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ASYMMETRIC SYNTHESIS OF OPTICALLY PURE (R)(-)-2-ACETYL-5,8-DIMETHOXY-1,2,3,4-TETRAHYDRO-2-NAPHTHOL, A KEY INTERMEDIATE FOR OPTICALLY ACTIVE ANTHRACYCLINONE SYNTHESIS

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Summary: Asymmetric reduction of 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene(3) with lithium aluminum hydride partially decomposed with (-)-N-methylephedrine and N-ethylaniline was found to give the optically active allylic alcohol((-)-4) in 92% optical yield. Optically pure (-)-4 obtained in 87% yield based on 3 by recrystallization, was elaborated to the title compound((R)(-)-1) according to the reaction scheme exploited in the preceding paper.

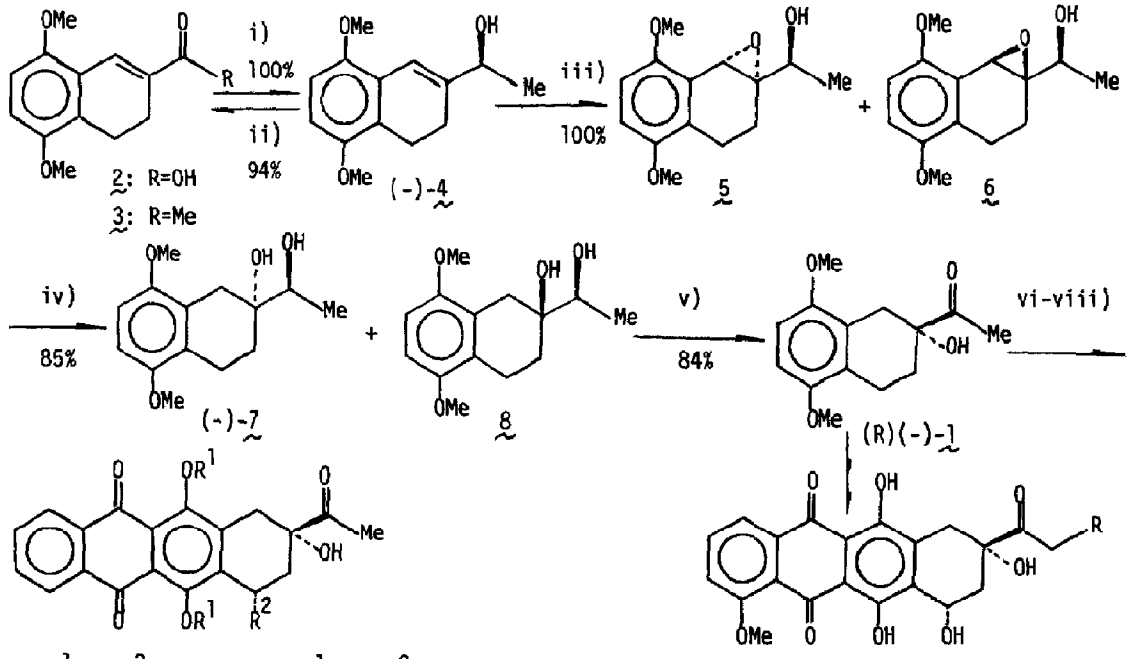
In the preceding paper,[1] we have described the novel synthetic route to racemic 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol((±)-1), a versatile synthetic intermediate of racemic anthracyclinone syntheses,[2] from readily available 5,8-dimethoxy-3,4-dihydro-2-naphthoic acid(2).[3] In order to apply the exploited synthetic scheme[1] to the production of optically active (R)(-)-1,[4] being potentially useful for the syntheses of optically active anthracyclinones,[2,5,6] an efficient method which could effect the asymmetric reduction of 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene(3) derived from 2,[1] was sought.

We have now found that the asymmetric reduction of 3 can be readily accomplished in high chemical and optical yields by employing lithium aluminum hydride($LiAlH_4$) partially decomposed with (-)-N-alkylephedrine[7] and N-alkylaniline, as a reducing agent.

Reduction of 3[1] with $LiAlH_4$(3.3 eq) partially decomposed with (-)-N-methylephedrine(3.4 eq) and N-ethylaniline(6.8 eq) in ether at -78°C for 3 hr, was found to give the optically active allylic alcohol((-)-4),[8a,9,10] mp 85-87°C, $[\alpha]_D^{20}$-18.9°(c=1.77, EtOH), in 94% yield after quenching with 5% aq HCl(stoichiometric amount[11]), extractive isolation with ether, and purification with preparative tlc(silica gel, C_6H_6-EtOAc 8:1). Recrystallization of this sample from hexane gave optically pure (-)-4[8,9,12] showing mp 88-89°C and $[\alpha]_D^{20}$-20.5°(c=1.07, EtOH) in more than 80% yield based on 3. Based on the optical rotation of optically pure (-)-4, the optical yield of the asymmetric reduction can be estimated as 92% ee.[13]

Results of the asymmetric reductions similarly examined by employing various amines as achiral additives, are summarized in Table I. It is quite obvious that N-alkylanilines having no steric hindrance in the vicinity of the nitrogen, especially N-ethylaniline, are the best achiral amine additives and that aliphatic secondary amines and heterocyclic amines afforded lower optical and chemical yields of (-)-4. Among other possible factors which may affect the optical and chemical yields of (-)-4, examinations on N-alkyl substituents of (-)-N-alkylephedrines,[7] reaction solvents, and reaction temperatures were also carried out, affording the

Scheme I



2: R=OH
3: R=Me

i) 100%
ii) 94%
iii) 100%
iv) 85%
v) 84%
vi-viii)

11: R^1=H, R^2=OH; (-)-12: R^1=Me, R^2=H

9: R=H; 10: R=OH

i) $LiAlH_4$-(-)-N-methylephedrine-PhNHEt in Et_2O, -78°C, 6 hr. ii)DDQ(1.0 eq) in C_6H_6, rt, 1 hr. iii) t-BuOOH-VO(acac)$_2$ in C_6H_6, rt, 1.5 hr. iv) $LiAlH_4$ in THF, rt, 2 hr. v-viii) See ref. 1, Scheme I.

Table I Asymmetric Reduction of 2-Acetyl-5,8-dimethoxy-3,4-dihydronaphthalene(3) by $LiAlH_4$ Decomposed with (-)-methylephedrine and Achiral Amine Additives[a)]

Run	Achiral Amine Additives	(-)-4 Chemical Yields(%)[b)]	(-)-4 Optical Yields(%)[c)]	Run	Achiral Amine Additives	(-)-4 Chemical Yields(%)[b)]	(-)-4 Optical Yields(%)[c)]
1	PhNHMe	97	86	8	n-BuNHMe	7	-[d)]
2	PhNHEt	94	92	9	Cyclohex-NHMe	46	24
3	PhNHn-Bu	96	86	10	Pyrrolidine	0	-
4	PhNHt-Bu	36	13	11	Piperidine	16	27
5	3,5-DiMePhNHEt	95	80	12	Morpholine	23	7
6	2,6-DiMePhNHMe	62	2	13	Pyrrole	0	-
7	PhNHPh	94	84	14	Carbazole	18	-[d)]

a) All reactions were carried out using $LiAlH_4$(3.3 eq) partially decomposed with (-)-N-methylephedrine(3.4 eq) and achiral amine additives(6.8 eq) in ether at -78°C for 3 hr. b) Based on 3 after purification with preparative tlc(silica gel, C_6H_6-EtOAc 8:1). c) Optically pure (-)-4 shows $[\alpha]_D^{20}$-20.5°(c=1.07, EtOH). d) Measurement of optical rotation was not attempted

results shown in Table II. These studies definitely established the optimized reaction condition for the asymmetric reduction of 3.[16)]

Table II Effects of N-Alkyl Substituents of (-)-N-Alkylephedrines(A), Reaction Solvents(B), and Reaction Temperatures(C) on the Asymmetric Reduction of 2-Acetyl-5,8-dimethoxy-3,4-dihydronaphthalene(3)[a]

A			B			C		
	(-)-4			(-)-4			(-)-4	
N-Alkyl Substs.	Chemical Yields(%)[b]	Optical Yields(%)[c]	Solvents	Chemical Yields(%)[b]	Optical Yields(%)[c]	Temp. (C°)	Chemical Yields(%)[b]	Optical Yields(%)[c]
Me	94	92	Ether	94	92	+35	95	69
Et	73	76	THF	59	5	0	98	79
i-Bu	58	75	Toluene	62	28	-20	93	82
$PhCH_2$	82	82	DME	16	-[d]	-78	94	92
			Methylal	0	-	-100	53	92

a) All reaction were performed using $LiAlH_4$ partially decomposed with (-)-N-alkylephedrine(for A)(3.4 eq) or (-)-N-methylephedrine(for B and C)(3.4 eq) and N-ethylaniline(6.8 eq) in ether (for A and C) at -78°C(for A and B) for 3 hr. b-d) See Table I, footnote b-d).

In a large scale preparation of (-)-4, evaporation of the ethereal extracts obtained after 6 hrs' reaction, gave crude optically active (-)-4,[8a,9,10] $[\alpha]_D^{20}$-18.8°(c=1.83, EtOH), 92% ee, in 100% yield. Direct recrystallization of this sample from hexane afforded optically pure (-)-4,[8,9] mp 88-89°C, $[\alpha]_D^{20}$-20.4°(c=1.55, EtOH), in 87% yield based on 3. Evaporation of the mother liquor from the recrystallization yielded (-)-4[8a,9] of low optical purity, $[\alpha]_D^{20}$ -3.6°(c=2.79, EtOH), 18% ee, in 15% yield, which on oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone(DDQ), recovered 3[1] in 94% yield. From the aqueous layer which was obtained by quenching with 5% HCl, a mixture of (-)-N-methylephedrine and N-ethylaniline was recovered as an oil in 98% yield by successive treatment with aq NaOH and extractive isolation with ethyl acetate. Fractional distillation of the mixture gave (-)-N-methylephedrine, bp 120°C(0.01 mmHg), $[\alpha]_D^{20}$-29.1°(c=4.59, MeOH), without racemization and N-ethylaniline, bp 87-90°C(15 mmHg), in 83% and 100% recovery yields, respectively.

Preparation of (R)(-)-1 from optically pure (-)-4 was readily accomplished according to the previously established reaction scheme.[1] Thus, epoxidation of (-)-4 gave a diastereomeric mixture of the α,β-epoxy alcohols(5 and 6)[8a,9] as an unstable oil, which, without separation, was subjected to reduction, giving the crystalline vicinal-diol as a mixture of two diastereomers((-)-7 and 8),[8a,9] mp 140-150°C, $[\alpha]_D^{20}$-39.3°(c=1.04, EtOH). The predominantly formed diastereomer((-)-7),[8,9] mp 154-155°C, $[\alpha]_D^{20}$-49.7°(c=0.50, EtOH), could be isolated by recrystallization from ether. Oxidation of (-)-7 with Fetizon reagent followed by recrystallization from chloroform-ether gave optically pure (R)(-)-1,[8a,9,12] mp 128-129°C, $[\alpha]_D^{20}$-47.1° (c=1.11, $CHCl_3$)(lit.,[3] mp 128-129°C, $[\alpha]_D^{20}$-48.2°(c=0.982, $CHCl_3$); lit.,[5] mp 130-132°C, $[\alpha]_D^{20}$ -50°(c=1, $CHCl_3$)). When the same oxidation was attempted using a mixture of (-)-7 and 8, partially optically active (R)(-)-1,[8a,9] mp 123-127°C, $[\alpha]_D^{20}$-42.5°(c=0.89, $CHCl_3$), was obtained after evaporation of the organic extracts. The optical purity of this sample calculated as 90% ee, reveals that the formation ratio of 5 to 6 on the epoxidation of (-)-4 is 95:5. This figure is in good agreement with the value for the racemic compound determined by NMR.[1]

While the synthetic routes from (R)(-)-1 to optically active anthracyclinones such as

daunomycinone(9), adriamycinone(10), and 4-demethoxydaunomycinone(11) have been established,[2] optically pure (-)-7-deoxy-4-demethoxydaunomycinone dimethyl ether((-)-12),[8a,9,12] mp 139-140 °C, $[\alpha]_D^{20}$-23.0°(c=1.06, $CHCl_3$)(lit.,[5a] mp 142-144°C, $[\alpha]_D^{20}$-32°(c=1, $CHCl_3$)), was prepared from (R)(-)-1 according to the reported procedure.[5] Tetracyclic (-)-12 is a key intermediate for the synthesis of 11, the aglycone of 4-demethoxydaunorubicin having improved therapeutic properties.[2]

It is worth noting that, considering high chemical and optical yields, operational simplicity, use of readily available (-)-N-methylephedrine[7] as a chiral source, and efficient recovery of the chiral source after the reduction, the exploited asymmetric reduction of 3 might fulfill the criteria required for the practical asymmetric synthesis.[17]

References and Notes

1) S. Terashima, N. Tanno, and K. Koga, Tetrahedron Letters, preceding paper.

2) See ref. 1, footnote 1.

3) S.-s. Jew, S. Terashima, and K. Koga, Chem. Pharm. Bull.(Tokyo), 27, 2351(1979).

4) Chemical resolution of (±)-1[5] and the asymmetric halolactonization utilizing (S)-proline as a chiral source[3] have been employed for synthesizing optically pure (R)(-)-1.

5) a) F. Arcamone, L. Bernardi, B. Pateri, and A. Di Marco, Ger. Offen., 2,601,785(July 29, 1976). b) F. Arcamone, et al., Cancer Treat. Rep., 60, 829(1976).

6) See ref. 1, footnote 4.

7) T. Mashiko, S. Terashima, and S. Yamada, Yakugaku Zasshi, 100, 319(1980).

8) a) IR and NMR spectra were in agreement with the assigned structure. b) Satisfactory analytical data were obtained for this compound.

9) This sample showed identical chromatographic(tlc) and spectral(IR and NMR) properties with those of the racemic modification.[1]

10) Taking into account the stereochemistry in the epoxidation of (-)-4 and the successful synthesis of (R)(-)-1 from (-)-4, the absolute configuration of (-)-4 was deduced to belong to (S)-series. Asymmetric reduction of acetophenone by the same condition as for 3 afforded (S)(-)-1-phenylethanol, bp 160°C(5 mmHg)(bath temp.), $[\alpha]_D^{20}$-37.2°(c=5.10, cyclopentane), 86% ee, in 87% yield(S. Terashima, N. Tanno, and K. Koga, unpublished results). This result also supports the assigned absolute configuration of (-)-4.

11) Use of an excess amount of aq HCl gave rise to the racemization of (-)-4.

12) The optical purity of this sample was further ascertained by its NMR spectra recorded in the presence of chiral shift reagent($Eu(hfc)_3$).

13) Attempted asymmetric reductions of 3 according to the reported methods gave (-)-4 in lower chemical and optical yields(reducing agent; condition; chemical yield; optical yield). $LiAlH_4$(3.3 eq)-(-)-N-methylephedrine(3.3 eq)-m-xylenol(6.6 eq) in ether;[14] -20°C, 3 hr; 11%; 13% ee. $LiAlH_4$(2.36 eq)-(S)-2-(anilinomethyl)pyrrolidine(2.73 eq) in ether;[15] -78°C, 5 hr; 60%; 54% ee.

14) J.P. Vigneron and I Jacquet, Tetrahedron, 32, 939(1976).

15) M. Asami, H. Ohno, S. Kobayashi, and T. Mukaiyama, Bull. Chem. Soc. Japan, 51, 1869(1978).

16) The detailed reduction mechanism will be discussed in the full paper.

17) D. Valentine, Jr. and J.W. Scott, Synthesis, 1978, 329.

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