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AN EFFICIENT SYNTHESIS OF OPTICALLY PURE ANTHRACYCLINONE INTERMEDIATES BY THE NOVEL USE OF MICROBIAL REDUCTION

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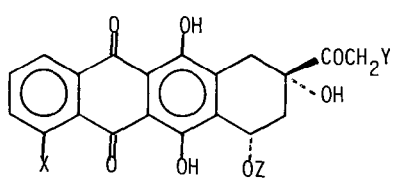
Summary Reduction of the racemic α-hydroxy ketones((±)-3a,b) with fermenting baker's yeast followed by fractional recrystallization and oxidation was found to readily afford optically pure anthracyclinone intermediates((R)(-)-3a,b) and their partially optically active antipodes ((S)(+)-3a,b) The useless enantiomers((S)(+)-3a,b) and diastereomeric vicinal-diols((+)-5a,b) could be recycled to (±)-3a,b and the achiral ketones(6a,b) by racemization and oxidative cleavage, respectively

The anthracycline antibiotics, adriamycin(1a) and daunorubicin(1b), are of current interest due to their promising anticancer activity [1] While chemotherapy employing 1a,b is hampered by a number of undesirable side effects, most notably dose-related cardiotoxicity, examinations on the structure-activity relationships have uncovered that improved therapeutic properties can be expected for unnatural 4-demethoxy analogs of 1a,b, 4-demethoxyadriamycin(1c) and 4-demethoxydaunorubicin(1d) [1,2]

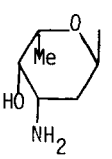
Recently, the optically active α-hydroxy ketones((R)-3a,b) attract much attention as the versatile key synthetic intermediates from which optically active natural and unnatural anthracyclinones(2a-d), the aglycones of 1a-d, can be elaborated [2] Synthesis of (R)-3a has been achieved originally by optical resolution of the corresponding racemic ketone((±)-3a) with (-)-α-methylbenzylamine,[3] and later by asymmetric synthesis employing halolactonization reaction[4] or reduction with the chiral hydride[5] as a key step Optically active (R)-3b which can be utilized for preparing 2c,d, has been synthesized from (R)-3a by Friedel-Crafts acylation [1-3,5]

Considering the importance of (R)-3a,b for the synthesis of optically active 2, another efficient method for producing optically pure (R)-3a,b more simply and effectively than the

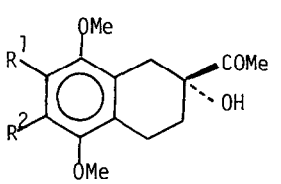


	X	Y		X	Y
a	OMe	OH	c	H	OH
b	OMe	H	d	H	H

1 Z=

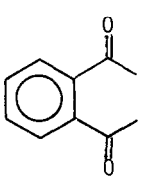


2 Z=H



(R)-3

a $R^1=R^2=H$ b $R^1,R^2=$



existing methods[3-5] is sought. We have now found that optically pure (R)-3a,b can be readily obtained by the novel use of microbial reduction followed by oxidation. Since the reaction schemes which can recycle useless enantiomers and diastereomers to reusable compounds are simultaneously explored, the overall process seems to have the same efficacy as that of asymmetric synthesis.

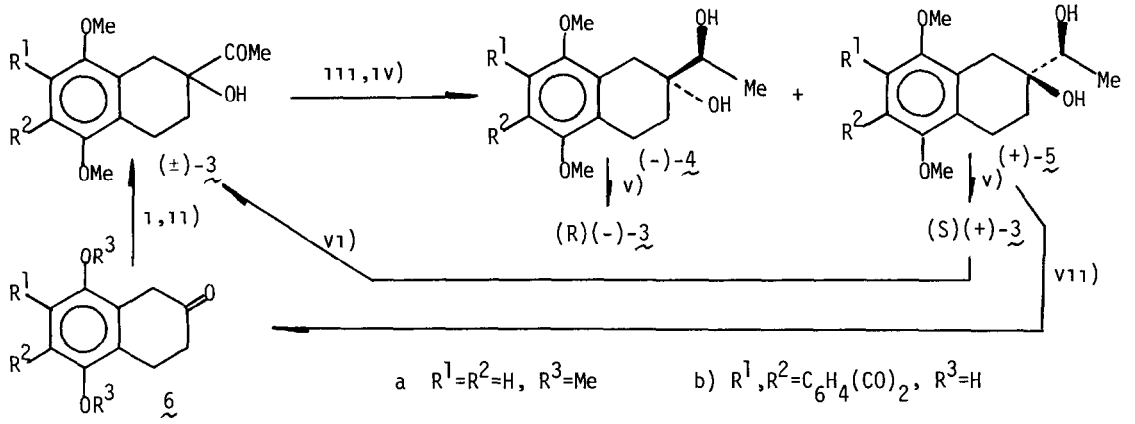
Thus, the racemic α-hydroxy ketone((±)-3a),[6a] mp 102-103°C, prepared from 5,8-dimethoxy-2-tetralone(6a)[7] according to the reported method,[8] was added to an aqueous suspension of actively fermenting baker's yeast(Saccharomyces cerevisiae(Sigma YSC-1), 17.5 g to 1.0 g of (±)-3a), and the whole suspension was stirred for 48 hr. Filtration through a pad of celite, followed by extractive isolation with ethyl acetate and simple separation of the nonpolar impurities derived from yeast by a short silica gel column(CH_2Cl_2), gave a mixture of the vicinal-diols((-)-4a and (+)-5a, 48:52(determined by HPLC))(91%), mp 55-140°C, $[\alpha]_D^{20}$+1.4°(c=0.97, EtOH). Three recrystallizations of the mixture gave pure (-)-4a[6a](32% based on (±)-3a), mp 154-155°C, $[\alpha]_D^{20}$-50.3°(c=0.66, EtOH)(lit.,[5] mp 154-155°C, $[\alpha]_D^{20}$-49.7°(c=0.50, EtOH)). Evaporation of the combined mother liquors from the recrystallization, in vacuo afforded a crude mixture of (-)-4a and (+)-5a[9](18:82[10])(58% based on (±)-3a).

Since (-)-4a(or (+)-5a) could be obtained as a sole reaction product(determined by HPLC) when pure (R)(-)-3a(vide infra)(or pure (S)(+)-3a[9]) was subjected to the same microbial reduction, it appeared evident that the reduction of (±)-3a proceeded stereospecifically, only giving a diastereomeric mixture of (-)-4a and (+)-5a. This result demonstrates that steric course of the reduction of (±)-3a completely follows the general rule(the Prelog rule: selective formation of an (S)-alcohol) proposed for the asymmetric reduction of achiral ketones with yeast,[11] and that the asymmetric center involved in (±)-3a will not provide any effects on the stereoselectivity for microbial reduction.

Oxidation of (-)-4a[5,12] afforded optically pure (R)(-)-3a[6a](90%), mp 128-128.5°C, $[\alpha]_D^{20}$ -46.3°(c=0.54, $CHCl_3$)(lit.,[5] mp 128-129°C, $[\alpha]_D^{20}$-47.1°(c=1.11, $CHCl_3$), lit.,[4] mp 128-129°C, $[\alpha]_D^{20}$-48.2°(c=0.982, $CHCl_3$)). Similar oxidation of the crude mixture of (-)-4a and (+)-5a yielded partially optically active (S)(+)-3a[6a](72%), mp 100-121°C, $[\alpha]_D^{20}$+30.2°(C=0.88, $CHCl_3$), 65% ee.

In order to improve efficacy of the exploited process, removal of the chirality present in the vicinal-diols((-)-4a and (+)-5a) and racemization of partially optically active (S)(+)-3a[13,14] were next examined. The former transformation could be simply achieved by oxidizing the mixture of (-)-4a and (+)-5a with sodium metaperiodate to give 6a[6a](99%), mp 98.5-99.5°C. However, racemization of the tertiary alcohol involved in (S)(+)-3a was found to be refractory.[13] After several unsuccessful attempts, it was found that heating a mixture of (S)(+)-3a, 65% ee, and p-toluenesulfonic acid(p-TsOH) in aq. acetic acid at 110°C for 20 hr afforded almost racemized (S)(+)-3a[6a](74%), mp 95-105°C, $[\alpha]_D^{20}$+3.9(c=0.98, $CHCl_3$), 8% ee(87% racemization).[15] Recrystallization from cyclohexane readily gave (±)-3a[6a](58% based on (S)-(+)-3a), mp 103-104°C. Recovered (±)-3a and 6a can be again utilized for the microbial reduction and for the preparation of (±)-3a, respectively.

The overall process described above can be similarly applied to the synthesis of (R)(-)-3b. Microbial reduction of (±)-3b,[6a] mp 186-187°C, which was prepared from (±)-3a by



i) HC≡CMgBr in THF, ii) HgO-aq H_2SO_4 in THF, iii) baker's yeast-sucrose in H_2O, 30-35°C, 48 hr (for a) or in H_2O-DMSO(10 l), 25-30°C, 31 hr(for b), iv) recrystallization from C_6H_6-C_6H_{14}(for a) or from C_6H_6(for b), v) SO_3 Py-DMSO-Et_3N, rt, 2 hr, v) p-TsOH(70 eq to (S)(+)-3) in aq AcOH (AcOH H_2O 7 4), 110°C, 20 hr(for a) or the same condition followed by Me_2SO_4-anhyd K_2CO_3 in Me_2CO(for b), vi) $NaIO_4$ in aq Me_2CO, rt, 1 hr(for a) or $AlCl_3$ in C_6H_6, 50°C, 2 hr, then $NaIO_4$ in aq AcOH, -5-0°C, 2 5 hr(for b)

the reported procedure,[5, 16] gave a mixture of (-)-4b and (+)-5b[17](90%), mp 153-165°C, $[\alpha]_D^{20}$ -2 9°(c=0 86, DMF) Five recrystallizations of the mixture afforded pure (-)-4b[6b,c](19% based on (±)-3b), mp 189-109°C, $[\alpha]_D^{20}$-39 0°(c=0.66, DMF) Evaporation of the combined mother liquors from the recrystallization afforded a crude mixture of (-)-4b and (+)-5b(39 61[10]) (72% based on (±)-3b), mp 140-165°C, $[\alpha]_D^{20}$+9 2°(c=1 76, DMF) Oxidation of (-)-4b and the mixture of (-)-4b and (+)-5b in a similar manner to that for (-)-4a[5,12] gave optically pure (R)(-)-3b[6a](86%), mp 140-140 5°C, $[\alpha]_D^{20}$-23 4°(c=0 39, $CHCl_3$)(lit ,[5] mp 139-140°C, $[\alpha]_D^{20}$-23 0° (c=1 06, $CHCl_3$)), and partially optically active (S)(+)-3b[6a](88%), mp 175-185°C, $[\alpha]_D^{20}$+5 2° (c=1 22, $CHCl_3$), 22% ee

Since a complex mixture of products was obtained when the mixture of (-)-4b and (+)-5b was directly subjected to the condition for cleaving the vicinal-diol, the cleavage reaction was carried out on a demethylated sample. Thus, successive treatments of the mixture of (-)-4b and (+)-5b with aluminum chloride and with sodium metaperiodate gave 6b[6a](71%), mp>280°C (lit ,[18] mp>310°C(decomp)), which is expected to be reused for the preparation of (±)-3b [2]

Being different from the case of (S)(+)-3a, racemization of partially optically active (S)(+)-3b proceeded along with complete demethylation Methylation of the product yielded almost racemized (S)(+)-3b[6a](70%), mp 160-180°C, $[\alpha]_D^{20}$+1 8°(c=1 20, $CHCl_3$), 8% ee(64% racemization) This was recrystallized from benzene-cyclohexane to give (±)-3b[6a](50% based on (S)-(+)-3b), mp 184-186°C

While reaction schemes similar to that exemplified above have been employed for producing optically pure steroid[11] and prostaglandin[11,19] intermediates, this is the first example in which asymmetric reduction with fermenting yeast can be successfully applied to the synthesis of optically pure anthracyclinone intermediates Considering the operational simplicity,

the use of readily available and cheap reagents including baker's yeast, the efficient recycle process for useless diastereomer, and the simple racemization of undesired enantiomer, the exploited overall process might have practical value in a large scale preparation of optically pure anthracyclinones

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6) a) IR and NMR spectra were identical with those reported b) IR and NMR spectra were in agreement with the assigned structure c) Satisfactory analytical data were obtained for this compound

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9) In a parallel experiment, almost pure (+)-5a [6b,c] ((-)-4a (+)-5a 7 93(determined by HPLC)), mp 70-75°C, $[\alpha]_D^{20}$+41 1°(c=0 32, EtOH), could be obtained by repeated recrystallizations of a mixture of (-)-4a and (+)-5a from benzene-hexane Oxidation of this sample followed by recrystallization gave pure (S)(+)-3a, mp 128-129°C, $[\alpha]_D^{20}$+46 7°(c=0 51, $CHCl_3$)

10) Determined by the optical rotation of (S)(+)-3a(or (S)(+)-3b) derived from this sample

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13) In the preparation of (R)(-)-3b from optically pure (R)(-)-3a, the authors had already observed that partial racemization occurred under the condition for Friedel-Crafts acylation to give (R)(-)-3b being 70-75% ee.[5)]

14) Recently, the enantiomeric conversion process which could afford (R)(-)-3a, 53% ee, from optically pure (S)(+)-3a was reported S D Nero, C Gandolfi, P Lombardino, and F Arcamone, Chem Ind , 1981, 810

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