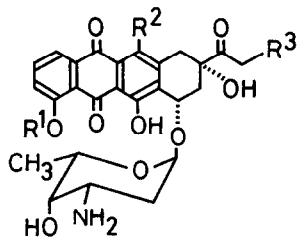
Tetrahedron Letters,Vol.25,No.11,pp 1167-1170,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

A BRIEF AND REGIOSPECIFIC SYNTHESIS OF THE LATE-STAGE INTERMEDIATE TO 11-DEOXYANTHRACYCLINONES

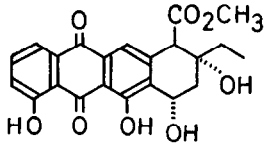
Y. Tamura, S. Akai, M. Sasho, and Y. Kita
Faculty of Pharmaceutical Sciences, Osaka University
1-6, Yamada-oka, Suita, Osaka, 565 Japan

Summary: The late-stage intermediate (8) to 11-deoxyanthracyclinones has been prepared by a strong base induced cycloaddition of 6-oxo-5,6,7,8-tetrahydrohomophthalic anhydride 1,2-ethanediyl acetal (9) to 3-bromojuglone methyl ether (10).

Anthracycline agents, e.g., adriamycin (1), daunomycin (2), and carminomycin (3), are widely used for treating certain kinds of cancer, such as acute leukemia,[1] but they have serious side effects, particularly their tendency to damage the heart.[1] In the past few years, several potentially useful 11-deoxyanthracyclines have been isolated. The most promising of these is aclacinomycin A, which exhibits good antitumor properties and, more importantly, shows 10 to 15 times less toxicity.[2] Very recently the three groups have published the total synthesis of aklavinone (4), the aglycone of aclacinomycin A.[3] Other 11-deoxyanthracyclines, 11-deoxyadriamycin (5), 11-deoxydaunomycin (6), and 11-deoxycarminomycin (7), also possess significant anticancer activity and are less cardiotoxic[4] than the clinically important agents, 1 and 2. The



1; $R^1=CH_3$, $R^2=R^3=OH$
2; $R^1=CH_3$, $R^2=OH$, $R^3=H$
3; $R^1=R^3=H$, $R^2=OH$
5; $R^1=CH_3$, $R^2=H$, $R^3=OH$
6; $R^1=CH_3$, $R^2=R^3=H$
7; $R^1=R^2=R^3=H$

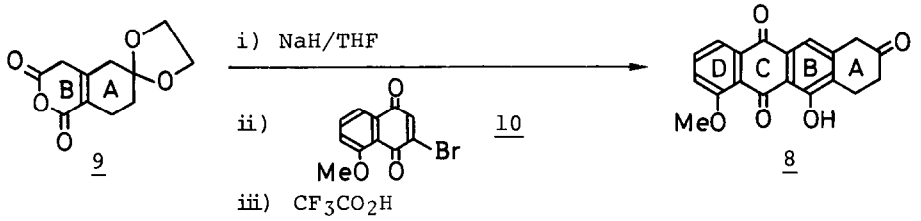


4

potential advantages have led to urgent interest in the synthesis of the common late-stage intermediate (8) to the 11-deoxyanthracyclinones (4-7) and some syntheses of 8 using regiospecific Diels-Alder reactions of 6-alkoxy-2-pyrones or vinyl ketene acetals with halogenated quinones have been published by Jung et al.,[5] Gesson et al.,[6] and Rapoport et al.[7] Recently, we have communicated a regiocontrolled synthesis of late-stage precursors of anthracyclinones using a strong base induced cycloaddition of homophthalic anhydrides to 2-chloro-6-oxo-5,6,7,8-tetrahydro-1,4-naphthoquinone 1,2-ethanediyl acetal

in three steps with high overall yields[8] and now can apply this method to an alternative efficient method for regiospecific synthesis of 8. We report here a facile preparation of the starting anhydride, 6-oxo-5,6,7,8-tetrahydrohomophthalic anhydride 1,2-ethanediyl acetal (9) and a strong base induced cycloaddition of 9 to 3-bromojuglone methyl ether (10) leading to 8 as shown in Scheme I.

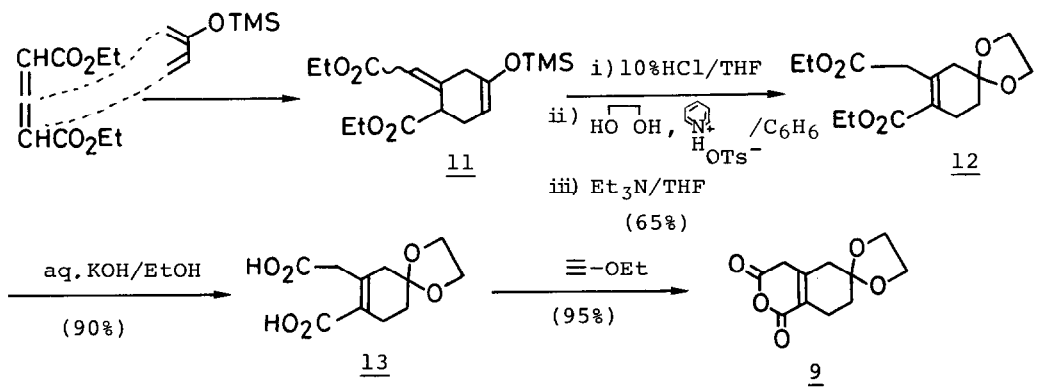
Scheme I



SYNTHESIS OF 6-OXO-5,6,7,8-TETRAHYDROHOMOPHTHALIC ANHYDRIDE 1,2-ETHANEDIYL ACETAL (9)

The requisite anhydride (9) was prepared from the readily available silyl enol ether (11)[9] in five steps with a 56% overall yield according to Scheme II. Desilylation of 11 with 10% HCl in THF gave the ketone [syrup; IR ν_{max} ($CHCl_3$) 1735, 1730, 1675 cm^{-1}], which was treated with ethylene glycol and pyridinium p-toluenesulfonate in refluxing benzene for 4 h to give an 1:4 mixture of exo and endo olefin acetals. Heating of the mixture in Et_3N-THF (1:1) gave the endo olefin acetal (12) [syrup; IR ν_{max} ($CHCl_3$) 1735, 1730, 1710, 1100, 1065 cm^{-1}]. Hydrolysis of 12 with aq. KOH in refluxing ethanol for 2 h followed by acidification with c. HCl gave the diacid (13) [mp 137.5-138.5°C; IR ν_{max} (KCl) 3200-2500, 1720, 1710, 1680, 1625, 1105, 1070, 1055 cm^{-1}], which was cyclized with ethoxyacetylene to give the desired anhydride (9) [mp 174-177°C; IR ν_{max} ($CHCl_3$) 1810, 1790, 1755, 1745, 1675, 1120, 1100, 1060, 1025, 980 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.00 (4H, s), 3.5-3.3 (2H, m), 2.85-2.4 (4H, m), 2.05-1.7 (2H, m)]. The starting 3-bromojuglone methyl ether (10) was directly prepared from 3-bromojuglone by methylation with methyl iodide and silver oxide.[10]

Scheme II



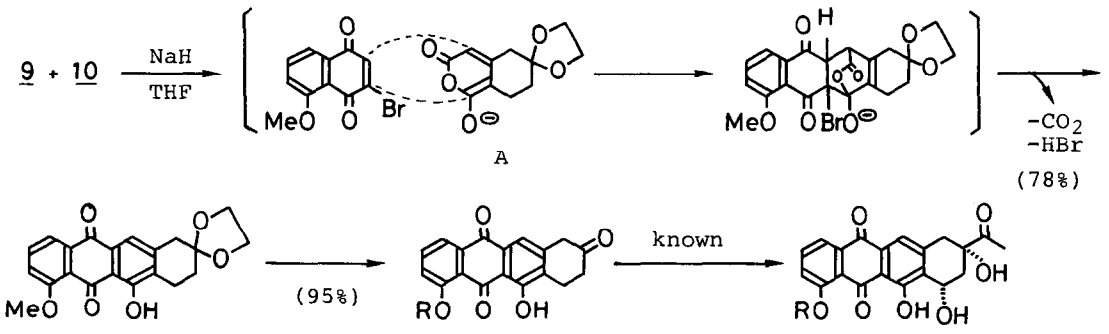
CYCLOADDITION OF 9 TO 3-BROMOJUGLONE METHYL ETHER (10)

Treatment of sodio anion of 6-oxo-5,6,7,8-tetrahydrohomophthalic anhydride 1,2-ethanediyl acetal (9), readily obtained from 9 and NaH in dry THF at 0°C, with 3-bromojuglone methyl ether (10) at r.t. for 7 h gave a 78% yield of the tetracyclic quinone acetal (14) as a sole product [mp 221-223°C lit.[7] 220-222°C); IR ν_{max} (KCl) 1670, 1620, 1580, 1120, 1060, 1050, 1010, 965 cm^{-1}]. A plausible pathway is the initial Diels-Alder type addition of the active diene moiety (A) to 10 regiospecifically, followed by spontaneous loss of CO_2 and HBr, giving 14. The orientation of the cycloaddition is in agreement with the previous behavior observed in the cycloaddition of homophthalic anhydrides to haloquinones.[8] Deacetalization of 14 with CF_3CO_2H in water at r.t. for 12 h gave the desired 8 [95% yield, mp 250-253°C dec. (lit.[6] 258-259°C, lit.[11] 256-258°C, lit.[12] 241-243°C dec.); IR ν_{max} (KCl) 1710, 1670, 1625, 1580 cm^{-1}], which was in all respects identical with an authentic sample provided by Professor Gesson. Since the conversion of 8 to 11-deoxydaunomycinone, the aglycone of 6, has already been described,[6] our synthesis of 8 constitutes a new route to 11-deoxydaunomycinone.

For the synthesis of 11-deoxycarminomycinone, the aglycone of 7, the ketone (8) was demethylated with aluminum chloride in refluxing dichloromethane for 3 h to give the tetracyclic 11-deoxy ketone (15) [90% yield, mp 240-241°C (lit.[6] 241-242°C, lit.[13] 242°C dec.); IR ν_{max} (KCl) 1710, 1665, 1615, 1605, 1280 cm^{-1}]. Since 15 has been converted to 11-deoxycarminomycinone,[13] our synthesis of 15 constitutes a new efficient synthesis of 11-deoxycarminomycinone.

Further elaboration of the compound (8) to other 11-deoxyanthracyclinones is under way, as well as studies of other more functionalized diene systems.

Scheme III



8; R=Me
15; R=H

Acknowledgement: We are grateful to Professor Jean-Pierre Gesson (University of Poitiers) for providing the variable sample (8) and thank Miss Kiyomi Nakagawa for technical assistance.

References and Notes

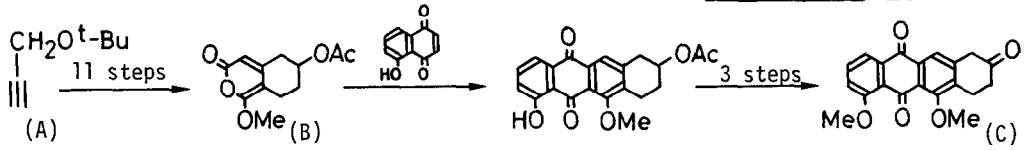
1) R. H. Blum and S. K. Carter, Ann. Intern. Med., 80, 249 (1974); F. Arcamone, "Topics in Antibiotic Chemistry", P. G. Sammes, Ed., Halstead Press, New York, 1978, Vol. 2; J. R. Brown, Prog. Med. Chem., 15, 125 (1978); W. A. Remers, "The Chemistry of Antitumor Antibiotics", Wiley-Intersciences; Somerset, N. J., 1979, Vol. 1, Chapter 2; T. Oki and T. Takeuchi, Yuki Gosei Kagaku Kyokai Shi, 40, 2 (1980).

2) T. Oki, Y. Matsuzawa, A. Yoshimoto, K. Numata, I. Kitamura, S. Hori, A. Takamatsu, H. Umezawa, M. Ishizuka, H. Naganawa, H. Suda, M. Hamada, and T. Takeuchi, J. Antibiotics, 28, 830 (1975); T. Oki, N. Shibamoto, Y. Matsuzawa, T. Ogasawara, A. Yoshimoto, I. Kitamura, T. Inui, H. Naganawa, T. Takeuchi, and H. Umezawa, Ibid., 30, 683 (1977); T. W. Doyle, D. E. Nettleton, R. E. Grulich, D. M. Balitz, D. L. Johnson, and A. L. Vulcano, J. Am. Chem. Soc., 101, 7041 (1979); S. Hori, M. Shirai, S. Hirano, T. Oki, T. Inui, S. Tsukagoshi, M. Ishizuka, T. Takeuchi, and H. Umezawa, Gann, 68, 685 (1977).

3) A. S. Kende and J. P. Rizzi, J. Am. Chem. Soc., 103, 4247 (1981); B. A. Pearlman, J. M. McNamara, I. Hasan, S. Hatakeyama, H. Sekizaki, and Y. Kishi, Ibid., 103, 4248 (1981); P. N. Confalone and G. Pizzolato, Ibid., 103, 4251 (1981).

4) F. Arcamone, G. Cassinelli, F. Dimatteo, S. Forenza, M. C. Ripamonti, G. Rivola, A. Vigevani, J. Clardy, and T. McCabe, J. Am. Chem. Soc., 102, 1462 (1980); G. Cassinelli, et al., J. Antibiotics, 35, 176 (1982).

5) Recently, Jung et al., have prepared substituted 6-alkoxy-2-pyrone (B) from tert-butyl propargyl ether (A) and synthesized the tetracyclic compound (C) using regiospecific Diels-Alder reaction in 15 steps with approximately 7% overall yield from A: M. E. Jung, M. Node, R. W. Pfluger, M. A. Lyster, and J. A. Lowe, III, J. Org. Chem., 47, 1150 (1982).



6) J. P. Gesson, J. C. Jacquesy, and M. Mondon, Tetrahedron Lett., 21, 3351 (1980); J. P. Gesson and M. Mondon, J. Chem. Soc. Chem. Commun., 1982, 421.

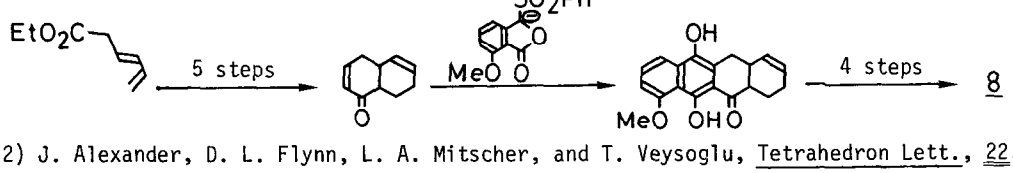
7) J. G. Bauman, R. B. Barber, R. D. Gless, and H. Rapoport, Tetrahedron Lett., 21, 4777 (1980).

8) Y. Tamura, A. Wada, M. Sasho, K. Fukunaga, H. Maeda, and Y. Kita, J. Org. Chem., 47, 4376 (1982); cf. Y. Tamura, M. Sasho, K. Nakagawa, T. Tsugoshi, and Y. Kita, Ibid., in press.

9) A. P. Kozikowski and R. Schmiesing, Synth. Commun., 8, 363 (1978).

10) Y. Tamura, A. Wada, M. Sasho, and Y. Kita, Chem. Pharm. Bull., 31, 2691 (1983).

11) Very recently, Hauser et al., have prepared 8 using the phthalide sulfone annulation reaction in 10 steps with approximately 27% overall yield: F. M. Hauser, S. Prasanna, and D. W. Combs, J. Org. Chem., 48, 1328 (1983).



12) J. Alexander, D. L. Flynn, L. A. Mitscher, and T. Veysoglu, Tetrahedron Lett., 22, 3711 (1981).

13) A. S. Kende and S. D. Boettger, J. Org. Chem., 46, 2799 (1981).

(Received in Japan 19 December 1983)