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PRACTICAL TOTAL SYNTHESIS OF 11-DEOXYDAUNOMYCINONE AND THE FIRST TOTAL SYNTHESIS OF 11-DEOXYDAUNOMYCIN

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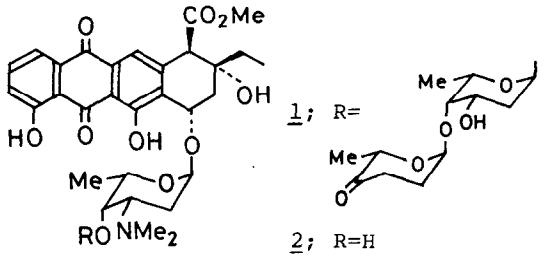
Summary: The first total synthesis of the naturally derived second generation anthracycline, 11-deoxydaunomycin (3) is described. Key steps in the synthesis of 3 include an efficient construction of α-hydroxy methyl ketone moiety at C_9-position, a highly stereoselective synthesis of cis-$C_{7,9}$-diol, and the first successful use of C_{13}-acetal derivative for the glycosidation.

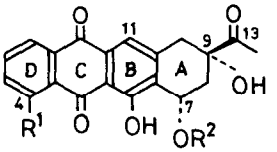
Since the 11-deoxyanthracyclines such as aclacinomycin A (1), aklavin (2), 11-deoxydaunomycin (3), and 4-demethoxy-11-deoxydaunomycin (4) have been found to exhibit strong antineoplastic activity and substantially reduced toxicity relative to the 11-oxyanthracyclines, the development of synthetic approaches to these reagents has been a subject of extensive study during these several years.[1] Although synthesis of 4 and total synthesis of 2 have been reported by Umezawa et al.[2] and Kishi et al.,[3] respectively, synthesis of 3 has never been accomplished yet. We would like to report here a practical total synthesis of racemic 11-deoxydaunomycinone (5), the aglycone of 3, and also report the first total synthesis of 3.

In planning a total synthesis of 3, there are three distinct problems; i) regioselective preparation of the key anthraquinone moiety, ii) efficient and stereoselective introduction of functionality on ring A, and iii) lack of investigation of glycosidation of 5. Many elegant approaches have been employed to solve the first of these objects and extensive literatures including our result exist in the preparation of the 11-deoxy-5,9,12-trioxonaphthacene (6).[4,5] Although conversion of 6 into 5 has been achieved by Gesson et al.,[5b] the elaboration method of 6 using ethynylmagnesium bromide is a low-yielding process probably due to a ready base-induced enolization under conditions used. The same problem in the synthesis of the 11-oxyanthracyclines has been solved by the reaction of (trimethylsilyl)ethynylcerium(III) chloride,

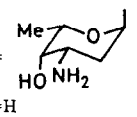


1; R=

2; R=H

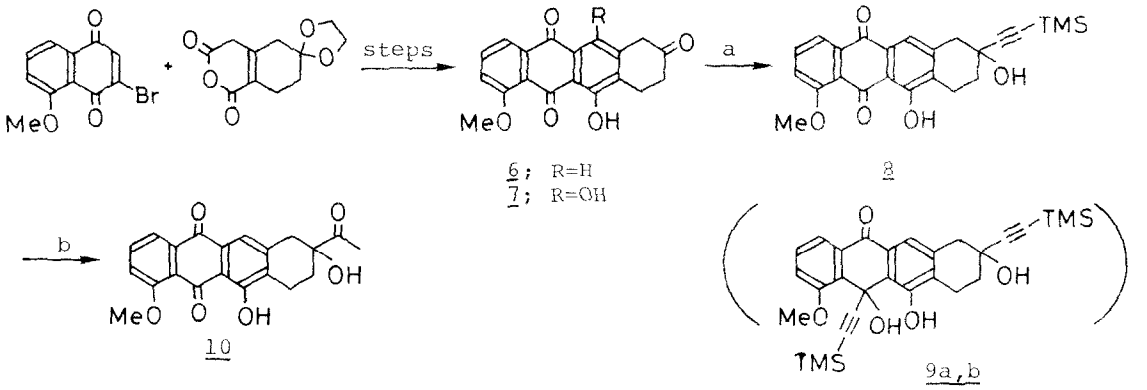


3; R^1=OMe
4; R^1=H
} R^2=



5; R^1=OMe, R^2=H

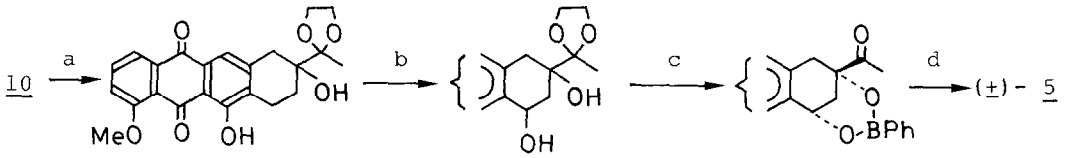
developed by Imamoto et al. with 11-oxy-5,9,10-trioxonaphthacene (7).[6] The application of this method to 6 did not give the desired 9-(trimethylsilyl)-ethynyl hydroxy compound (8) but gave a mixture of unexpected diastereomers (9a,b) in 84% yield:[7] A solution of 6 in THF was added to the cerium reagent, prepared from (trimethylsilyl)ethynyllithium and anhydrous $CeCl_3$, at -78°C to give 9a,b [9a: 43%, mp 183.5-185°C, 9b: 41%, mp 163-165°C]. Among various reaction conditions examined changing the amount of the cerium reagent, concentration, the speed of the addition, and so on, the reverse addition was found to solve this problem and provided a good yield of the desired 8: An excess (4 equiv) of the cerium reagent was added to a stirred solution of 6 over 4h at -78°C to give 8 [59% (94% from the reacted 6), mp 203.5-205°C]. Treatment of 8 with HgO/d.H_2SO_4 in refluxing THF gave the 9-hydroxyacetone compound (10) [quant, mp 218.5-220°C; lit.[6c] 218-219.5°C], which was identical in all respects with an authentic sample.



a) TMS-≡-$CeCl_2$, -78°C, 4h; b) HgO-d.H_2SO_4/THF, reflux, 1.5h

Scheme I

The introduction of a C_7-cis hydroxyl group into 10 has been a troublesome step,[2,5b,7,8] which involves tedious chromatographic separations of the always produced 7-cis and 7-trans isomers. In our hands, all the reported conversions of 10 to racemic 11-deoxydaunomycinone (5) via the 13-acetal derivatives (11) gave poor results. Better result was obtained by the following reactions (Scheme II). Bromination of 11 with N-bromosuccinimide-AIBN, hydrolysis of the 7-bromo compound with wet silica gel in THF leading to the 7-hydroxy compound (12, cis/trans=15/1), formation of cyclic cis-benzeneboronate (13) from the cis/trans-mixture of 12 by the reaction with benzeneboronic acid in CF_3CO_2H,[9,10] and deprotection of 13 with 2-methyl-2,4-pentanediol -AcOH gave racemic 5, which has the required cis-$C_{7,9}$-diol, in 49% overall yield from 11 [(±)-5: mp 250-251°C (dec.); lit.[7,8] 210-213°C]. The structure gave a satisfactory elemental analysis and spectroscopic data were completely in accord with those of the authentic sample generously provided by Prof Arcamone.



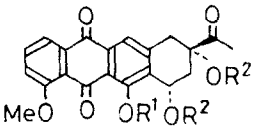
11 12 cis/trans=15/1 13

a) $HO(CH_2)_2OH$-p.TsOH/C_6H_6, reflux, 3h, b) i) NBS-AIBN/CCl_4, 80°C 80min, ii) wet SiO_2/THF, 0°C-r.t., 1.5h, c) $PhB(OH)_2$-CF_3CO_2H/toluene, 0°C, 2h→r.t., 12h, d) 2-methyl-2,4-pentanediol-AcOH/CH_2Cl_2-acetone, r.t., 2d

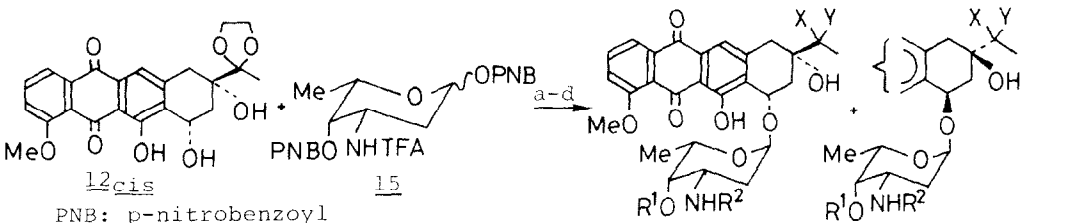
Scheme II

The serious problem was the final glycosidation step. There has been no report on the glycosidation of 5 or its derivatives. Condensation of 5 with suitably protected L-daunosamines by using Koenigs-Knorr method and Terashima's method[11] could not give any glycoside at all probably due to the extremely low solubility of 5 in the common organic solvents. Condensation using more soluble derivatives (14a-c) whose hydroxyl groups were protected with Me_3Si and acyl groups failed to give glycosides. After many unsuccessful attempts, condensation of the 13-acetal derivative (12_{cis}) with 4-O-p-nitrobenzoyl sugar (15) under Terashima's conditions gave a 42% yield of the expected α-glycosides (16 and 17) and a 29% yield of recovered 12_{cis} [16: mp 195-199°C (dec.), $[\alpha]_D^{20}$ -105.4° (c=0.04, $CHCl_3$), 17: mp 179-183°C (dec.), $[\alpha]_D^{20}$ -208.1° (c=0.05, ($CHCl_3$)]. Careful deacetalization of 16 and 17 with 80% AcOH gave 18 and 19 in 41 and 53% yields, respectively [18: 174.5-177.5°C, $[\alpha]_D^{20}$ -80.6° (c=0.05, $CHCl_3$), 19: mp 170-174°C, $[\alpha]_D^{20}$ -202.2°C (c=0.03, $CHCl_3$)]. The absolute configuration of these novel glycosides (16-19) was deduced from their ^1H NMR and CD spectral data and finally confirmed by the direct induction of 18 into 3 (vide infra). Stepwise hydrolysis of 18 with 0.1N NaOH gave N-trifluoroacetyl-11-deoxydaunomycin [20: mp 151-155°C, $[\alpha]_D^{20}$ +86° (c=0.05, $CHCl_3$)] and 11-deoxydaunomycin (3), respectively (Scheme III). The hydrochloride of 3 was identical in all respects with the authentic sample generously provided by Prof. Arcamone [3.HCl: mp 215-220°C (dec.), 170-177°C (dec.),[12] $[\alpha]_D^{20}$ +135° (c= 0.01, MeOH); lit.[13] 175-176°C (dec.), $[\alpha]_D^{20}$ +139° (c=0.2, MeOH)]. All known products were identified by comparison with authentic samples. New compounds were characterized by 500 MHz ^1H NMR, IR, and analytical data.

Acknowledgement: We are grateful to Professor F. Arcamone for providing the sample of 3 and the spectroscopic charts of 3 and 5.



14a; $R^1=R^2=SiMe_3$
b; $R^1=COMe$, $R^2=H$
c; $R^1=CO^tBu$, $R^2=H$



12cis 15

PNB: p-nitrobenzoyl
TFA: trifluoroacetyl

a) TMSOTf, molecular sieves 4A/ CH_2Cl_2-Et_2O, -15°C, 4h; b) 80% AcOH, 45°C, 40h; c) 1 equiv 0.1N NaOH/CH_2Cl_2-MeOH, 0°C, 20min; d) excess 0.1N NaOH, r.t., 20min

	X Y	R^1	R^2
16	O,O	PNB	TFA
18	=O	PNB	TFA
20	=O	H	TFA
3	=O	H	H

	X Y	R^1	R^2
17	O,O	PNB	TFA
19	=O	PNB	TFA

Scheme III

Rererences and Notes

1) a) S. Terashima, Yuki Gosei Kagaku Kyokai Shi, 40, 20 (1982); b) Tetrahedron Symposia-in-Print Number 17, "Recent Aspects of Anthracyclinone Chemistry," ed. by T. R. Kelly, Tetrahedron, 40, 4537-4793 (1984); K. Krohn, Angew. Chem. Int. Ed. Engl., 25, 790 (1986).
2) H. Umezawa, Y. Takahashi, M. Kinoshita, H. Naganawa, K. Tatsuta, and T. Takeuchi, J. Antibiot., 33, 1581 (1980).
3) B. A. Pearlman, J. M. McNamara, I. Hasan, S. Hatakeyama, H. Sekizaki, and Y. Kishi, J. Am. Chem. Soc., 103, 4248 (1981).
4) a) J. G. Bauman, R. B. Barber, R. D. Gless, and H. Rapoport, Tetrahedron Lett., 21, 4777 (1980); b) J. Alexander, D. L. Flynn, L. A. Mitscher, and T. Veysoglu, ibid., 22, 3711 (1981); c) M. E. Jung, M. Node, R. W. Pfluger, M. A. Lyster, and J. A. Lowe, III, J. Org. Chem., 47, 1150 (1982); d) F. M. Hauser, S. Prasanna, and D. W. Combs, ibid., 48, 1328 (1983); e) E. Vedejs, W. H. Miller, and J. R. Pribish, ibid., 48, 3611 (1983); f) Y. Tamura, S. Akai, M. Sasho, and Y. Kita, Tetrahedron Lett., 25, 1167 (1984); g) P. N. Preston, T. Winwick, and J. O. Morley, J. Chem. Soc., Perkin Trans. 1, 1985, 39.
5) a) J. -P. Gesson, J. -C. Jacquesy, and M. Mondon, Tetrahedron Lett., 21, 3351 (1980); b) J. -P. Gesson and M. Mondon, J. Chem. Soc., Chem. Commun., 1982, 421; cf. A. S. Kende, Y. -g. Tsay, and J. E. Mills, J. Am. Chem. Soc., 98, 1967 (1976); A. S. Kende, D. P. Curran, Y. -g. Tsay, and J. E. Mills, Tetrahedron Lett., 1977, 3537.
6) a) T. Imamoto, Y. Sugiura, and H. Takiyama, ibid., 25, 4233 (1984); b) M. Suzuki, Y. Kimura, and S. Terashima, Chem. Lett., 1984, 1543; c) Y. Tamura, M. Sasho, H. Ohe, S. Akai and Y. Kita, Tetrahedron Lett., 26, 1549 (1985); d) Y. Tamura, M. Sasho, S. Akai, H. Kishimoto, J. Sekihachi, and Y. Kita, ibid., 27, 195 (1986).
7) The structures were assigned as 9a,b on the basis of spectral evidence [9a,b; $\nu_{max}^{CHCl_3}$ 1665 cm^{-1} (non-chelated quinone carbonyl band), m/z 500 (M^+-18)]. Similar result, see: A. A. Abdallah, J. -P. Gesson, J. -C. Jacquesy, and M. Mondon, Bull. Soc. Chim. Fr., 1986, 93.
8) S. D. Kimball, D. R. Walt, and F. Johnson, J. Am. Chem. Soc., 103, 1561 (1981).
9) The use of benzeneboronate intermediate in the anthracycline synthesis, see: a) M. J. Broadhurst, C. H. Hassall, and G. J. Thomas, J. Chem. Soc., Perkin Trans. 1, 1982, 2239; b) K. Ravichandran, F. A. J. Kerdesky, and M. P. Cava, J. Org. Chem., 51, 2044 (1986).
10) Epimerization of the 7-trans isomer (12trans) in CF_3CO_2H in the absence of benzeneboronic acid resulted in the 7-cis isomer, along with a small amount of the fully aromatized product.
11) Y. Kimura, M. Suzuki, T. Matsumoto, R. Abe, and S. Terashima, Chem. Lett., 1984, 501; b) Idem, Bull. Chem. Soc. Jpn., 59, 423 (1986).
12) The crude 3.HCl, which contains a small amout of the aromatized compound decomposes at 170-177°C.
13) G. Cassinelli, F. D. Matteo, S. Forenza, M. C. Ripamonti, G. Rivola, F. Arcamone, A. D. Marco, A. M. Casazza, C. Soranzo, and G. Pratesi, J. Antibiot., 33, 1468 (1980).

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