Synthesis of Anhydro-bridged Disaccharide Subunits of Anthracycline Antibiotics

Joachim Thiem* and Werner Klaffke

Organisch-Chemisches Institut, Westfälische Wilhelms-Universität, Orléansring 23, D-4400 Münster, Federal Republic of Germany

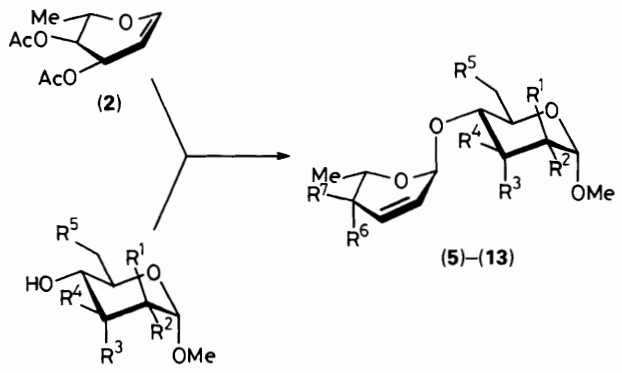
Following Ferrier glycosylations the hex-2-enopyranosyl disaccharides (**5**) and (**11**) are obtained, then converted by allylic oxidation to the Michael-acceptor systems (**10**) and (**13**), which are subsequently transformed into the ether-bridged disaccharides (**14**) and (**16**) by base catalysed intramolecular vinylogue addition; this approach provides the first straightforward access to novel ether-bridged and glycosidically linked saccharide units of anthracycline class II antibiotics such as cinerubin B.

Anthracycline antibiotics have been known for more than three decades and are well established as chemotherapeutics in the treatment of human lymphatic leukaemia.[1,2] This communication centres on a structural subunit in serirubicin,[3] ditrisarubicin,[4] sulfurmycin,[5] and cinerubin B (**1**),[6,7] all of which are found to express antineoplastic activity in tumour cell lines which are unaffected by adriamycin, aclacinomycin A, or cinerubin A. The decisive structural feature of these subunits is based on the additional 2′,3-ether bond bridging the α,1→4-glycosidically linked deoxy saccharide units *B* and *C*.

Starting with diacetylrhamnal (**2**)[8] and the easily available

epoxide (**3**)[9] the hex-2′-enopyranosyl-α(1→4) disaccharide (**5**) was obtained exclusively following the Ferrier glycosylation procedure (73%) (see Scheme 1).[10] As known from previous investigations[11,12] the epoxide with the *allo*-configuration was cleaved stereoselectively with lithium iodide in chloroform, to give both the *trans* diequatorial (**6**) and the *trans* diaxial (**7**) products in a 1:3 ratio according to Fürst–Plattner's rule.[13] The iodo altroside (**7**) was reduced by tri-n-butyltin hydride[14] to give the 2,6-dideoxy compound (**8**) and this in turn deblocked under mild basic conditions (potassium carbonate in methanol) to give methyl 4-*O*-(2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranosyl)-2,6-dideoxy-α-D-ribohexopyranoside (**9**). *In situ* allylic oxidation by manganese dioxide in anhydrous dichloromethane[15] gave the corresponding enone (**10**) (81%).

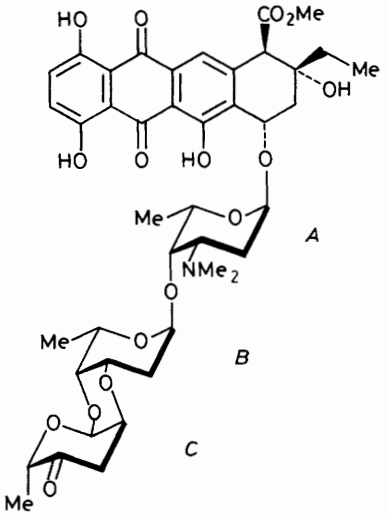
Treatment of (**10**) in dry dichloromethane at 0 °C with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), followed by warming to room temperature within 2 h, gave the anhydro-bridged disaccharide (**14**) as a colourless syrup in 59% yield (see Scheme 2). The ^{1}H NMR analysis of the coupling constants as well as the nuclear Overhauser enhancement

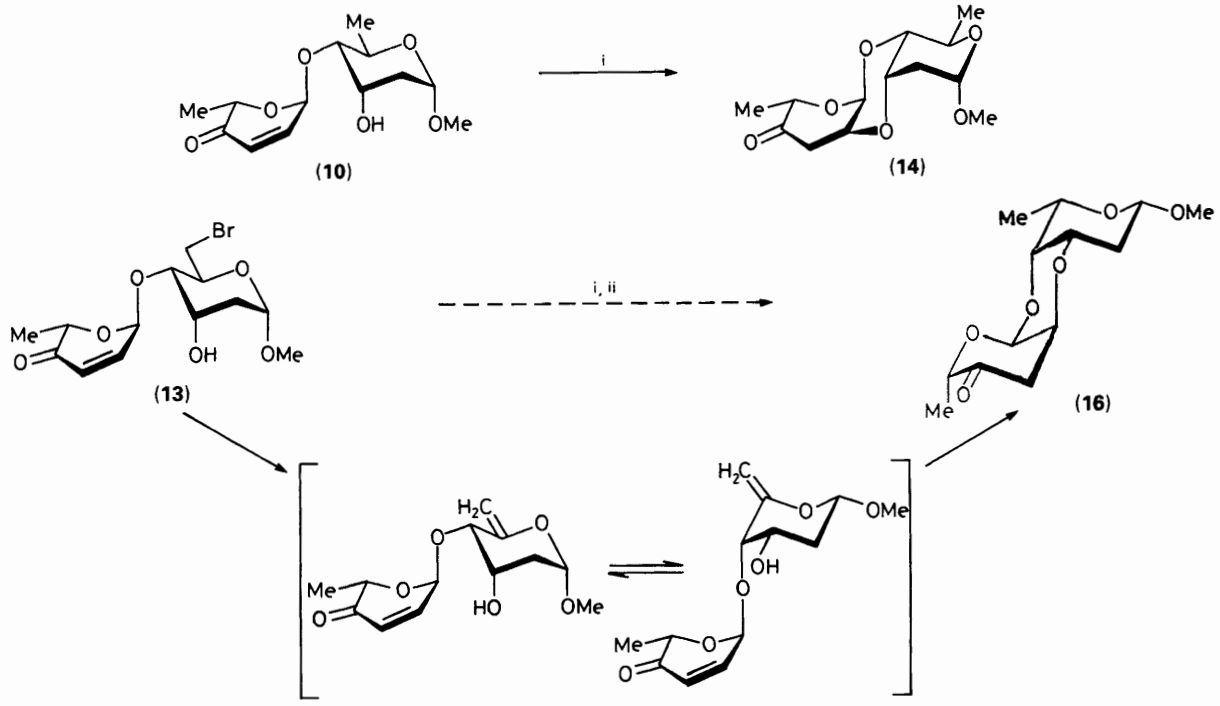


(**3**) $R^1 = R^4 = R^5 = H$; R^2, R^3 = —O—
(**4**) $R^1 = R^2 = R^4 = H$; R^3 = OAc, R^5 = Br

	R^1	R^2	R^3	R^4	R^5	R^6	R^7
(**5**)	H	–O–		H	H	H	OAc
(**6**)	H	OH	H	I	H	H	OAc
(**7**)	I	H	OH	H	H	H	OAc
(**8**)	H	H	OH	H	H	H	OAc
(**9**)	H	H	OH	H	H	H	OH
(**10**)	H	H	OH	H	H	=O	
(**11**)	H	H	OAc	H	Br	H	OAc
(**12**)	H	H	OH	H	Br	H	OH
(**13**)	H	H	OH	H	Br	=O	

Scheme 1. *Reagents*: BF_3–OEt_2





Scheme 2. *Reagents*: i, DBU; ii, H_2, Pd/C.

(NOE) for H-1′ and H-5 support the conformation depicted to be $^4C_1$ for the reducing and $^1S_0$ for the nonreducing rings, respectively.

In order to circumvent difficulties in the glycosylation reaction of such C-4 hydroxy groups in the *lyxo* series, as observed previously in Koenigs–Knorr[16] and *N*-iodosuccinimide[15] reactions, a synthetic deviation was applied which formerly proved useful in corresponding cases.[17,18] Thus, methyl 6-bromo-2,6-dideoxy-α-D-hexopyranoside (**4**) was synthesized by several steps described previously[17] and served as the key intermediate in this 'D-trick-strategy' approach.[18] Ferrier glycosylation of (**2**) and (**4**) generated the unsaturated α(1→4) linked disaccharide (**11**) in 54% yield. Further deacetylation to (**12**) and subsequent oxidation by manganese dioxide gave the labile enone derivative (**13**). Formation of the desired compound (**16**) could be observed after reaction with DBU in dichloromethane followed by a hydrogenation step. This result may be rationalized by a two-step process. Under basic conditions the elimination of hydrogen bromide occurs and simultaneously a Michael addition generates the anhydro bridge. Final hydrogenation of the assumed unsaturated intermediate (**15**) inverts the stereochemistry at C-5 and thus sets up the L-configuration in the reducing sugar ring of the ether-linked methyl β-glycoside (**16**). This *in situ* four-step procedure gave an overall 14% yield of (**16**) based on the disaccharide precursor (**11**).

In conclusion, this contribution describes the first approach to anhydro-bridged deoxy oligosaccharide compounds of class II anthracyclines following a biomimetic approach.[6]

We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for support of this work.

Received, 6th June 1989; Com. 9/02378J

References

1 S. T. Crooke and S. D. Reich, 'Anthracyclines—Current Status and Development,' Academic Press, New York, 1980.
2 'Molecular Aspects of Anti Cancer Drug Action,' eds. S. Neidle and M. J. Waring, VCH-Verlagsgesellschaft, Weinheim, 1983.
3 T. Uchida, M. Imoto, T. Masuda, H. Yoshimoto, K. Immamura, T. Sawa, H. Naganawa, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, 1985, **38**, 795.
4 T. Uchida, M. Imoto, T. Masuda, K. Imamura, Y. Hatori, T. Sawa, H. Naganawa, M. Hamada, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, 1983, **36**, 1080.
5 T. Uchida, M. Imoto, Y. Watanabe, K. Miura, T. Dobashi, N. Matsuda, T. Sawa, H. Naganawa, M. Hamada, T. Takeudu, and H. Umezawa, *J. Antibiot.*, 1985, **38**, 1171.
6 W. Richle, E. K. Winkler, D. M. Hawley, M. Dobler, and W. Keller-Schierlein, *Helv. Chim. Acta*, 1972, **55**, 467.
7 B. Iselin and T. Reichstein, *Helv. Chim. Acta*, 1944, **27**, 1200.
8 H. Paulsen and V. Sinnwell, *Chem. Ber.*, 1978, **111**, 879.
9 T. Oki, I. Kitamura, Y. Matsuzawa, N. Shibamoto, T. Ogasawara, A. Yoshimoto, and T. Inui, *J. Antibiot.*, 1979, **32**, 801.
10 R. J. Ferrier and N. Prasad, *Chem. Commun.*, 1968, 476; *J. Chem. Soc. (C)*, 1969, 570.
11 J. Thiem and J. Schwentner, *Chem. Ber.*, 1979, **112**, 3126.
12 J. Thiem, P. Ossowski, and J. Schwentner, *Angew. Chem.*, 1979, **91**, 242; *Angew. Chem., Int. Ed. Engl.*, 1979, **26**, 238.
13 A. Fürst and P. A. Plattner, 12th Int. Congr. Pure Appl. Chem., New York, 1952, Abstr. Papers, p. 409.
14 H. G. Kuivila, *Synthesis*, 1970, 499; H. Arita, N. Ueda, and Y. Matsushima, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 567.
15 B. Fraser-Reid, D. L. Walker, S. Y. Tam, and N. L. Holder, *Can. J. Chem.*, 1973, **51**, 3950.
16 A. Martin, M. Pais, and C. Monneret, *Tetrahedron Lett.*, 1986, **27**, 575.
17 D. Springer and J. Thiem, unpublished work; D. Springer, Ph.D. Thesis, Univ. Hamburg, 1985.
18 J. Thiem and W. Klaffke, *Top. Curr. Chem.*, in the press.
19 J. Thiem and P. Ossowski, *Liebigs Ann. Chem.*, 1983, 2215.