Regio- and Stereo-selective Construction of Anthracyclinones: Total Synthesis of (−)-γ-Rhodomycinone

Hiromichi Fujioka,* Hirofumi Yamamoto, Hiroshi Kondo, Hirokazu Annoura, and Yasuyuki Kita*

Faculty of Pharmaceutical Sciences, Osaka University, 1—6, Yamada-oka, Suita, Osaka 565, Japan

The first asymmetric synthesis of (−)-γ-rhodomycinone (**1a**) was achieved through a novel regioselective coupling reaction of the chiral *AB*- (**2**) and *CD*-building blocks (**3**).

The rhodomycinones (**1a,b**) are the principal aglycones of rhodomycins[1] and recently isolated potent anthracycline antibiotics such as betaclamycin A[2] and distrisarubicin B.[3] Although many asymmetric syntheses of anthracyclinones[4] have been accomplished,[5] there are few[6] studies on the asymmetric syntheses of rhodomycinones and no one has yet succeeded in the synthesis of optically active natural rhodomycinones. We now report the first asymmetric synthesis of (−)-γ-rhodomycinone (**1a**) involving a novel regioselective coupling reaction of the new chiral *AB*- (**2**) and *CD*-building blocks (**3**).

The requisite *AB*-synthon (**2**) was obtained from 5,8-dimethoxy-2-tetralone-1-acetal (**4**) by a previously reported asymmetric alkylation[4b] followed by stereoselective reduction of the 1-oxo group. Treatment of (**4**) with ethylmagnesium chloride in dry tetrahydrofuran (THF) at −78 °C for 5 h gave the 2*R*-2-ethyl-2-hydroxy acetal (**5**) which was hydrolysed with trifluoroacetic acid (CF_3CO_2H) to give the α-hydroxy ketone (**6**) in 84% overall yield.† Reduction of (**6**) with potassium borohydride (KBH_4) in methanol afforded a mixture of (**7a**) and (**7b**) in a ratio of 15 : 2,‡ which was easily separated by column chromatography to give (**7a**) in 82% yield. Oxidation of (**7a**) with ceric ammonium nitrate (CAN) in 50% aqueous MeOH afforded (**2**) {87%, m.p. 110—112 °C, $[\alpha]_D$ −32.6° (*c* 0.96)}.

The strong base induced coupling reaction[7] of 4-acetoxy-5-methoxyhomophthalic anhydride (**3**) with (**2**) was achieved in the following way. The anhydride (**3**) was treated with sodium hydride and reacted with (**2**) at 0 °C for 0.5 h to give the adduct (**8**) {55%, m.p. 115—117 °C, $[\alpha]_D$ −18.9° (*c* 0.12)}. Treatment of (**8**) with 66% aqueous CF_3COOH at 50—55 °C caused deacetylation and the shift of the quinone moiety to the *C*-ring to give (**9**) {93%, m.p. 100—102 °C, $[\alpha]_D$ +2.25° (*c* 0.133)}. Similarly, the reaction of 4-acetoxy-8-methoxyhomophthalic anhydride (**10**) with (**2**) afforded (**11**) {62%, m.p. 94—96 °C, $[\alpha]_D$ −12.3° (*c* 0.11)}, which was converted to (**12**) {91%, m.p. 237—239 °C, $[\alpha]_D$ −9.26° (*c* 0.11)}. Compounds (**9**) and (**12**) are easily distinguished from each other by their ^1H n.m.r. spectroscopic analyses§ and t.l.c. patterns.¶ Since crude (**9**) and crude (**12**) did not contain regioisomers of each other, it was proved that the cycloaddition reactions of (**2**) and (**3**) and of (**2**) and (**10**) proceeded regioselectively.††

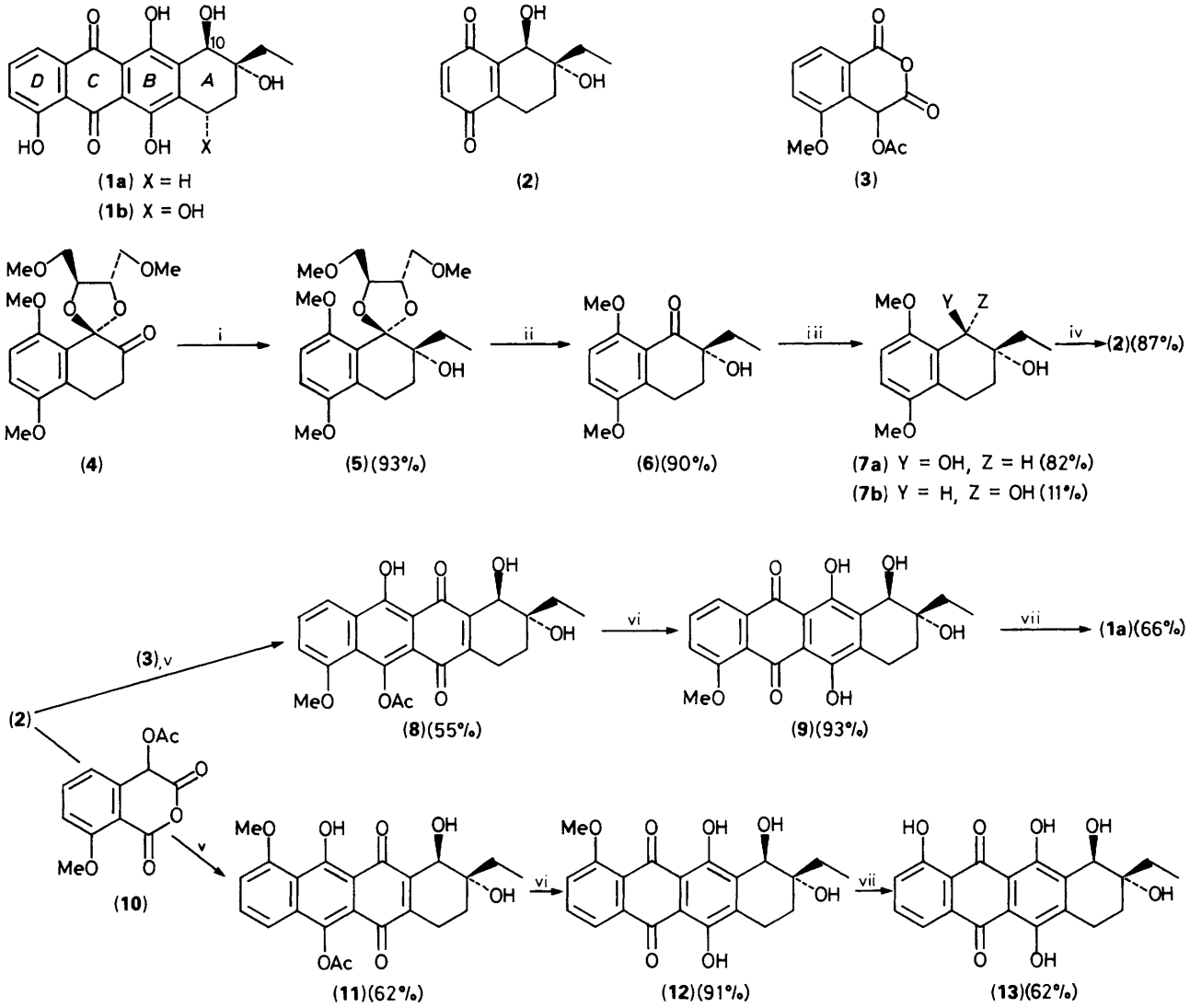
† Details of the preparation of (**6**) will be published in a full paper.

‡ The stereochemistries of the secondary alcohols were determined as *R* for (**7a**) and as *S* for (**7b**) since the acetonide was formed in the reaction of (**7b**) with 2,2-dimethoxypropane in the presence of acid catalyst and not formed in the case of (**7a**).

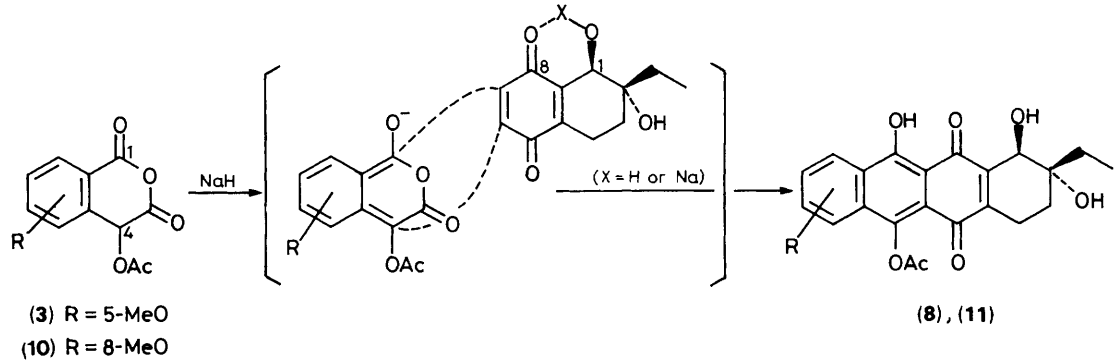
§ The signals of two singlets in (**9**) (δ 13.68 and 13.7) and two singlets in (**12**) (δ 13.34 and 14.09) are due to the two phenolic hydroxy functions.

¶ Compounds (**9**) and (**12**) showed good separation on t.l.c. (silica gel, $CHCl_3/Me_2CO$, 5/1 or CH_2Cl_2/ether, 1/3).

†† Although the strong base induced cycloaddition of homophthalic anhydrides is known to react regioselectively with halonaphthaloquinone derivatives,[7] this is the first example of regiocontrolled addition to 6,7-unsubstituted naphthoquinone derivatives.



Scheme 1. i, EtMgCl, THF, room temp.; ii, 80% aq, CF_3COOH, room temp.; iii, KBH_4, MeOH, −78 °C; iv, CAN, aq. MeCN, 0 °C; v, NaH, THF, 0 °C; vi, 66% aq, CF_3COOH, 50—55 °C; vii, $AlCl_3$, benzene, room temp.



Scheme 2

This extremely high regioselectivity might be explained as follows. The hydrogen bonding or chelation between C(1), the secondary hydroxy function, and C(8), the quinoid carbonyl, of (**2**) caused an electron poor (δ+) centre at the C(6) position and an electron rich (δ−) centre at C(7). The cycloaddition reactions proceeded as shown in Scheme 2.

The structures of (**9**) and (**12**) were determined by conversion to (−)-γ-rhodomycinone (**1a**) and 4-dehydroxy-1-hydroxy-γ-rhodomycinone (**13**), respectively (*vide infra*). Thus, demethylation of (**9**) with anhydrous aluminium chloride ($AlCl_3$) in benzene afforded (**1a**) in 66% yield. In the same manner, (**12**) afforded (**13**) in 62% yield. The melting point (m.p.), ^1H n.m.r., and i.r. spectra of (**1a**) obtained were identical to those previously reported.[8] The optical rotation of (**1a**) showed good agreement with that of natural rhodomycinone {$[\alpha]_D$ −20.69° (*c* 0.058); natural −20.16° (*c* 0.060)}. The enantiomeric excess (100% e.e.) of (**1a**) was determined from h.p.l.c. analysis using a chiral column [Daicel chiralcel OA; eluent, hexane : EtOH : MeOH : AcOH, 170 : 20 : 10 : 1, flow rate, 0.5 ml min^{-1}; t_R, 29.25 min for (−)-(**1a**), 21.43 and 29.10 min for (±)-(**1a**).

In conclusion, the strong effect of the benzylic secondary hydroxy function of (**2**) towards the regioselectivity was observed in the coupling reactions with homophthalic anhydrides [(**3**) and (**10**)] and the first asymmetric synthesis of optically pure (**1a**) was achieved. The present route will open an effective way to synthesize other anthracyclinones, having a C(10) (anthracycline numbering) hydroxy function such as (**1b**) and feudomycinones,[9] in a regioselective manner.

We thank Prof. K. Krohn (Technischen Universitat Braunschweig) for his gift of (±)-γ-rhodomycinone and Prof. Yongle Chen (Sichuan Industrial Institute of Antibiotics) for (−)-γ-rhodomycinone.

Received, 7th June 1989; Com. 9/02404B

References

1 H. Brockmann, *Fortschr. Chem. Org. Naturst*, 1963, **21**, 127.
2 A. Yoshimoto, Y. Matsuzawa, T. Ishikura, T. Sawa, T. Takeuchi, and H. Umezawa, *J. Antibiotics*, 1984, **37**, 920.
3 S. Kunimoto, Y. Takahashi, T. Uchida, T. Takeuchi, and H. Umezawa, *J. Antibiotics*, 1988, **41**, 655.
4 (a) For our synthetic studies on anthracyclines see, Y. Tamura and Y. Kita, *Yuki Gosei Kagaku Kyokaishi*, 1988, **46**, 205; Y. Tamura, S. Akai, H. Kishimoto, M. Sasho, M. Kirihara, and Y. Kita, *Chem. Pharm. Bull.*, 1988, **36**, 3897, and references cited therein; (b) For an asymmetric synthesis of (−)-7-deoxydaunomycinone see, Y. Tamura, H. Annoura, H. Yamamoto, H. Kondo, Y. Kita, and H. Fujioka, *Tetrahedron Lett.*, 1987, **28**, 5709.
5 For examples of recent syntheses see, M. Suzuki, Y. Kimura, and S. Terashima, *Tetrahedron Lett.*, 1985, **26**, 6481; M. Sodeoka, T. Iimori, and M. Shibasaki, *ibid.*, 1985, **26**, 6497; R. A. Russell, R. W. Irvine, and R. N. Warrener, *J. Org. Chem.*, 1986, **51**, 1595 M. Suzuki, T. Matsumoto, M. Ohsaki, Y. Kimura, and S. Terashima, *Chem. Lett.*, 1986, 1739; K. Krohn and H. Rieger, *Liebigs Ann. Chem.*, 1987, 515; K. Tomioka, N. Nakajima, and K. Koga, *J. Am. Chem. Soc.*, 1987, **109**, 6213; M. Kawasaki, F. Matsuda, and S. Terashima, *Tetrahedron Lett.*, 1988, **29**, 791.
6 Synthetic studies on racemic rhodomycinones see, A. S. Kende and Y. Tsay, *J. Chem. Soc., Chem. Commun.*, 1977, 140; M. Braun, *Tetrahedron*, 1984, **40**, 4585; K. Krohn and W. Priyono, *ibid.*, 1984, **40**, 4609, and references cited therein: J. A. Rao, K. Ravichaudrau, G. J. O'Malley, and M. P. Cava, *Can. J. Chem.*, 1987, **65**, 31; Synthetic studies on optically active rhodomycinones, see: K. Krohn and U. Muller, *Tetrahedron*, 1986, **42**, 6635; J. C. Florent, J. Ughetto-Monfrin, and C. Monneret, *J. Org. Chem.*, 1987, **52**, 1051; A. Genot, J. C. Florent, and C. Monneret, *Tetrahedron Lett.*, 1989, **30**, 711.
7 Y. Tamura, F. Fukata, M. Sasho, T. Tsugoshi, and Y. Kita, *J. Org. Chem.*, 1985, **50**, 2273; Y. Tamura, M. Sasho, K. Nakagawa, T. Tsugoshi, and Y. Kita, *ibid.*, 1984, **49**, 473.
8 K. Krohn and B. Behukee, *Chem. Ber.*, 1980, **113**, 2294.
9 For the conversion of 4-*O*-methylrhodomycinone (**9**) to feudomycinone see, K. Krohn and W. Priyono, *Tetrahedron*, 1984, **40**, 4609.