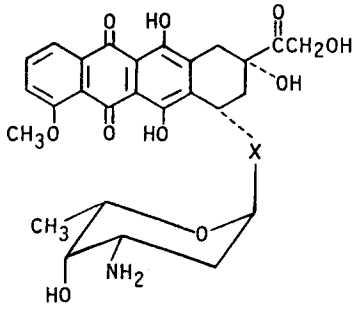
Tetrahedron Letters,Vol.25,No.50,pp 5743-5746,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

SYNTHETIC APPROACH TO ANTHRACYCLINONE C-GLYCOSIDES

Edward M. Acton,* Kenneth J. Ryan, and Michael Tracy
Bio-Organic Chemistry Laboratory
SRI International, Menlo Park, California 94025, USA

Abstract: Stereospecific coupling of a pentadienyl chain to C.1 of daunosamine followed by Diels-Alder reactions with quinones gave a new synthesis of C-glycosides, including the first intermediates to anthracycline C-glycosyl isosteres.

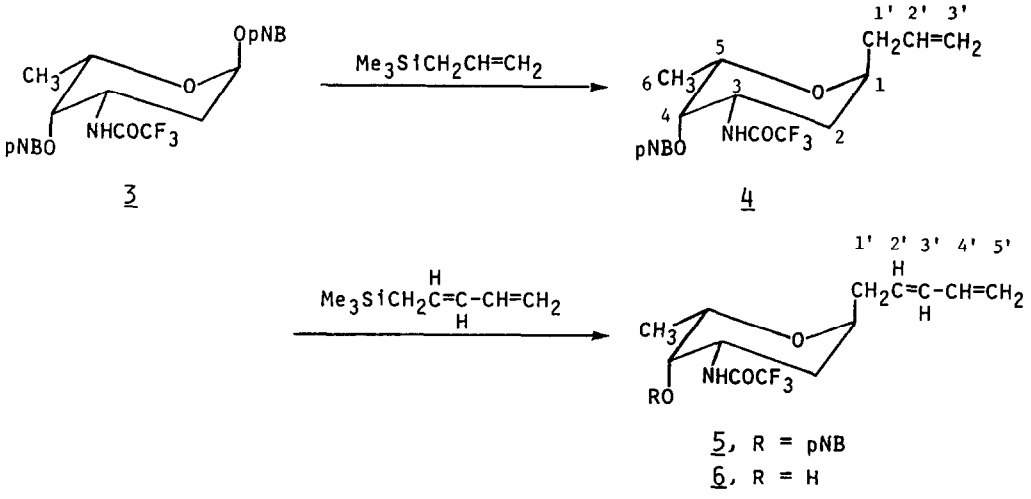
Among the hundreds of anthracyclines that have been prepared in a search for better antitumor analogs of doxorubicin (1), none so far are C-glycosides (2). Metabolically, anthracyclines are inactivated by reductive deglycosidation, and deletion of this step in C-glycosyl analogs should give important changes in biological properties, perhaps leading to therapeutic advantages. An important synthetic approach to anthracyclines involves construction of the A-ring by Diels-Alder addition of a quinone (comprising rings B, C, and usually D) to a diene. We now report the stereospecific coupling of a 2,4-pentadienyl chain to C.1 of a daunosamine derivative and successful use of the resulting diene in the Diels-Alder construction of versatile 7-(daunosaminyl)methyl anthracyclinone intermediates to 2.



1, X = O
2, X = CH_2

First, C.1-allylation of daunosamine was accomplished by treatment of the 1,4-di-O-p-nitrobenzoyl (pNB) N-trifluoroacetyl derivative 3[1,2], with allyltrimethylsilane and $BF_3 \cdot OEt_2$ in acetonitrile[3,4] to give 4 (mp 138-9°, 84% yield, Et_2O-hexane) as the only product,[5] in the desired α-L configuration at C.1 judging by the absence of $J_{1,2}$ values for diaxial coupling (required of the β-L form) in the ^1H NMR region for H-1 ($CDCl_3$ δ 4.22 quartet, $J_{1e,2e} < 1$ Hz, $J_{1e,2a} = 5.9$ Hz). In previous C-allylations, use of 1-O-p-nitrobenzoyl as leaving group and $BF_3 \cdot OEt_2$ as catalyst was found to enhance axial attack on the intermediate pyranose oxonium ion owing to the anomeric effect of the ring O and give high[3] or complete[4] stereospecificity. In this case, stereospecificity may be further enhanced by participation of the 4-O-p-nitrobenzoyl group.[2]

The same treatment of 3 with 3 equivalents of (E)-2,4-pentadienyltrimethylsilane[6] and BF_3•OEt (10% excess) in acetonitrile at 0°-room temperature for 3 hr likewise gave the C-glycoside 5 of daunosamine as the only product (> 90% yield). ^1H NMR two-dimensional Fourier transform correlation spectroscopy at 400 MHz (5 in $CDCl_3$) showed that attachment was at C.1' of the pentadienyl chain (1'-H x 2 as pentets at δ 2.45, 2.72, each with $J_{1,1'}$ = 7.3 Hz, $J_{1',2'}$ = 7.5 Hz; J_{gem} = 14.5 Hz). The 2,4-diene retained[7] (E)-isomerism (2'-H as pentet at δ 5.70 and 3'-H as quartet at δ 6.20; trans $J_{2',3'}$ = 15.1 Hz; 4'-H as sextet at δ 6.36, $J_{3',4'}$ = 10.5 Hz; 5'-H x 2 as doublets at δ 5.07, $J_{4',5'}$ = 10.0 Hz and δ 5.20, $J_{4',5'}$ = 17.0 Hz, J_{gem} < 1 Hz). The C.1-C.1' glycosidic bond was in the α-L-configuration (1-H as quartet at δ 4.25, $J_{1e,2e}$ < 1 Hz, $J_{1e,2a}$ = 5.9 Hz; 2a-H as sextet at δ 2.12, $J_{2a,3a}$ = 13 Hz; 2e-H as quartet at δ 1.85, $J_{2e,3a}$ = 6.0 Hz; 3-H m at δ 4.53; 4-H as broad s at δ 5.41, $J_{3a,4e}$ and $J_{4e,5a}$ ca. 0.5 Hz; 5-H as quartet at δ 4.05; 6-H x 3 as d at δ 1.19, $J_{5,6}$ = 6.2 Hz). Removal of the 4-O-p-nitrobenzoyl group by treatment with methanolic diisopropylamine at room temperature overnight afforded 6 (mp 111-112°, 77% yield) with virtually no NMR change except for upfield shifts at H-4 (δ 5.41 → 3.50), H-1 (4.25 → 4.03), and H-2a (2.12 → 1.82).



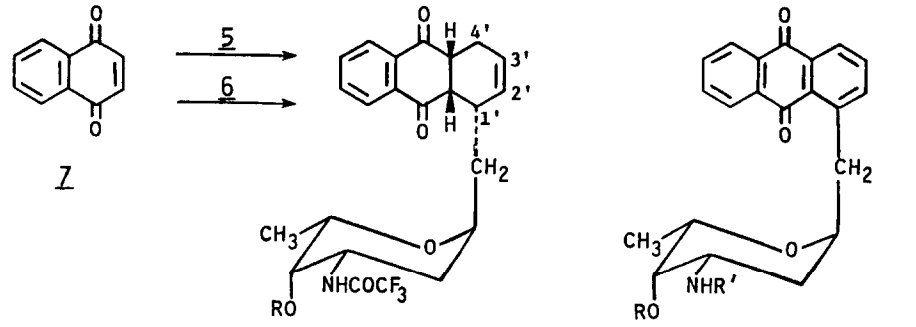
3

4

5, R = pNB
6, R = H

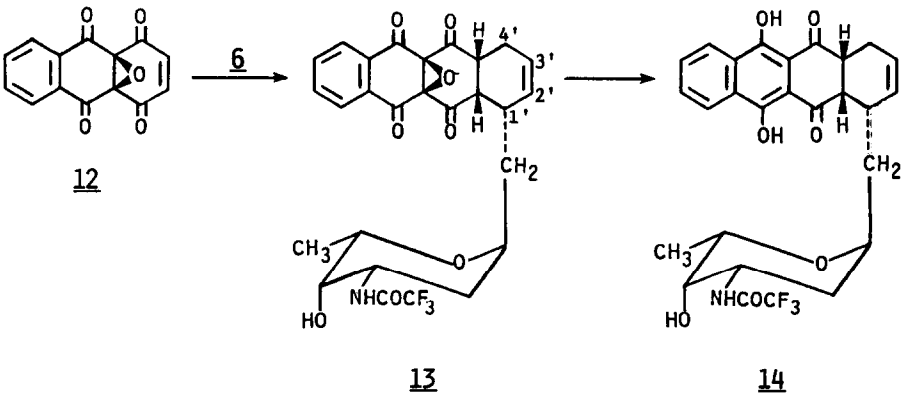
Both 5 and 6 efficiently underwent Diels-Alder reactions with naphthoquinone (7) in toluene at 90-100° for 18 hr. The adducts[5] (8 and 9, respectively; 60-65% yields) showed δ 5.7 m for HC=CH in ^1H NMR. They appeared to be diastereoisomeric mixtures from the presence of two doublets (each J = 6 Hz) for CH_3 of 8 (δ 1.16 and 1.03) and 9 (δ 1.25 and 1.14; also, 9 was resolved into 2 equal peaks by C-18 reverse-phase HPLC in phosphate buffer-CH_3CN). We assume the H's at 1'a, 4'a, and 1' are cis, as expected from an endo transition state and as previously assigned[12] to the quinone adducts of (E)-2,4-pentadiene. Hence, 8 and 9 also stand for the structures with 1'a, 4'a, and 1' inverted.[12] Upon treatment with Et_3N in toluene at 80-90° for 4 hr, 8 and 9 were converted in ca. 80% yields to the fully aromatized and homogeneous anthraquinones 10 (mp 253-6° MeOH-H_2O) and 11 (mp 288-292°, MeOH-H_2O).[5] The linker CH_2 was characterized by ^1H NMR of 10 at 300 MHz as two quartets (δ 3.78, J = 5.5 Hz; δ 3.69, J = 8.3 Hz; J_{gem} = 14 Hz).

Similarly, Diels-Alder reaction of 6 with the diquinone epoxide 12[13,14] gave adduct 13 (80-90% yields; δ 5.7 m HC=CH). Occurrence of 13 as a mixture of two diastereoisomers indicated that the extent of diastereocontrol reported with a chiral 1-glycosyloxy[13] butadiene and 12 or with chiral 1-acyloxy[15] butadienes and juglone was not observed.[16] We tentatively assume the diastereoisomers consist of 13 and the structure with the epoxide and H's at 1'a, 4'a and 1' inverted. Electron impact mass spectroscopy (m/e = 547 and 531 for M^+ and $M^+ - O$) indicated fragmentation between the aglycone and the linker CH_2 (m/e = 308 and 291). Treatment[14] of 13 with $Na_2S_2O_4$ removed the epoxide to give the red solid 14[5] (recrystallized from CCl_4, 17% yield; δ 13.70s and 13.48s, H-bonded OH's; 6.0 m, HC=CH) with a 52:48 ratio of diastereoisomers (reverse phase HPLC; δ 1.32 d and 0.85 d, J = 6 Hz, CH_3). Hence we have demonstrated the C.1-allylation of daunosamine with α-L stereospecificity, the C.1-pentadienylation with (E) and α-L stereospecificity, and successful quinone cycloadditions of the diene. Conversion of 14 to anthracycline analogs and syntheses of other quinone C-glycosides are being pursued.



8, R = pNB ⟶ 10, R = pNB, R' = $COCF_3$

9, R = H ⟶ 11, R = H, R' = $COCF_3$



13 14

Acknowledgment

This investigation was supported by PHS grant CA 32250 awarded by the National Cancer Institute, DHHS. We thank Dr. J. N. Shoolery of Varian Associates for the 2DFT COSY ^1H NMR spectrum of 5.

References

1. E. M. Acton, A. N. Fujiwara, and D. W. Henry. J. Med. Chem. 17, 659 (1974).
2. T. H. Smith, A. N. Fujiwara, W. W. Lee, H. Y. Wu, and D. W. Henry. J. Org. Chem. 42, 3653 (1977).
3. M. D. Lewis, J. K. Cha, and Y. Kishi. J. Am. Chem. Soc. 104, 4976 (1982).
4. A. P. Kozikowski, K. L. Sorgi, B. C. Wang, and Z. Xu. Tetrahedron Lett. 24, 1563 (1983).
5. All isolated compounds were characterized by ^1H NMR and mass spectra. Compounds 4-6 and 10,11 were obtained chromatographically homogenous. Compounds, 4, 6, 10, 11, and 14 were crystalline and characterized by elemental analysis. Numbering of aglycone carbons is with use of primes, as shown in structures 4-6, 8, 9, and 13, with the bridgehead carbons as 1'a and 4'a.
6. D. Seyferth, J. Pornet, and R. M. Weinstein. Organometallics 1, 1651 (1982).
7. This appears to be the first pentadienylation where (E) stereochemistry in both starting material and product has been defined, except for the case of trifluoroacetolysis.[8] The question of whether pentadienyl transposition occurs in these reactions remains unsettled.[9-11]
8. M. Jones and W. Kitching. J. Orgmet. Chem. 247, C5 (1983).
9. D. Seyferth and J. Pornet. J. Org. Chem. 45, 1722 (1980).
10. J. Pornet. Tetrahedron Lett. 21 2049 (1980).
11. A. Hosomi, M. Saito, and H. Sakurai. Tetrahedron Lett. 21, 3783 (1980).
12. I. Tegmo-Larsson, M. D. Rozeboom, and K. N. Houk. Tetrahedron Lett. 22, 2043 (1981). Presumably the products were enantiomeric pairs, although depicted as single enantiomers. With 8 and 9, the structural pairs are diastereoisomers because of the presence of the chiral sugar.
13. R. C. Gupta, P. A. Harland, and R. J. Stoodley. JCS Chem. Commun. 754 (1983).
14. M. Chandler and R. J. Stoodley. J. Chem. Soc. Perkin I 1007 (1980).
15. B. M. Trost, D. O'Krongly, and J. L. Belletire. J. Am. Chem. Soc. 102, 7595 (1980).
16. We are unaware of a precedent for addition of a chiral 1-substituted pentadiene to a quinone.

(Received in USA 11 September 1984)