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(+)- AND (-)-1-O, 4-O-BIS(p-CHLOROBENZYL)THREITOL AS NOVEL RESOLVING AGENTS FOR OPTICALLY ACTIVE ANTHRACYCLINONE SYNTHESIS   AN EFFICIENT SYNTHESIS OF OPTICALLY PURE 4-DEMETHOXYDAUNOMYCINONE

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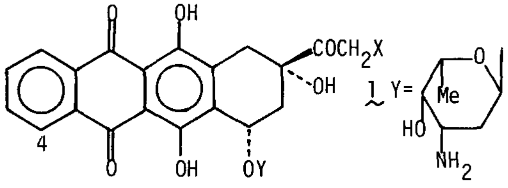
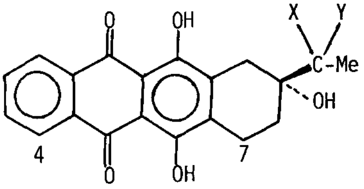
Summary (±)-7-Deoxy-4-demethoxydaunomycinone((±)-3) was cleanly resolved by forming a mixture of the diastereomeric acetals((-)-9 and (+)-10 or (+)-9 and (-)-10) with the title *vicinal*-diol((+)- or (-)-5) to give optically pure (R)(-)-3   The method for racemizing the undesired enantiomer((S)(+)-3) was also explored   Optically pure (+)-4-demethoxydaunomycinone((+)-2b) was elaborated from (R)(-)-3 according to the reported reaction scheme.

The 4-demethoxyanthracyclines, 4-demethoxyadriamycin(1a) and 4-demethoxydaunorubicin(1b), attract much attention since improved therapeutic indexes can be expected for these modified antibiotics which exhibit antineoplastic activity *ca*. 10 times higher than that of the natural anthracyclines.1)   While most of the reported synthetic works on anthracyclinones, the aglycones of anthracycline antibiotics, have been focused on synthesis of 4-demethoxyanthracyclinones such as 4-demethoxyadriamycinone(2a) and 4-demethoxydaunomycinone(2b),2) a limited number of methods is only available for producing optically active 2a,b 2)

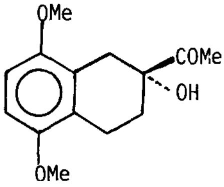
Optically pure (R)(-)-7-deoxy-4-demethoxydaunomycinone((R)(-)-3), from which optically active 2a,b can be readily elaborated,3-5) is anticipated to hold a pivotal position in the synthesis of optically active 2a,b, and has been synthesized from the optically pure α-hydroxyketone((R)(-)-4) produced by optical resolution3,6) or by asymmetric synthesis 5,7)   However, this synthetic route seems to reduce its practical value since we have found that, being different from the reported results,3,4) the simultaneous inter- and intramolecular Friedel-Crafts acylation of (R)(-)-4 always accompanies a slight racemization to afford (R)(-)-3 being *ca* 70-75% ee 5)



a X=OH   b X=H   2 Y=H



(R)(-)-3 X,Y=O
(R)(-)-11 X,Y=-O(CH$_2$)$_2$O-



(R)(-)-4

We wish to report here that preparation of optically pure (R)(-)-3 can be readily achieved by the optical resolution in which (+)- or (-)-1-0-, 4-0-bis(p-chlorobenzyl)threitol ((+)- or (-)-5) is utilized as a resolving agent to form a mixture of the diastereomeric acetals((-)-9 and (+)-10 or (+)-9 and (-)-10) from the racemic α-hydroxy ketone((±)-3) [5,8,9]

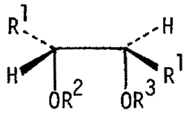
After several unsuccessful attempts,[13] (+)- and (-)-5 were chosen as the most suitable _vicinal_-diols for the optical resolution of (±)-3 due to excellent crystallization and separation properties of the diastereomeric acetals, and were readily prepared from unnatural D-(-)- and natural L-(+)-tartaric acid((-)- and (+)-6) Thus, alkylation (NaH-p-$ClC_6H_4CH_2Cl$ in THF, 50°C, 3 hr, 86%) of the oily (-)-1,4-diol((-)-7),[14a] $[\alpha]_D^{20}$-4 2°(c=5 31, $CHCl_3$), prepared from (-)-6 according to the reported procedure,[15] followed by acidic hydrolysis(conc HCl in THF-dioxane, reflux, 6 hr, 93%) of the formed (+)-acetal((+)-8),[14b] $[\alpha]_D^{20}$+8 1°(c=6 17, $CHCl_3$), gave (+)-5[14b,c] as a colorless solid, mp 76-78°C, $[\alpha]_D^{20}$+6 3°(c=3 08, $CHCl_3$) _Levo_-rotatory _vicinal_-diol((-)-5),[14b,c] mp 74-77°C, $[\alpha]_D^{20}$-6 5°(c=3 01, $CHCl_3$), was similarly prepared from (+)-6 by way of (+)-7,[14a,16] $[\alpha]_D^{20}$+4 5°(c=5 06, $CHCl_3$), and (-)-8,[14b] $[\alpha]_D^{20}$-8 2°(c=6 14, $CHCl_3$)

Whereas unnatural (-)-6 is fairly expensive for a large scale preparation, (-)-7 could be also obtained from D-(-)-mannitol according to the reported procedure with a little modification.[17] Thus, triacetal formation(Me_2CO-conc H_2SO_4, 70%) of D-(-)-mannitol, followed by partial deacetalization of the triacetal(AcOH-H_2O, 80%), oxidative cleavage($NaIO_4$ in MeOH-H_2O) of the two terminal 1,2-diols, and reduction of the dialdehyde($NaBH_4$ in MeOH-H_2O, 2 steps, 69%), successfully gave (-)-7,[14a] $[\alpha]_D^{20}$-4 4°(c=5 11, $CHCl_3$)(_vide supra_)

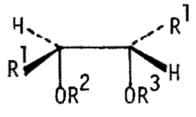
Acetalization(p-TsOH(0 06 eq) in C_6H_6, reflux, 13 hr, 100%) of (±)-3,[5,8] mp 214-216°C, with (+)-5(1 1 eq) gave an oily mixture of the diastereomeric acetals((-)-9 and (+)-10), $[\alpha]_D^{20}$ +4 8°(c=0 65, $CHCl_3$). This was triturated in ether at room temperature for 15 hr, giving crude (-)-9((-)-9 (+)-10 85 15[18])(47%), mp 132-136°C Evaporation of the mother liquor _in vacuo_ afforded crude (+)-10((-)-9 (+)-10 20 80[18])(49%) as a red foam Two recrystallizations of crude (-)-9 from acetonitrile gave pure (-)-9[14b,c](35%), mp 141-142°C, $[\alpha]_D^{20}$ -53 6°(c=0 50, $CHCl_3$). On the other hand, three recrystallizations of crude (+)-10 from ether afforded pure (+)-10[14b,c](18%), mp 120-121°C, $[\alpha]_D^{20}$+66 8°(c=0 51, $CHCl_3$)

The same acetalization of (±)-3 with (-)-5 as that described above, gave a crude mixture of (+)-9 and (-)-10(100%), $[\alpha]_D^{20}$-5 4°(c=0.61, $CHCl_3$), from which crude (+)-9((+)-9 (-)-10 85 15[18])(45%), mp 133-138°C, and (-)-10((+)-9 (-)-10 17 83[18])(50%) were obtained by the trituration with ether Similar sequential recrystallizations of crude (+)-9 and (-)-10 yielded pure (+)-9 [14b,c](39%), mp 141-142°C, $[\alpha]_D^{20}$+53 8°(c=0.55, $CHCl_3$), and pure (-)-10[14b,c](21%), mp 120-121°C, $[\alpha]_D^{20}$-66 4°(c=0.53, $CHCl_3$), respectively

Treatment of pure (-)-9 under the condition for transacetalization(BF_3 Et_2O(10 eq) in Me_2CO, reflux, 13 hr) or hydrolysis(conc HCl in dioxane-H_2O, reflux, 2 hr), followed by filtration through a short silica gel column(C_6H_6-CH_2Cl_2 3 1), gave optically pure (R)(-)-3[14a] (98% or 97%), mp 218-219°C, $[\alpha]_D^{20}$-89 9°(c=0 102, $CHCl_3$), or mp 218-219°C, $[\alpha]_D^{20}$-90 3°(c=0 106, $CHCl_3$)(lit ,[4a] mp 228-230°C, $[\alpha]_D^{20}$-87°(c=0 1, $CHCl_3$), lit ,[5] mp 218-220°C, $[\alpha]_D^{20}$-87 0°(c= 0.115, $CHCl_3$)) Similar transacetalization or hydrolysis of crude (-)-9, mp 132-136°C (_vide supra_), gave partially optically active(R)(-)-3,[14a] mp 195-200°C, $[\alpha]_D^{20}$-64 2°(c=0.108,

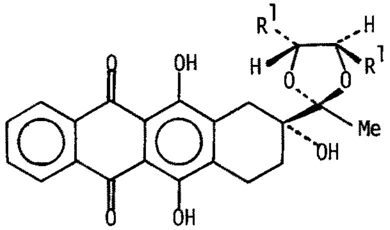


(+)-5, (-)-7
(-)-6, (+)-8

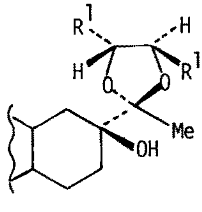


(-)-5; (+)-7
(+)-6, (-)-8

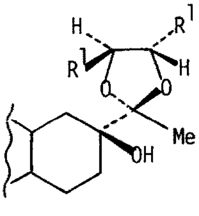
5. R^1=$CH_2OCH_2C_6H_4$-Cl-p, R^2=R^3=H
6 R^1=COOH, R^2=R^3=H
7 R^1=CH_2OH, R^2,R^3=CMe_2
8. R^1=$CH_2OCH_2C_6H_4$-Cl-p, R^2,R^3=CMe_2



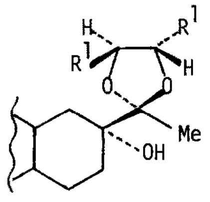
(-)-9



(+)-10



(+)-9



(-)-10

R^1=$CH_2OCH_2C_6H_4$-Cl-p

CHCl$_3$), 71% ee, or mp 190-197°C, $[\alpha]_D^{20}$-62.5°(c=0.110, CHCl$_3$), 69% ee. When pure and crude (+)-10(*vide supra*)were similarly subjected to transacetalization, there could be obtained optically pure (S)(+)-3[14a](97%), mp 219-220°C, $[\alpha]_D^{20}$+89.5°(c=0.102, CHCl$_3$), and partially optically active (S)(+)-3[14a](90%), mp 190-196°C, $[\alpha]_D^{20}$+55.5°(c=0 110, CHCl$_3$), 61% ee. In completely the same manner, optically pure and partially optically active (S)(+)-3(or (R)(-)-3) could be obtained from pure and crude (+)-9(or pure and crude (-)-10), respectively Recovery of the resolving agents((+)- and (-)-5) might be simply accomplished since (+)-8(70%), $[\alpha]_D^{20}$+7.8° (c=5 97, CHCl$_3$), and (+)-5(75%), mp 76-78°C, $[\alpha]_D^{20}$+5 7°(c=2 98, CHCl$_3$), could be readily separated by the short silica gel column which was utilized for isolating (R)(-)-3 produced by transacetalization and hydrolysis(*vide supra*)

In order to improve efficacy of the exploited optical resolution, racemization of the undesired enantiomer((S)(+)-3) was next examined. While attempted racemization of (S)(+)-3, 61% ee, under the same condition as that previously reported,[6] was fruitless(only 30% racemization), the use of trifluoromethanesulfonic acid(70 eq to (S)(+)-3 in AcOH-H$_2$O(7.4), 110°C, 20 hr) in place of p-toluenesulfonic acid was found to afford racemized (S)(+)-3,[14a] $[\alpha]_D^{20}$+20.3° (c=0 118, CHCl$_3$), 22% ee(62% racemization), from partially optically active (S)(+)-3, $[\alpha]_D^{20}$ +52.8°(c=0.108, CHCl$_3$), 58% ee.

Since the preparation of optically pure (R)(-)-3 was completed, synthesis of (+)-2b was attempted according to the reported procedure.[4] Successive bromination and substitution (Br$_2$-AIBN in CHCl$_3$-CCl$_4$-H$_2$O) of the C$_7$-position of (R)(-)-acetal((R)(-)-11),[14b,c] mp 224-226°C, $[\alpha]_D^{20}$-81.0°(c=0.120, CHCl$_3$), prepared(HOCH$_2$CH$_2$OH-p-TsOH in C$_6$H$_6$, 98%) from (R)(-)-3, followed by hydrolysis and epimerization(80% CF$_3$COOH, rt, 15 hr), gave optically pure (+)-2b[14a,19](41% based on (R)(-)-11), mp 184-185.5°C, $[\alpha]_D^{20}$+157°(c=0.114, dioxane)(lit.,[3] mp 185-187°C, $[\alpha]_D^{20}$ +165°(c=0.1, dioxane), lit.,[5] mp 183 5-184.5°C, $[\alpha]_D^{20}$+153°(c=0.09, dioxane))

Since (+)-2b had been transformed to (+)-2a,[2,5] it became also possible to obtain optically pure (+)-2a from (R)(-)-3 produced by the optical resolution of (±)-3. Considering operational simplicity, possible uses of both enantiomers of the resolving agents, and simple racemization of the undesired enantiomer((S)(+)-3), the exploited optical resolution of (±)-3 should have wide practical values in the synthesis of optically pure (+)-2a,b

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9) Optical resolutions of racemic ketones have been also reported in the optically active terpene,10) steroid,11) and prostaglandin12) syntheses

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13) Prior to selecting (+)- and (-)-5 as acetalizing reagents, acetalization of (±)-3 was attempted using L-(+)-dimethyl tartrate, (S)(+)-1-phenyl-1,2-ethanediol, and (-)-1-O, 4-O-bis(benzyl)threitol However, the acetal formation was not observed for L-(+)-dimethyl tartrate, and a mixture of the four diastereomeric acetals was obtained from (S)(+)-1-phenyl-1,2-ethanediol. Although (-)-1-O, 4-O-bis(benzyl)threitol successfully gave a mixture of the diastereomeric acetals in a quantitative yield, separation of the acetals attempted by column chromatography or by recrystallization turned out to be fruitless

14) 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(or mass spectral) data were obtained for this compound

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18) Determined by the optical purity of (R)(-)-3(or (S)(+)-3) derived from this sample

19) Separation of the C_7-epimer of (+)-2b was not attempted

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