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A NOVEL RACEMIZATION MECHANISM FOR THE α-HYDROXY KETONE MOIETY(C_9-POSITION) OF OPTICALLY ACTIVE ANTHRACYCLINONE DERIVATIVES

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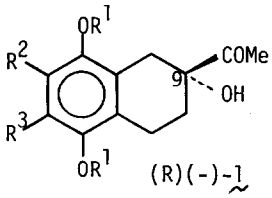
Summary——The facile acid-catalyzed racemization of optically active anthracyclinone derivatives((S)(+)-1a,b) was found to proceed through the ring-expanded seven-membered α-hydroxy ketones(2 and/or 3 for (S)(+)-1a) by subjecting various plausible intermediates to the racemization condition.

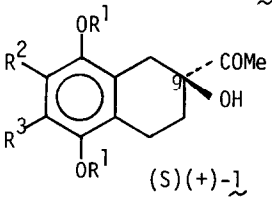
The anthracycline antibiotics are of current interest because of their promising anticancer activity.[1] While numerous synthetic studies have culminated in the regiospecific preparation of anthracyclinones, the aglycones of anthracyclines,[1] only few reports deal with the convergent synthetic methods which can produce highly optically active anthracyclinones.[1-3]

With the aim for synthesizing optically pure 4-demethoxyanthracyclinones whose glycosides had been reported to exhibit improved therapeutic indexes,[1] we recently explored two novel resolution methods of the racemic key synthetic intermediates((R,S)-1a,b)[3] by employing stereospecific reduction with fermenting baker's yeast[3a] and acetal formation with readily available C_2-symmetric vicinal-diol.[3b] Practical and economical features of the exploited methods were clearly amplified by the successful racemization of the undesired enantiomers((S)(+)-1a,b) by heating them under strongly acidic condition(Table I: runs 1-3).

Since the asymmetric carbons[C_9-position(anthracycline numbering)] racemized are involved in the α,α-disubstituted-α-hydroxy ketone system, we were interested in the facile loss of the optical integrity. By subjecting various plausible intermediates to the conditions applied to (S)(+)-1a, we have now found that the racemization of (S)(+)-1a,b could proceed through the novel ring-expanded seven-membered α-hydroxy ketones(2 and/or 3 for (S)(+)-1a).

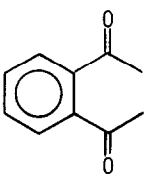


(R)(-)-1



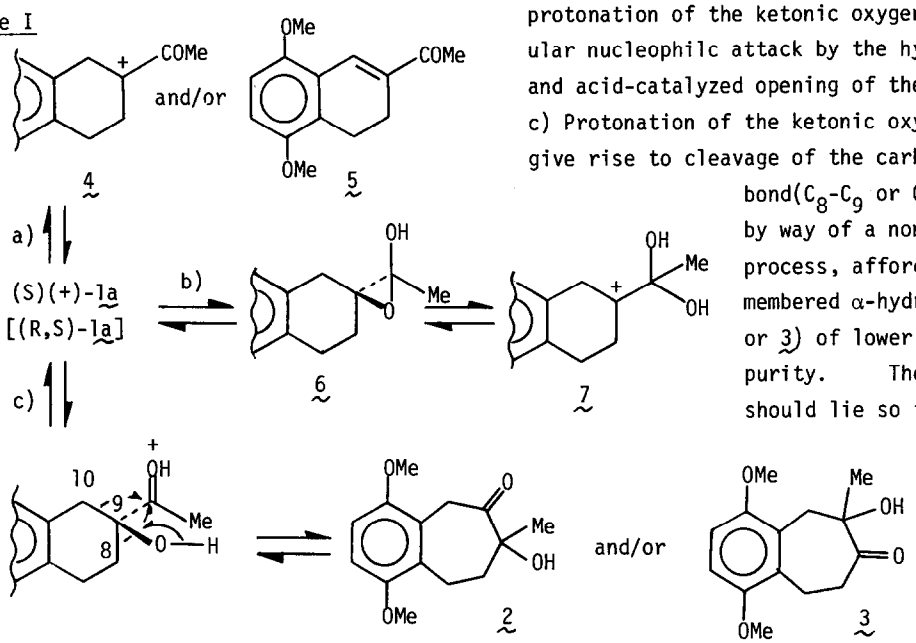
(S)(+)-1

a: R^1=Me, R^2=R^3=H

b: R^1=H, R^2, R^3= 

As the racemization mechanism of (S)(+)-1a, three possible equilibria shown in Scheme I could be anticipated. Thus, a) protonation of the hydroxy group of (S)(+)-1a followed by elimination of water would produce the acetyl carbonium ion(4) and/or the enone(5). b) Formation of the carbonium ion(7) carrying the hydrated acetyl group might be possible by successive

Scheme I



protonation of the ketonic oxygen, intramolecular nucleophilc attack by the hydroxyl group, and acid-catalyzed opening of the epoxide(6). c) Protonation of the ketonic oxygen might give rise to cleavage of the carbon-carbon bond(C_8-C_9 or C_9-C_{10}) partly by way of a non-concerted process, affording the seven-membered α-hydroxy ketone(2 or 3) of lower opticaly purity. These equilibria should lie so far to the left since more than 70% recovery yield of (R,S)-1a can be realized after the racemization.

In order to discriminate these possiblities, optical and chemical behavior of the (R)(-)-tertiary alcohol((R)(-)-8) and the enone(5) under the racemization condition for (S)(+)-1a was first studied. The former alcohol((R)(-)-8)[4b,5] was prepared from (-)(9R,13S)-diol((-)-9),[3a] via the (+)-epoxide((+)-10),[4a,5] $[\alpha]_D^{20}$+34.5°(c=0.96, $CHCl_3$), by sequential tosylation(TsCl/Pr), epoxide formation(NaOH/i-PrOH, 67%(2 steps)), and reduction($LiAlH_4$/THF, 83%).

It was found that (R)(-)-8 completely decomposed when treated under the condition which induced 88% racemization of (S)(+)-1a(Condition A)(Table I: runs 1 and 4). Under the milder condition which racemized 41% of (S)(+)-1a(Condition C), (R)(-)-8 could be obtained in 28% recovery yield with 2% racemization(Table I: runs 3 and 5). The enone(5)[2c,d] could not survive at all even under Condition C(Table I: run 6). Since (R)(-)-8 can afford the tertia-

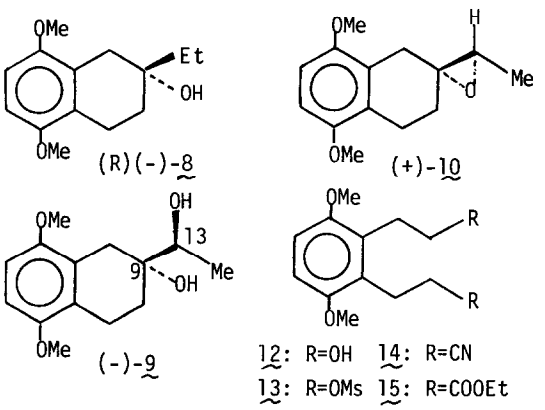


Table I Results for the Reactions under Acidic Conditions

Run	Reaction Substrates: Structure	$[\alpha]_D^{20}$ (c, $CHCl_3$)	Optical Purity(%)	Reaction Conditions[a]	Reaction Products[b]: Structure	Chemical Yield(%)[c]	$[\alpha]_D^{20}$ (c, $CHCl_3$)	Optical Purity(%)[d]	Racemization(%)
1[e]	(S)(+)-1a	+30.3°(0.88)	65	A	(S)(+)-1a	(74)	+3.9°(0.98)	8	88
2[f]	(S)(+)-1b	+52.8°(1.22)	58	B	(S)(+)-1b	(77)	+20.5°(1.20)	22	62
3	(S)(+)-1a	+33.1°(1.01)	71	C	(S)(+)-1a	(89)	+19.5°(0.94)	42	41
4	(R)(-)-8	-24.5°(1.31)	100	A	-[g]	-	-	-	-
5	(R)(-)-8	-24.5°(1.31)	100	C	(R)(-)-8	(28)	-23.9°(1.03)	98	2
6	5	-	-	C	-[g]	-	-	-	-
7	2	-	-	A	(R,S)-1a	6	-	-	-
8	2	-	-	C	(R,S)-1a	10	-	-	-
9	3	-	-	A	(R,S)-1a	66	-	-	-
10	3	-	-	C	(R,S)-1a	79	-	-	-

a) A: A mixture of the reaction substrate and TsOH-H_2O(70 eq) in aq AcOH(AcOH:H_2O 1.75:1) was heated in a sealed tube at 110°C for 20 hr under an argon atmosphere. B: CF_3SO_3H(70 eq) was used in place of TsOH-H_2O under Condition A. C: TsOH-H_2O(10 eq) was used under Condition A. b) Identified by spectral(IR and NMR) and chromatographic(TLC) properties. c) Figures in parentheses show a recovery yield of the starting material. d) See ref. 3 and the text. e) Reported in ref. 3a. f) Reported in ref. 3b. g) TLC analysis of the reaction mixture shows complete decomposition of the starting material.

ry carbonium ion which might be similar to 7 and should be more stable than 4, these results clearly show that the reaction courses a) and b) might be incompatible with the observed optical instability of (S)(+)-1a.

Next, the chemical properties of two isomeric seven-membered ketones(2 and 3) under the racemization condition for (S)(+)-1a were investigated. These isomeric ketones(2 and 3) were regiospecifically synthesized from the olefin(11).[6] Thus, epoxidation(NBS-KOH/DMSO-H_2O, 89%) of 11 followed by acid-catalyzed epoxide opening(10% H_2SO_4/THF-H_2O), glycol cleavage($NaIO_4$/THF-H_2O), and reduction($NaBH_4$/THF-H_2O, 86%(3 steps)) gave the diol(12).[4a,5] Sequential mesylation(MsCl/Py, 97%), substitution(KCN/MeOH, 83%), hydrolysis(50% KOH/MeOH), and esterification (conc. H_2SO_4/EtOH, 85%(2 steps)) yielded the diester(15)[4b,5] via the mesylate(13)[4a,5] and the cyanide(14).[4a,5] The diester(15) was subjected to the Dieckmann condensation(NaH/C_6H_6-EtOH (1 drop), 76%), affording the seven-membered β-keto ester(16),[4a,5] which on acidic treatment (conc. HCl/MeOH-H_2O, 84%) afforded the symmetrical ketone(17).[4a,5] This was transformed to desired 2[4a,5] via the alcohol(18),[4a,5] the olefin(19),[7] and the diol(20),[4a,5] by successive Grignard addition(MeMgI/THF-Et_2O, 68%), elimination(TsCl/Py, 78%),[7] dihydroxylation[a)OsO_4/Py-C_6H_6; b)$NaHSO_3$/Py-H_2O; c)separation of the isomer,[7] 67%], and oxidation(SO_3·Py/DMSO-Et_3N, 80%). On the other hand, methylation(MeI-NaH/DMF, 94%) of 16, followed by simultaneous hydrolysis and decarboxylation(conc. HCl/AcOH, 72%), gave the methyl ketone(21).[4a,5]

Sequential regiospecific enol acetate formation(Ac_2O/TsOH-H_2O, 54%) of 21, oxidation(OsO_4/Py-C_6H_6) of the enol acetate(22), and hydrolysis($NaHSO_3$/Py-H_2O, 63%(2 steps)) gave 3.[4a,5]

Treatments of 2 and 3 under Condition A were found to give (R,S)-1a in 6% and 66% yields, respectively, after chromatographic separation(Table I: runs 7 and 9). Higher yields of (R,S)-1a could be obtained by treating 2 and 3 under Condition C(Table I: runs 8 and 10). While other reaction products were found to be complex mixtures, the starting ketones(2 and 3) could not be detected by TLC and spectral(NMR) analyses.

Since the intervention of a non-concerted process between (S)(+)-1a and 2 or 3 is anticipated to be reasonable, the mechanism c) should be responsible for the facile racemization under the acidic condition. Although the higher chemical yield of (R.S)-1a from 3 than from 2 might be construed by the difference of stability between the aryl methyl and the aryl ethyl anion, the reason why the thermal equilibrium lie so far to (R,S)-1a is quite obscure and might be explained by the intrinsic conformational strain of cyclohept-3- and 4-en-1-one systems.

While the above studies are carried out on the AB ring system of anthracyclinones((S)(+)-1a), the same mechanistic explanation might hold for the acid-catalyzed racemization of optically active 7-deoxy-4-demethoxydaunomycinone((S)(+)-1b)(Table I: run 2) which is one of the most valuable reactions for the industrial preparation of optically pure 4-demethoxyanthracyclinones.

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4) IR and NMR spectra were in agreement with the assigned structure. Satisfactory a) analytical or b) mass spectral data were also obtained for this compound.

5) Following melting(or boiling) points(recrystallization solvents) were recorded. 2: mp 110-111°C(C_6H_{12}); 3: mp 56-57°C(C_6H_{12}); (R)(-)-8: oil; (+)-10: mp 100-103°C(i-Pr_2O); 12: mp 173-175°C(C_6H_6-Et_2O); 13: mp 103-104°C(EtOH); 14: mp 132-133.5°C(EtOH); 15: bp 250°C (3 mmHg); 16: mp 98-99.5°C(EtOH); 17: mp 124-125.5°C(MeOH); 18: mp 100-101°C(i-Pr_2O); 20: mp 93-94°C(i-Pr_2O); 21: mp 86-87°C(MeOH); 22: mp 107-109°C(C_6H_{12}).

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7) Elimination of 18 gave a mixture of 19 and the exo-methylene olefin(5:1 by NMR), which was directly subjected to the next dihydroxylation without separation. Desired 20 was isolated from the reaction mixture by preparative TLC(SiO_2, Et_2O-petr. ether 10:1).

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