthracyclines based on the use of 6-methoxy-2-pyrones as dienes in Diels-Alder cycloadditions with quinones for the preparation of the tetracyclic ring system in which bonds C5a-C6 and C11-C11a are formed in the key constructive step.[5] We were interested in the possibility of a somewhat similar approach using a pyrone lacking the 6-alkoxy group as a diene for the construction of the A-ring with all the required functionality in place. For example, dehydration of 7-formyl-4,6-dihydroxy-anthraquinone-8-acetic acid 5 might proceed with loss of aromaticity in the benzene ring to produce the benzopyrone derivative 6. This compound is essentially an ortho-quinodimethane bridged by CO_2 and thus should

be highly reactive toward cycloaddition with simple olefins. In particular a 1,1-disubstituted olefin **7** should add regiospecifically (due to stabilization of zwitterionic-like character in the transition state) to give the desired regioisomers **8ab** as a mixture of stereoisomers. Opening of the lactone to the hydroxy ester followed by known[2b,6] epimerization at C7 would convert **8a** into aklavinone **1** while formation of the hydroxy ester from **8b** would produce 1-deoxy-ε-pyrromycinone (analogous to **3**) which could be epimerized at C10 to also give **1**. Thus this route seemed to offer a rapid route to the functionalized A ring and we decided to test it in a model system.
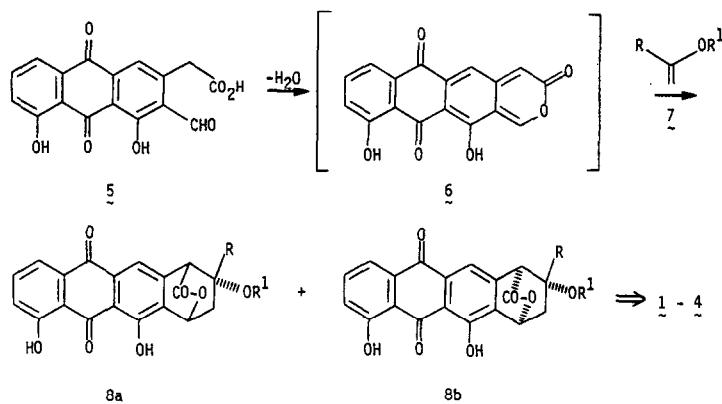

The original work in this area was due to Jones[7] who showed that (2-benzoylphenyl)phenyl-acetic acid **9a** could be dehydrated to 1,4-diphenyl-3H-2-benzopyran-3-one **10a**, an isolable crystal-line compound. The unsubstituted compound **10b** could also be prepared from **9b** but was too reactive to be isolated. Both compounds underwent Diels-Alder reactions when generated in the presence of dienophiles to give bicyclic lactones with either _endo_ or _exo_-specificity depending on the system. With isoprene and butadiene the diphenyl pyrone **10a** gave mainly the regioisomer **11** as a mixture of stereoisomers.
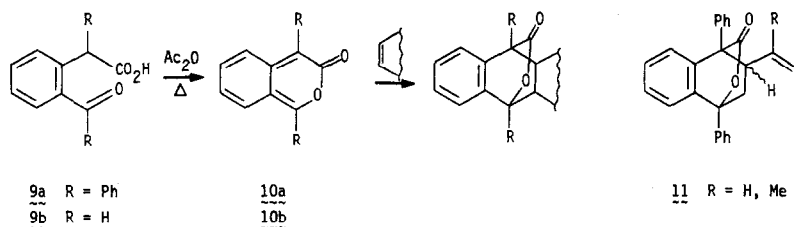
Conversion of 2-indanone (available in two steps from indene in 72% yield[8]) via ozonolysis of its trimethylsilyl enol ether into 2-formylphenylacetic acid **9b** was straightforward. Dehydra-tion of **9b** in refluxing acetic anhydride in the presence of various olefins produced the desired regiochemically pure bicyclic lactones. Use of a slight excess of the enol acetate of biacetyl **12** produced a 54% yield of two compounds,[10] **13a** (slightly yellow oil, 22%) and **13b** (colorless cry-stals, mp 191.5-192.5°, 32%) shown by high field NMR to be stereoisomers with the desired regio-chemistry. That the major compound was the product with acetate _syn_ to the lactone bridge, **13b**,

was determined by a single crystal x-ray analysis. Under these conditions the reaction was regiospecific. However under more vigorous conditions (12 hr, 95°C), a small amount of the regioisomer **13c** (colorless oil, 5%) was produced along with **13a** (26%) and **13b** (20%).

Several other commercially available olefins could be used in this cycloaddition process. For example, isopropenyl acetate **14** gave a 31% yield of a 1.5:1 mixture of the two stereoisomers **15a** (colorless crystals, mp 72-4°C, 19%) and **15b** (colorless crystals, mp 95-8°C, 12%).
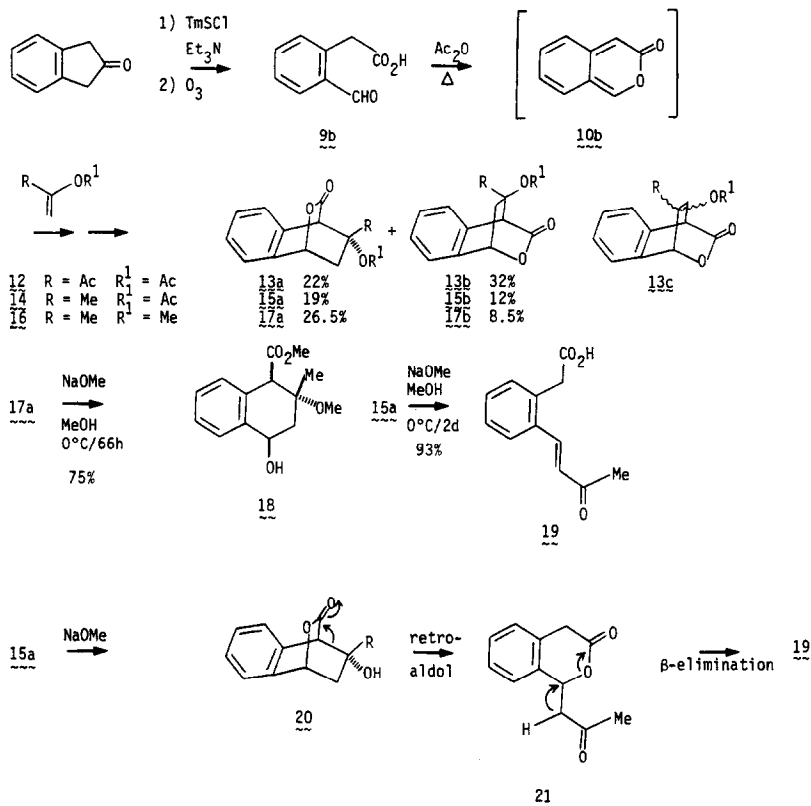
Isopropenyl methyl ether **16** afforded a 35% yield of an approximately 3:1 mixture of stereoisomers, **17a** (colorless crystals, mp 104-105.5°C, 26.5%) and **17b** (colorless, 8.5%). We have not yet really tried to improve the yields in this cycloaddition process. The assignment of structure for compounds **15ab** and **17ab** was impossible by simple spectroscopic means (e.g., high field ^{1}H NMR). We therefore again utilized single crystal x-ray spectroscopy to determine the structure of **17a**, and then used similarities in the ^{1}H NMR data to assign the structure of **15a**.

To demonstrate the potential utility of these bicyclic lactones for the synthesis of the A-ring of anthracyclines, we subjected the methyl ether **17a** to basic methanolysis to produce the hydroxy ester **18** in 75% yield. This compound is an analogue of the anthracycline antitumor antibiotics having a β-methyl group at C9 (e.g., nogalamycin,[11] ε_1-pyrromycin,[11b] and aura-mycin.[11c] This base-catalyzed methanolysis could not be successfully applied to the acetate **15a** however. Treatment of **15a** under identical conditions produced an excellent yield of the acid **19**

[colorless oil, 93%: ^{1}H NMR δ 8.32 (1H, bs), 7.96 (1H, d, J = 17 Hz), 7.3-7.8 (4H, m), 6.69 (1H, d, J = 17 Hz), 3.82 (2H, s), 2.40 (3H, s). IR (CDCl$_3$) 3300-2800, 1735-1700, 1675, 1610, 1365, 1265, 1075 cm^{-1}]. The clean formation of the acid (and the absence of the corresponding methyl ester) implies that the tertiary acetate is methanolized faster than the lactone to produce the alcohol **20**. This alcohol can then undergo a base-catalyzed retro-aldol reaction to give the keto lactone **21** which then suffers β-elimination to give **19**.

We are currently attempting to prepare the aldehyde acid **5** and apply this route to the synthesis of the natural anthracyclines.

References and Notes

(1) Camille and Henry Dreyfus Foundation Teacher-Scholar, 1978-1983; Alfred P. Sloan Foundation Fellow, 1979-1981.
(2) (a) Kende, A.S.; Rizzi, J.P. J. Am. Chem. Soc. **1981**, _103_, 4247. (b) Pearlman, B.A.; McNamara, J.M.; Hasan, I.; Hatakeyama, S.; Sekizaki, H.; Kishi, Y. ibid. **1981**, _103_, 4248. (c) Confalone, P.N.; Pizzolato, G. ibid. **1981**, _103_, 4251. (d) Li, T.-t.; Wu, Y.L. ibid. **1981**, _103_, 7007. (e) Boeckman, R.K., Jr.; Sum, F.-W. ibid. **1982**, _104_, 4604. (f) Hauser, F.M.; Mal, D. ibid. **1984**, _106_, 1098. (g) McNamara, J.M.; Kishi, Y. ibid. **1982**, _104_, 7371.
(3) (a) Oki, T.; Matsuzawa, Y.; Yoshimoto, A.; Numata, K.; Kitamura, I.; Hori, S.; Takamatsu, A.; Umezawa, H.; Ishizuka, M.; Maganawa, H.; Suda, H.; Hamada, M.; Takeuchi, T. J. Antibiot. **1975**, _28_, 830. (b) Oki, T.; Kitamura, I.; Yoshimoto, A.; Matsuzawa, Y.; Shibamoto, N.; Ogasawara, T.; Inui, T.; Takamatsu, A.; Takeuchi, T.; Masuda, T.; Hamada, S.; Suda, H.; Ishizuka, M.; Sawa, T.; Umezawa, H. ibid. **1979**, _32_, 791. (c) Oki, T.; Kitamura, I.; Matsuzawa, Y.; Shibamoto, N.; Ogasawara, Y.; Yoshimoto, A.; Inui, T.; Naganawa, H.; Takeuchi, T.; Umezawa, H. ibid. **1979**, _32_, 801. (d) Hori, S.; Shirai, M.; Shinchi, H.; Oki, T.; Inui, T.; Tsukagoshi, S.; Ishizuka, M.; Takeuchi, T.; Umezawa, H. Gann **1977**, _68_, 685. (e) Tanaka, H.; Yoshioka, T.; Shimauchi, Y.; Matsuzawa, Y.; Oki, T.; Inui, T. J. Antibiot. **1980**, _33_, 1323 and references cited therein.
(4) Doyle, T.W.; Nettleton, D.E.; Grulich, R.E.; Balitz, D.M.; Johnson, D.L.; Vulcano, A.L. J. Am. Chem. Soc. **1979**, _101_, 7041.
(5) (a) Jung, M.E.; Lowe, J.A., III; Lyster, M.A.; Node, M.; Pfluger, R.W.; Brown, R.W. Tetrahedron **1984**, in press. (b) Jung, M.E.; Node, M.; Pfluger, R.W.; Lyster, M.A.; Lowe, J.A., III J. Org. Chem. **1982**, _47_, 1150. (c) Jung, M.E.; Brown, R.W. Tetrahedron Lett. **1981**, 3355. (d) Jung, M.E.; Lowe, J.A. J. Chem. Soc., Chem. Commun. **1978**, _95_. For related work see: (e) Jung, M.E.; Hagenah, J.A. J. Org. Chem. **1983**, _48_, 5359. (f) Jung, M.E.; Blum, R.B. J. Chem. Soc., Chem. Commun. **1981**, 962.
(6) (a) Brockmann, H.; Niemeyer, J. Chem. Ber. **1967**, _100_, 3578. (b) Kende, A.S.; Tsay, Y.; Mills, J.E. J. Am. Chem. Soc. **1976**, _98_, 1967. (c) Smith, T.H.; Fujiwara, A.N.; Henry, D.W.; Lee, W.W. ibid. **1976**, _98_, 1969.
(7) (a) Holland, J.M.; Jones, D.W. J. Chem. Soc. (C) **1970**, 530, 536. (b) Jones, D.W.; Kneen, G.; J. Chem. Soc., Chem. Commun. **1973**, 420. (c) Jones, D.W.; Wife, R.L. ibid. **1973**, 421.
(8) Horan, J.E.; Schiessler, R.W. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. 5, p 647.
(9) Tamariz, J.; Vogel, P. Helv. Chim. Acta **1981**, _64_, 188.
(10) All new compounds exhibited spectroscopic data (200 MHz ^{1}H NMR, ^{13}C NMR, IR, elemental analysis and/or high resolution mass spectroscopy) in full agreement with their proposed structures.
(11) (a) Wiley, P.F.; Kelly, R.B.; Caron, E.L.; Wiley, V.H.; Johnson, J.H.; MacKeller, F.A.; Mizsuk, S.A. J. Am. Chem. Soc. **1977**, _99_, 542. (b) Tax, J.; Sedmera, P.; Vokoun, J.; Eckardt, K.; Konersova, I.; Vanek, Z. Collect. Czech. Chem. Commun. **1973**, _83_, 2661. (c) Fujiwara, A.; Hoshino, T.; Tazoe, M.; Fujiwara, M. J. Antibiot. **1982**, _35_, 164.