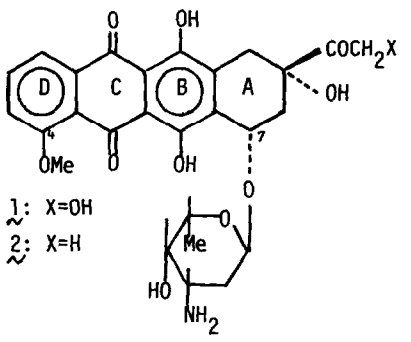
Tetrahedron Letters No. 49, pp 4937 - 4940.
0040-4039/78/1201-4937$02.00/0

ASYMMETRIC SYNTHESIS OF OPTICALLY ACTIVE ANTHRACYCLINONES

Shiro Terashima,* Sang-sup Jew, and Kenji Koga
Faculty of Pharmaceutical Sciences, University of Tokyo,
Hongo, Bunkyo-ku, Tokyo 113, Japan

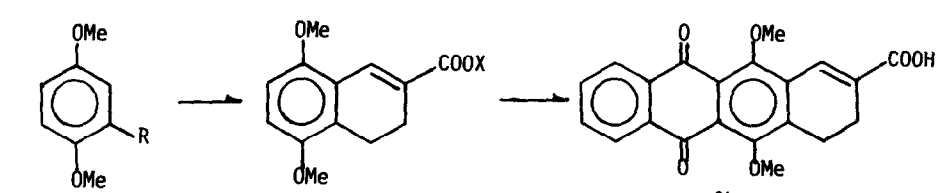
The anthracycline antibiotics adriamycin(1) and daunorubicin(2) are of current interest because of their activity against various experimental tumors as well as certain types of human cancer.[1] Studies on the structure-activity relationship have revealed that 4-demethoxy analogues of 1 and 2 show improved therapeutic properties.[1,2] Although various syntheses of the anthracyclinones, aglycones of the anthracyclines, have been reported in racemic modifications,[3-8] efficient methods to produce optically active anthracyclinones seem quite limited,[9] and no attempts have been made in the area of their asymmetric syntheses.

Recently the asymmetric bromolactonization reaction was developed as an effective method for converting α,β-unsaturated acid into highly optically active α-hydroxy acid.[12] Applicability of this novel asymmetric reaction to the preparation of optically active anthracyclinones has already been proven to be quite promising by the model study.[13] Based on these results, asymmetric synthesis of optically active anthracyclinones is attempted using two different types of α,β-unsaturated acids(3a,b) which possess AB and ABCD ring systems of anthracyclinones, as reaction substrates.



Two types of α,β-unsaturated acids(3a,b) were prepared from 1,4-dimethoxybenzene(4) following the reaction scheme shown in Scheme I. Thus, acylation of 4 with succinic anhydride[14] followed by Clemmensen reduction[15] according to the reported procedure,[14,15] afforded the known acid(5), mp 60-62°C(lit.,[15a] mp 64.5-67°C; lit.,[15b] mp 61-62°C), which on esterification(conc. H_2SO_4-EtOH) gave the ethyl ester(6)[16a](63%), bp 155-158°C(3 mmHg).

Scheme I



4: R=H
5: R=$(CH_2)_3COOH$
6: R=$(CH_2)_3COOEt$

7: X=Et
3a: X=H

3b

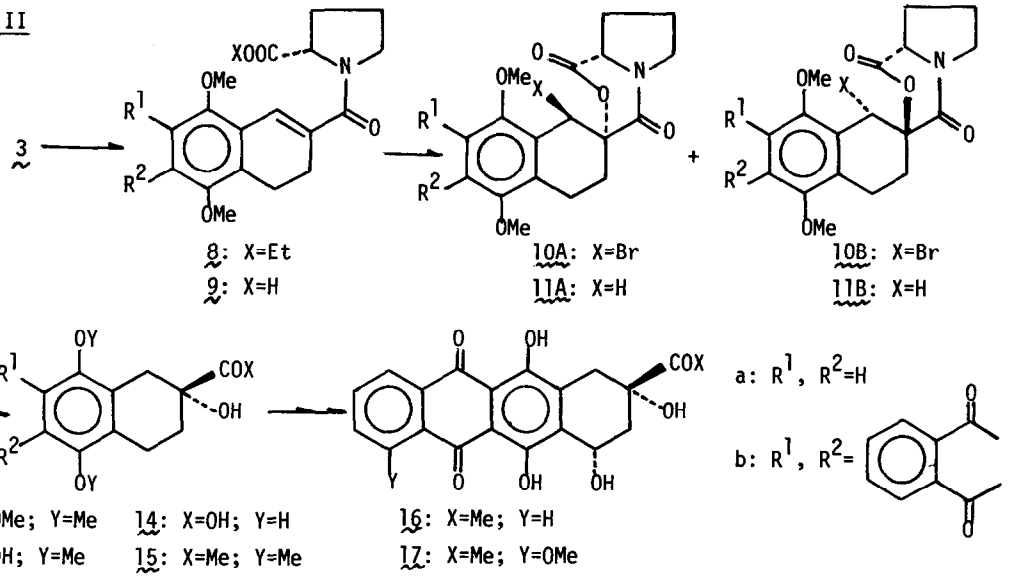
Conversion of 6 into the ethyl ester(7),[16] mp 76-77°C, was accomplished by successive condensation with ethyl formate(NaH(2.0 eq) in Et_2O) and acid-promoted cyclization(90%H_3PO_4-98%H_2SO_4 5:1 by volume)(two steps 43%). The ester(7) was hydrolyzed(2N-NaOH-EtOH 1:2) to give the acid(3a)[16] as colorless needles(97%), mp>220°C. On the other hand, acylation of 7 with o-methoxycarbonylbenzoyl chloride[17](5.0 eq)($AlCl_3$(5.5 eq) in CH_2Cl_2, rt 3hr) afforded a regioisomeric mixture of the diester[16a](48%) with recovery of the starting material(7)(56%) Alkaline hydrolysis(8%NaOH-EtOH 1:1) of the diester(87%), followed by treatment with liquid hydrogen fluoride(rt 43 hr) furnished the crystalline acid(3b)[16] as yellow needles(from AcOH)(67%), mp>250°C.

Since preparation of 3a,b was completed, the asymmetric synthesis of optically active anthracyclinones was examined as shown in Scheme II. Condensation of 3a and (S)(-)-ethyl prolinate(diethyl phosphorocyanidate-Et_3N in DMF, 0°C 2 hr, then rt 48 hr)[18] gave (S)(-)-ethyl N-acylprolinate(8a)[16a] as a caramel(100%), $[\alpha]_D^{20}$-10.3°(c=2.28, EtOH), which was then hydrolyzed(aq. KOH-EtOH) to (S)(-)-N-acyl proline(9a)[16](97%), mp 198-200°C(from EtOH), $[\alpha]_D^{20}$-3.0°(c=3.01, 2N-NaOH). The same successive treatments of 3b as for 3a gave 9b[16a] as a caramel(two steps 42%), $[\alpha]_D^{20}$-30.4°(c=1.40, C_6H_6), by way of its ethyl ester(8b),[16] mp 68-70°C(from EtOH), $[\alpha]_D^{20}$-13.4°(c=0.538, $CHCl_3$).

Asymmetric bromolactonization of 9a(NBS(1.9 eq)-t-BuOK(1.0 eq) in DMF, -20°C 2 hr, then rt 20 hr) proceeded in a highly stereospecific manner similar to that previously reported,[12,13] giving a mixture of the bromolactones(10Aa and 10Ba)[16a](10Aa:10Ba 98.5:1.5(vide infra)) as an unstable caramel(87%), $[\alpha]_D^{20}$+36.0°(c=1.38, $CHCl_3$). Immediate debromination of the mixture of 10Aa and 10Ba(n-Bu_3SnH-azobisisobutyronitrile(catalytic amount) in C_6H_5Br, 60°C 9 hr) yielded the crude lactone as a mixture of two diastereomers(11Aa and 11Ba)[16a](95%), mp 169-174°C, $[\alpha]_D^{20}$-138°(c=0.368, $CHCl_3$), from which the predominantly formed lactone(11Aa)[16] could be isolated in a pure state on recrystallization from $CHCl_3$-Et_2O, mp 187-188°C, $[\alpha]_D^{20}$ -152°(c=0.424, $CHCl_3$). The structures of 10Aa,Ba and 11Aa,Ba were assigned according to the reported mechanistic studies[12,13] and to the fact that predominantly formed 10Aa could be transformed to optically pure α-hydroxy ketone(15a) which had (R)-configuration(vide infra).[1,2,10] Similar asymmetric bromolactonization of 9b followed by debromination of the very unstable diastereomeric bromolactones(10Ab and 10Bb)(10Ab:10Bb 93.5:6.5(vide infra)) gave the crude lactones as a mixture of two diastereomers(11Ab and 11Bb)[16a](two steps 50%), mp 205-212°C. Recrystallization of the mixture of 11Ab and 11Bb from $CHCl_3$-Et_2O afforded the predominantly produced diastereomer(11Ab)[16] in a pure state, mp 214-215°C, $[\alpha]_D^{20}$+11.9° (c=0.216, $CHCl_3$). Assignment of the structures of 10Ab,Bb and 11Ab,Bb was performed by assuming that the asymmetric bromolactonization of 9b should proceed through the same mechanism as that for the bicyclic compound(9a).

The recrystallized 11Aa was submitted to acidic hydrolysis(7.5N-aq. HCl-MeOH 1:1, reflux 8 hr) to simultaneously cleave the ester and amide functions, and the reaction product obtained as a mixture of the methyl ester(12a) and the acid(13a) was directly treated with diazomethane to afford optically pure 12a[16a] as a colorless caramel(two steps 87%), $[\alpha]_D^{20}$-34.5° (c=1.69, $CHCl_3$). Since the same treatment of the diastereomeric mixture of 11Aa and 11Ba, $[\alpha]_D^{20}$-138°(c=0.368, $CHCl_3$), gave partially optically active 12a,[16a] $[\alpha]_D^{20}$-33.3°(c=1.76,

Scheme II



8: X=Et
9: X=H
10A: X=Br
11A: X=H
10B: X=Br
11B: X=H
12: X=OMe; Y=Me
13: X=OH; Y=Me
14: X=OH; Y=H
15: X=Me; Y=Me
16: X=Me; Y=H
17: X=Me; Y=OMe
a: R^1, R^2=H
b: R^1, R^2=

$CHCl_3$), the optical purity of 12a obtained from the mixture of 11Aa and 11Ba and the ratio of 10Aa to 10Ba could be calculated as 97% and 98.5:1.5, respectively. Being different from the above case, partial hydrolytic cleavage of the two methyl ether groups occurred when the diastereomeric mixture of 11Ab and 11Bb was treated under the same acidic condition as that for 11Aa and 11Ba. Therefore, the mixture of 11Ab and 11Bb was hydrolyzed under more acidic condition(conc. HCl-dioxane 1:4, reflux 7 hr), and the formed trihydroxy acid(14b) was successively treated with diazomethane in DMSO-MeOH-Et_2O and dimethyl sulfate(anhyd. K_2CO_3 in Me_2CO, reflux 6 hr), giving the partially optically active methyl ester(12b)[16a] as a yellow powder (three steps 87%), mp 148-153°C, $[\alpha]_D^{20}$-6.8°(c=0.590, Me_2CO). Purification of this sample by preparative tlc(silica gel, Et_2O) and recrystallization from hexane-Et_2O gave optically pure 12b,[16] mp 154-155°C, $[\alpha]_D^{20}$-7.8°(c=0.613, Me_2CO). The optical purity of 12b obtained from the mixture of 11Ab and 11Bb and the ratio of 10Ab to 10Bb could be calculated as 87% and 93.5:6.5, respectively, when the purified 12b was assumed to be optically pure.

Alkaline hydrolysis(aq. KOH-MeOH) of the optically pure esters(12a,b) readily afforded the optically pure α-hydroxy acids(13a,b)(13a(96%) and 13b(100%)); 13a:[16] mp 91-93°C(from hexane-Et_2O), $[\alpha]_D^{20}$-39.3°(c=0.353, $CHCl_3$); 13b:[16] mp 200-201°C(from hexane-EtOAc), $[\alpha]_D^{20}$ +13.6°(c=0.430, $CHCl_3$).

Unfortunately, reaction of 13b with excess methyllithium(10-30 eq) in Et_2O-THF was found to afford many products, all of which were more polar than the authentic α-hydroxy ketone(15b) on tlc analysis(silica gel, Et_2O). This might be due to the preferential attack of methyllithium on the anthraquinone carbonyl moiety. However, treatment of the other α-hydroxy acid(13a) with methyllithium(10 eq) in Et_2O successfully gave the optically pure α-hydroxy ketone(15a)[16,19](63%), mp 128-129°C(from $CHCl_3$-Et_2O), $[\alpha]_D^{20}$-48.2°(c=0.982, $CHCl_3$)(lit.,[10] mp 130-132°C, $[\alpha]_D^{20}$-50°(c=1, $CHCl_3$)). Since the synthetic route to 15b from 15a is completely established by Arcamone et al.,[2,10] it has become possible to prepare optically pure 15b

via 15a by asymmetric synthesis.

The optically pure tetracyclic α-hydroxy ketone(15b) has been elaborated to optically pure 4-demethoxydaunomycinone(16),[2,10] and the reported syntheses of racemic[3] and optically active[10] daunomycinone(17) utilizes the racemic and optically active bicyclic α-hydroxy ketone (15a) as a key intermediate. Accordingly, our successful synthesis of optically pure 15a constitutes the first asymmetric synthesis of several structural types of optically active anthacyclinones.

Acknowledgement: The authors are indebted to Prof. C.M. Wong, University of Manitoba, and Prof. F. Arcamone, Farmitalia, for providing us with authentic samples of racemic and optically active 15b and their copies of infrared and nuclear magnetic resonance spectra. Experiments with liquid hydrogen fluoride were performed at Organic Chemistry Research Laboratory, Tanabe Seiyaku Co. Ltd. under the direction of Drs. K. Shigezane and T. Mizoguchi, to whom the authors' thanks are due.

References and Notes

1) F. Arcamone, Lloydia, 40, 45(1977)

2) F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. Di Marco, A.M. Casazza, G. Pratesi, and P. Reggiani, Cancer Treat. Rep., 60, 829(1976).

3) C.M. Wong, R. Schwenk, D. Popien, and T-L. Ho, Can. J. Chem., 51, 466(1973).

4) A.S. Kende, Y-g. Tsay, and J.E. Mills, J. Am. Chem. Soc., 98, 1967(1976).

5) F. Suzuki, S. Trenbeach, R.D. Gleim, and C.J. Sih, J. Am. Chem. Soc., 100, 2272(1978).

6) P.W. Raynolds, M.J. Manning, and J.S. Swenton, Tetrahedron Letters, 1977, 2383.

7) T.R. Kelly, J.W. Gillard, R.N. Goerner, Jr., and J.M. Lyding, J. Am. Chem. Soc., 99, 5513 (1977).

8) F.A.J. Keredesky and M.P. Cava, J. Am. Chem. Soc., 100, 3635(1978).

9) Optically active daunomycinone and its 4-demethoxy analogue have been prepared by chemical resolution of the racemic intermediate,[1,2,10] and synthesis of optically active 1 utilizes optically active 7-deoxydaunomycinone obtained by reductive cleavage of natural 2, as a relay compound.[11]

10) F. Arcamone, L. Bernardi, B. Patelli, and A. Di Marco, Ger. Offen., 2601785.

11) T.H. Smith, A.N. Fujiwara, W.W. Lee, H.Y. Wu, and D.W. Henry, J. Org. Chem., 42, 3653(1978).

12) a) S. Terashima and S-s. Jew, Tetrahedron Letters, 1977, 1005. b) S. Terashima, S-s. Jew, and K. Koga, Chemistry Letters, 1977, 1109.

13) S. Terashima, S-s. Jew, and K. Koga, Tetrahedron Letters, 1977, 4507.

14) J.A. Moore and M. Rahm, J. Org. Chem., 26, 1109(1961).

15) a) L.F. Fieser, M.D. Gates, Jr., and G.W. Kilmer, J.Am. Chem. Soc., 62, 2966(1940). b) E.L. Martin, Ibid., 58, 1438(1936).

16) a) Infrared and nuclear magnetic resonance spectra were in agreement with the assigned structure. b) Satisfactory analytical data were obtained for this compound.

17) a) G. Losse and H. Raue, Chem. Ber., 98, 1522(1965). b) B. Taub, H.A. Leipold, and J.B. Hino, J. Org. Chem., 24, 2062(1959).

18) T. Shioiri, Y. Yokoyama, Y. Kasai, and S. Yamada, Tetrahedron, 32, 2211(1976).

19) The undesired tertiary alcohol, (R)-5,8-dimethoxy-2(2-hydroxy-2-methyl)propyl-1,2,3,4-tetrahydro-2-naphthol, was obtained in 26% yield as the sole side product.

(Received in Japan 16 September 1978)