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Synthesis of Chiral 5-Deazaflavin Derivatives and Their Use in Asymmetric Reduction of Ethyl Benzoylformate[1)]

KIYOSHI TANAKA, TEIJI KIMURA, TOMOYA OKADA, XING CHEN and FUMIO YONEDA*

Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606, Japan

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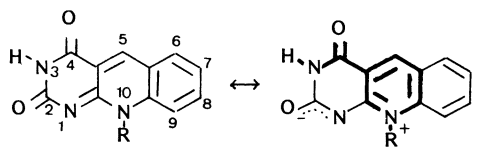
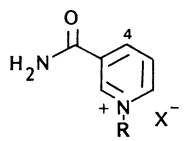
Some 1,5-dihydro-5-deazaflavin (1,5-dihydropyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-dione) derivatives possessing chiral substituents at the N-3 position were synthesized. Asymmetric reduction of ethyl benzoylformate in the presence of magnesium perchlorate was carried out with these chiral 1,5-dihydro-5-deazaflavin derivatives to give ethyl mandelate in moderate optical and chemical yield. The influence of metal additives other than magnesium upon the asymmetric induction and yield of the reduction was investigated, and it was suggested that intermediate ternary complexation is probably involved in the reaction. No improvement of chiral induction was obtained by changing the metal catalyst.

Keywords——chiral 5-deazaflavin; 1,5-dihydro-5-deazaflavin; asymmetric reduction; ethyl benzoylformate; coenzyme model; metal additive; ethyl mandelate; α-methylbenzylamine

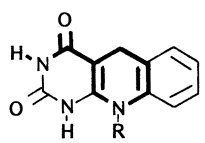
5-Deazaflavin (pyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-dione) derivatives were first synthesized in 1970 by Cheng and co-workers[2)] as part of a search for antagonists of riboflavin. The only structural difference between the flavin (isoalloxazine) and the 5-deazaflavin is the replacement of N-5 of the flavin by CH. This derivation causes the 5-deazaflavins to resemble structurally not only the parent flavins but also nicotinamide nucleotides (NAD) (Chart 1), and this is the reason why 5-deazaflavins are often referred to as "flavin-shaped nicotinamide analogs." In fact, the chemistry of flavin and 5-deazaflavin is fundamentally different[3)] and it has been reported that the chemical behavior of 5-deazaflavin



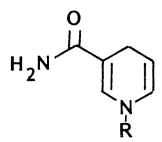
5-deazaflavin



NAD^+



1,5-dihydro-5-deazaflavin



NADH

Chart 1

resembles that of NAD rather than that of flavin.[4] On the other hand, since the discovery of coenzyme F_{420},[5] 5-deazaflavin derivatives have received considerable attention because of their significant roles in redox reactions (anoxybionic metabolism) as well as in the repair of damaged deoxyribonucleic acid (DNA)[6] (DNA photoreactivating function) in biological systems. These findings stimulated extensive work on the chemistry and function of 5-deazaflavin derivatives in both enzymatic and model systems.[7]

Biomimetic reactions using nicotinic acid derivatives have been widely investigated since the pioneering work by Westheimer *et al.*[8] in 1957, in order to provide mechanistic insight into NAD(P)–NAD(P)H catalyzed reactions in the field of bioorganic chemistry.[9] The results of the many investigations have made an important contribution to asymmetric synthesis.[10,11] For example, when a chiral group is substituted on the amide nitrogen of an NADH model compound (Chart 2), asymmetric reduction takes place in the presence of a metal ion. The stereochemical and mechanistic considerations in (net) hydride transfer from and to NAD(P)–NAD(P)H models have also been reported.[12] One of the authors,[13] F. Y., has previously reported that 1,5-dihydro-5-deazaflavin reduced simple carbonyl compounds under acidic conditions to afford the corresponding alcohols, so we turned our attention to asymmetric reduction using chiral 5-deazaflavin derivatives.

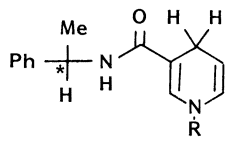
In contrast to NADH models, asymmetric hydrogen transfer to and from 5-deazaflavins and flavins had not been examined until our recent communication,[1] and to our knowledge, there are still only a few reports dealing with asymmetric reduction with chiral 5-deazaflavins and flavins.[14]

In this paper, we describe the preparation of chiral 5-deazaflavin derivatives and their use for the asymmetric reduction of ethyl benzoylformate. The influence of metal ions as additives which might influence the rate and stereoselectivity in the reduction will also be discussed briefly.

We designed and synthesized compounds of type (**1**) in which a chiral substituent exists on the N-3 position of the 5-deazaflavin framework. This compound is essentially similar in structure to the above-mentioned NAD(P)H model by which successful asymmetric reduction was achieved (Chart 2). 7-Methyl-5-deazaflavin derivatives were also prepared because the 7-methyl derivatives showed a potential reductive power in "autorecycling reduction."[15]

The use of such 5-deazaflavins in the asymmetric reduction of ethyl benzoylformate was expected to give a comparable degree of stereo (enantio) selectivity due to their structural similarity to NADH models and the greater rigidity of the 5-deazaflavin skeleton.

Treatment of nitrourea[16] with commercially available (*R*)-(+)-α-methylbenzylamine in water gave (*R*)-(+)-*N*-α-methylbenzylurea (**2a**) in good yield. Similar treatment with (*S*)-(−)-α-methylbenzylamine also afforded the corresponding urea (**2b**). These optically active urea derivatives were converted to the barbituric acid derivatives (**3a**, **b**) in 75—80% yield by a conventional method in which the urea derivatives were treated with the mixed anhydride derived from malonic acid and acetic anhydride. Unlike the common barbituric acid



R = $PhCH_2$: BNPH

R = C_3H_7 : PNPH

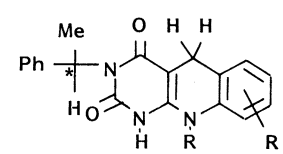


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Chart 2

derivatives, **3** could not be converted into the chlorides (**4**) with various kinds of reagents. One-carbon extension reaction of 3-(*R*)-(+)- and 3-(*S*)-(−)-α-methylbenzylbarbituric acids with Vilsmeier-type reagent[17] was carried out to yield the corresponding 6-chloro-5-formyluracils (**5a** and **5b**) as oily substances, which were labile on standing and were therefore used for the following cyclization step without purification. Heating of the 6-chloro-5-formyluracil derivatives (**5a, b**) with an appropriate *N*-alkylarylamine or *N*-alkylnaphthylamine in dimethylformamide (DMF) gave the desired optically active 5-deazaflavin derivatives (**6**—**8**) in good yields. These results are summarized in Table I. *N*-Butyl-*p*-toluidine and *N*-butyl-α-naphthylamine were synthesized *via* the corresponding *N*-trifluoroacetyl derivatives from *p*-toluidine and α-naphthylamine, respectively. Of these 5-deazaflavin derivatives, the tetracyclic compound (**8a**) is rather unstable and the yield of this compound was less satisfactory.

Next, we examined asymmetric reduction with the 5-deazaflavin derivatives thus

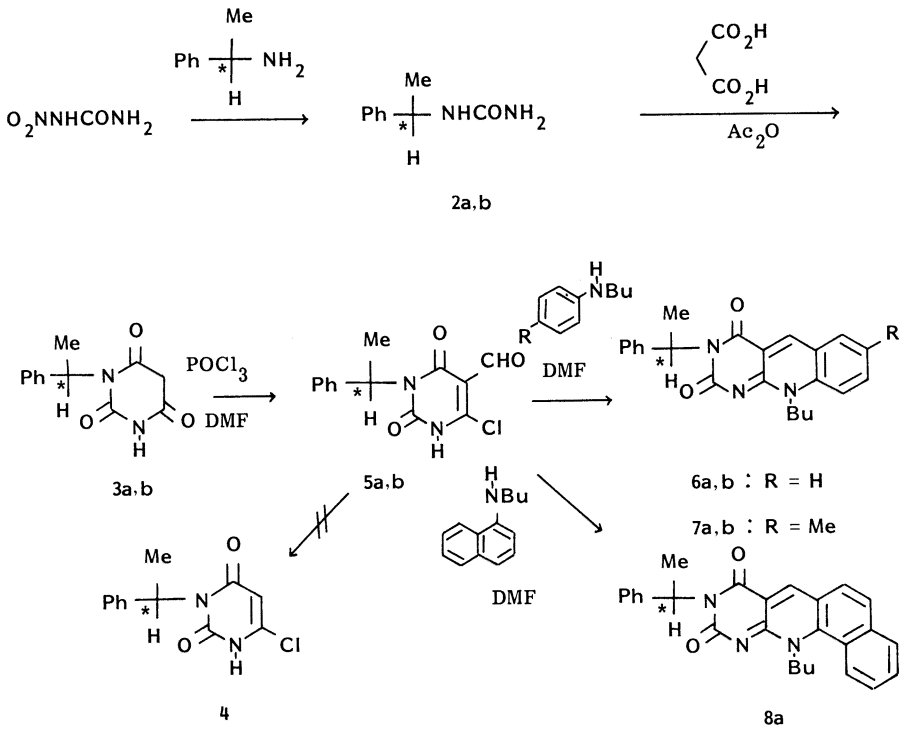

Chart 3

TABLE I. Chiral 5-Deazaflavin Derivatives

5-Deazaflavin	Configuration at N-3 side chain	% Yield[a] from **3**	$[\alpha]_D$ (degree) in chloroform	mp (°C)
6a (R=H)	*R*	55	+147[b]	114—116
6b (R=H)	*S*	53	−147[b]	114—116
7a (R=Me)	*R*	26	+111.5	71—73
7b (R=Me)	*S*	39	−117.4	84—87
8a	*R*	20.5	+205.6	203

a) Isolated yield. *b*) In ethanol.

obtained. Ethyl benzoylformate has been widely used in asymmetric reduction with 1,4-dihydropyridine derivatives,[10-12] as mimics of coenzyme NADH, and is a suitable substrate for the present asymmetric reduction because of its high reactivity and the ease of evaluation of the degree of chiral induction in the product.[18] 5-Deazaflavin derivatives (**6**, **7**) bearing the chiral group at the *N*-3 position were transformed into their reduced form, 1,5-dihydro-5-deazaflavin derivatives (**9**, **10**), quantitatively by reduction with sodium borohydride in methanol or sodium dithionite in water.[19] In this procedure, the 1,5-dihydro-5-deazaflavin derivatives (**9**, **10**) are quite reactive to atmospheric oxygen, and so strict exclusion of oxygen and light was required. Nevertheless, the reaction residue of the reduction was always contaminated by starting 5-deazaflavin (oxidized form) derivatives in the range of 3—15%. Under the highly acidic reaction conditions reported for the reduction of simple ketones by achiral 5-deazaflavin derivatives,[13] racemization of the resulting alcohol might occur, so we employed milder conditions similar to those used for NADH model studies. With equimolar 1,5-dihydro-5-deazaflavin derivative and ethyl benzoylformate, the asymmetric reduction was carried out in the presence of one equivalent amount of magnesium perchlorate in a mixture of acetonitrile–acetic acid (1 : 1) or acetonitrile alone at room temperature under an atmosphere of argon in the dark until most of the 1,5-dihydro-5-deazaflavin derivative had disappeared (checked by thin layer chromatography (TLC)) (Chart 4). The reaction progress can also be monitored by high performance liquid chromatography (HPLC) (μ-Porasil, hexane–ethyl acetate (8 : 1), ultraviolet (UV) 254 nm). After the reaction, the mixture was worked up and the reaction products, ethyl mandelate, recovered ethyl benzoylformate, and

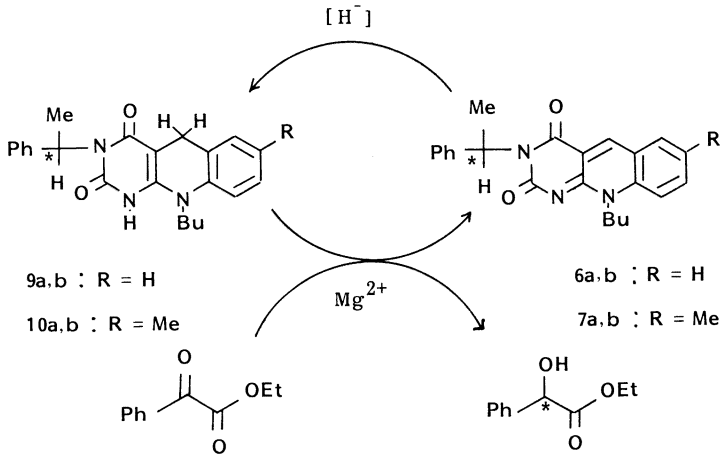

Chart 4

TABLE II. Asymmetric Reduction of Ethyl Benzoylformate

1,5-Dihydro-5-deazaflavin	$[\alpha]_D^{25}$ a)	Ethyl mandelate			
		Chemical yield (%) b)	Configuration	$[\alpha]_D^{25}$ c)	Optical yield (% ee) d)
9a	+125°	12	*S*	+14.2°	14
9b	−127°	15	*R*	−21.8°	21
10b	—	15.4	*R*	−15.1°	14.5

a) In chloroform. *b*) Isolated yield. *c*) In ethanol. *d*) Pure (*R*)-ethyl mandelate[18]: $[\alpha]_D^{24} = -104°$ (in ethanol).

the 5-deazaflavin derivative, were isolated by preparative-TLC (p-TLC) on silica gel. The reaction conditions employed and the results are summarized in Table II. As can be seen, asymmetric induction was observed by using chiral 5-deazaflavin derivatives, but its degree was not so high as had been expected. The optical yield (% ee) was determined on the basis of the reported $[\alpha]_D$ value[18] of ethyl mandelate. Though ethyl mandelate was obtained in moderate chemical and optical yield, the exact chemical yield could not be determined due to the sensitivity of the 1,5-dihydro-5-deazaflavin derivatives to oxygen, and the actual chemical yield might be higher. Since no products other than ethyl mandelate and starting ethyl benzoylformate were isolated, the chemical yield based on the consumed starting ketone may be nearly quantitative. This is a first example of a nonenzymatic, stoichiometric asymmetric reduction using 5-deazaflavin derivatives. The 1,5-dihydro derivative of the compound (**8a**) was not used for reduction because of its poor formation yield and its lability.

In reduction with NADH models, metal ions, especially magnesium ion, play an important role and it was suggested that both rate-enhancement and enantioselectivity depend significantly upon the nature and concentration of the metal ion. The role of the metal ion has been interpreted in terms of electron transfer[20] and complexation[12] between the reductant (mimic model) and metal. In order to improve the asymmetric induction with 1,5-dihydro-5-deazaflavin derivatives, we investigated the reduction of ethyl benzoylformate in the presence of a variety of metal ions under neutral conditions at room temperature. The reaction was carried out in methylene chloride to minimize racemization of the resulting mandelate till no more 1,5-dihydro-5-deazaflavin was detected on a TLC plate. The results and reaction conditions are included in Table III. From the Table III, a higher isolated chemical yield was obtained with aluminum chloride, whereas a better optical yield was

TABLE III. Effect of Metal Additives on Asymmetric Reduction

1,5-Dihydro-5-5-deazaflavin	Metal additive	(eq)	Reaction time (d)	Ethyl mandelate		
				Chemical yield (%)[a]	Configuration	Optical yield (% ee)
9a or **9b**	None	—	7	15—16	—	0
9b	$BF_3 \cdot AcOH$	1	2.5	10.5	*R*	13.6
10b[b]	$Mg(ClO_4)_2$	1	7	15.4	*R*	14.5
10b	$AlCl_3$	1	3	34.5	*R*	5.3
10b	SiO_2	1	4	10.0	*R*	6.0
10b	PPh_3	1	6	13.4	—	0
10b	$CaCl_2$	1	4	3.8	*R*	8.0
10b	$Ga(NO_3)_3$	0.3	4	8.0	—	0
10b	$Eu(fod)_3$	0.1	3	18.5	*R*	4.3

a) Isolated yield. *b*) In AcOH–CH_3CN (1 : 5).

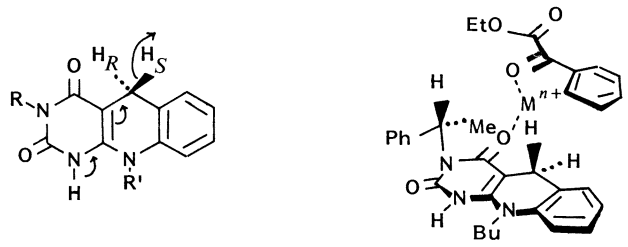

Chart 5

observed with magnesium perchlorate and boron trifluoride–acetic acid. Aluminum chloride probably caused racemization of the alcohol due to its potential Lewis acidity.

In these reductions, (net) hydride transfer might take place from the 1,5-dihydro-5-deazaflavin derivative. Introduction of a chiral substituent into the 5-deazaflavin skeleton at the N-3 position causes the two hydrogens on the achiral carbon atom at the C-5 position in the 1,5-dihydro-5-deazaflavin to be sterically discriminated, and one of the diastereotopic hydrogens (pro-*R* or pro-*S*) is transferred preferentially to the substrate. Furthermore, no asymmetric induction was observed in our present study or in NADH mimic studies in the absence of metal (magnesium) ion. Thus, the transition state for the reduction shown in Chart 5 may be postulated. The moderate or low optical yield observed in our case may be attributable to the flexibility or low degree of participation of the proposed intermediate, a ternary complex.[21] Metal ions having a larger atomic radius such as gallium and europium are not suitable catalysts in terms of this ternary complexation. Racemization by metal additives may not be negligible in our reduction.

Further investigations of asymmetric reduction with 5-deazaflavin derivatives having other types of chiral auxiliary, such as axial (plane) chirality, and reduction in chiral media (chiral catalyst) are in progress.

Experimental

Melting points were determined with a Yanagimoto melting point apparatus and are uncorrected. The infrared (IR ν_{max}) spectra were determined on a Shimadzu IR-400 spectrophotometer in chloroform. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained in dimethyl sulfoxide-d_6 (DMSO-d_6) or chloroform-*d* ($CDCl_3$) at 60 MHz on a JEOL PMX-60 or at 200 MHz on a JEOL FX 200 instrument with chemical shifts being reported in δ units from tetramethylsilane as an internal standard and couplings in hertz. Mass spectra (MS) were taken on a JEOL JMS 01SG-2 instrument by direct insertion at 75 eV. Optical rotation was recorded on a JASCO DIP-360 digital polarimeter. p-TLC was run on 20 × 20 cm plates coated with a 0.1—1.5 mm layer of Merck Silica gel PF_{254} or GF_{254}.

(*R*)-(+)- and (*S*)-(−)-*N*-α-Methylbenzylurea (2a and 2b): General Procedure——α-Methylbenzylamine (13.8 g, 113 mmol) was added to a solution of 10 g (95 mmol) of nitrourea[16] in water (100 ml). The mixture was refluxed for 30 min on a water bath, and cooling of the mixture gave the corresponding *N*-α-methylbenzylurea as colorless needles in 80—90% yield.

(*R*)-(+)-*N*-α-Methylbenzylurea (**2a**): mp 121 °C (from water). ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 1.33 (3H, d, J=7, CH_3), 4.74 (1H, m, CH), 5.44 (2H, s, NH_2), 6.43 (1H, d, J=9, NH), 7.31 (5H, s, Ar). $[\alpha]_D^{24}$ +47.8° (c=2.0, ethanol). *Anal.* Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.91; H, 7.41; N, 16.87.

(*S*)-(−)-*N*-α-Methylbenzylurea (**2b**): mp 121 °C (from water). ^{1}H-NMR: the same as above. $[\alpha]_D^{24}$ −48.2° (c=2.0, ethanol). *Anal.* Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.79; H, 7.35; N, 16.90.

3-(*R*)-(+)- and 3-(*S*)-(−)-α-Methylbenzylbarbituric Acid (3a and 3b): General Procedure——Acetic anhydride (3 ml) was added dropwise to a stirred solution of optically active α-methylbenzylurea (2.0 g, 12 mmol) and malonic acid (1.3 g, 12.5 mmol) in acetic acid (10 ml) at 70 °C. Then, the mixture was heated at 80—90 °C for 3 h with stirring. Concentration of the mixture under reduced pressure followed by crystallization of the residue from ethanol afforded the corresponding barbituric acid (**3a** and **3b**) in 75—80% yield as an off-white powder.

3-(*R*)-(+)-α-Methylbenzylbarbituric Acid (**3a**): mp 130 °C. ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 1.73 (3H, d, J=7.5, CH_3), 5.94 (1H, q, J=7.5, CH), 7.33 (5H, s, Ar), 11.3 (1H, s, NH). IR ν_{max} cm^{-1}: 3370, 1725, 1690. $[\alpha]_D^{25}$ +161.5° (c=1.0, ethanol). *Anal.* Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.18; H, 5.32; N, 12.15.

3-(*S*)-(−)-α-Methylbenzylbarbituric Acid (**3b**): mp 131 °C. ^{1}H-NMR and IR: the same as those of **3a**. $[\alpha]_D^{24}$ −159.3° (c=1.0, ethanol). *Anal.* Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.23; H, 5.28; N, 11.88.

***N*-Butyl-*p*-toluidine**——A mixture of *p*-toluidine (1.07 g), methylene chloride (5 ml), triethylamine (1 ml) and trifluoroacetic anhydride (1.0 ml) was kept standing at 0—5 °C in a refrigerator overnight. The mixture was poured into ice-water and extracted with ether. The ether extract was successively washed with cold diluted hydrochloric acid and brine, and dried over magnesium sulfate. Evaporation of the ether left a crystalline residue. Recrystallization from ether gave 1.1 g of *N*-trifluoroacetyl-*p*-toluidine, mp 114 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.40 (3H, s, CH_3), 7.33 (2H, d, J=8, Ar), 7.67 (2H, d, J=8, Ar), 8.30 (1H, br s, NH). IR ν_{max} cm^{-1}: 3400, 1720.

A mixture of the above *N*-trifluoroacetyl-*p*-toluidine (1.1 g), 1-bromobutane (1.50 g), potassium carbonate (2.0 g)

and acetone (20 ml) was refluxed for 10 h and then concentrated to give a residue containing *N*-butyl-*N*-trifluoroacetyl-*p*-toluidine. Methanol (20 ml) was added to the residue and the mixture was refluxed for 3 h. Concentration of the mixture under reduced pressure gave a residue, which was extracted with ether. The ether layer was washed with water, dried over magnesium sulfate and then concentrated to dryness to give an oily residue. Purification of the residue by short column chromatography on silica gel gave *N*-butyl-*p*-toluidine (730 mg) as a colorless oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.10 (3H, br t, $J=6$, CH_3), 1.36—1.93 (4H, m, $2\times CH_2$), 2.36 (3H, s, CH_3), 3.15 (2H, br t, $J=6$, CH_2), 3.53 (1H, s, NH), 6.50 (2H, d, $J=8$, Ar), 6.97 (2H, d, $J=8$, Ar). IR ν_{max}cm^{-1}: 3400, 1612.

***N*-Butyl-α-naphthylamine**——Starting from α-naphthylamine (1.43 g, 10 mmol), *N*-trifluoroacetyl-α-naphthylamine (1.60 g) was obtained in the same manner as above, as colorless needles, mp 107 °C. *N*-Trifluoroacetyl-α-naphthylamine: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.30—7.86 (7H, m, Ar), 8.47 (1H, br s, NH). IR ν_{max}cm^{-1}: 3400, 1735, 1598.

By the same procedure as above, 1.60 g of *N*-trifluoroacetyl-α-naphthylamine was converted to 1.27 g of *N*-butyl-α-naphthylamine as an oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.94 (3H, d, $J=7.5$, CH_3), 1.44 (2H, sextet, $J=7.5$, CH_2), 1.65 (2H, quintet, $J=7.5$, CH_3), 3.18 (2H, t, $J=7.5$, CH_2), 4.11 (1H, br s, NH), 6.56 (1H, d, $J=7.8$, Ar), 7.14—7.80 (6H, m, Ar). IR ν_{max}cm^{-1}: 3420, 1622, 1580.

Optically Active 5-Deazaflavin Derivatives (6a, b, 7a, b and 8a): General Procedure——3α-Methylbenzylbarbituric acid (**3a** or **3b**) (6 mmol) was added a mixture of phosphoryl chloride (5 ml) and DMF (1 ml), and the resulting mixture was heated at 100 °C with stirring for 3 h under an atmosphere of argon. The reaction mixture was concentrated under reduced pressure to give a residue, which was poured into ice-water and then extracted with chloroform. The chloroform extract was washed with water, dried over magnesium sulfate and then evaporated to dryness to give 6-chloro-5-formyl-3α-methylbenzyluracil (**5a** or **5b**) as a brownish oil, which shows absorption bands at 3380, 2760, 2860, 1725, 1700 and 1668 cm^{-1} in the IR spectrum. Because of its instability, this compound was used for the next cyclization step without further purification.

A solution of the above 6-chloro-5-formyluracil and an appropriate amine (*N*-butylaniline, *N*-butyl-*p*-toluidine or *N*-butyl-α-naphthylamine) (6.0 mmol) in 10 ml of dimethylformamide was heated at 90 °C for 3 h with stirring under an atmosphere of argon. Evaporation of dimethylformamide under reduced pressure and purification of the residue by extraction with chloroform followed by column chromatography on silica gel with chloroform gave the corresponding yellow (**6a**, **b** and **7a**, **b**) or green (**8a**) optically active 5-deazaflavin derivatives in 20.5—55% yield from the barbituric acid derivatives (**3a** or **3b**) (also see Table I).

(+)-10-Butyl-3-(*R*)-α-methylbenzyl-5-deazaflavin (**6a**): mp 114—117 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.02 (3H, t, $J=8$, CH_3), 1.94 (3H, d, $J=7$, CH_3), 4.72 (2H, br t, CH_2), 6.40 (1H, q, $J=7$, CH), 7.15—7.90 (9H, m, Ar), 8.78 (1H, s, =CH–). IR ν_{max}cm^{-1}: 1695, 1640, 1617, 1568, 1532. $[\alpha]_D^{25}+147.0°$ ($c=10$, ethanol). *Anal.* Calcd for $C_{23}H_{23}N_3O_2$: C, 73.97; H, 6.21; N, 11.25. Found: C, 73.82; H, 6.40; N, 11.22.

(−)-10-Butyl-3-(*S*)-α-methylbenzyl-5-deazaflavin (**6b**): mp 114—117 °C. ^{1}H-NMR and IR: the same as those of **6a**. $[\alpha]_D^{25}-147.0°$ ($c=10$, ethanol). *Anal.* Calcd for $C_{23}H_{23}N_3O_2$: C, 73.97; H, 6.21; N, 11.25. Found: C, 73.89; H, 6.32; N, 11.38.

(+)-10-Butyl-7-methyl-3-(*R*)-α-methylbenzyl-5-deazaflavin (**7a**): mp 71—73 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.01 (3H, t, $J=7$, CH_3), 1.55 (2H, sextet, $J=7$, CH_2), 1.72 (2H, quintet, $J=7$, CH_2), 1.94 (3H, d, $J=7.5$, CH_3), 2.47 (3H, s, CH_3), 4.70 (2H, br t, CH), 6.39 (1H, q, $J=7.5$, CH_3), 7.18—7.69 (8H, m, Ar), 8.72 (1H, s, =CH–). IR ν_{max}cm^{-1}: 1695, 1641, 1619. $[\alpha]_D^{32}+111.5°$ ($c=0.3$, chloroform). MS *m/z*: 387 (M^+).

(−)-10-Butyl-7-methyl-3-(*S*)-α-methylbenzyl-5-deazaflavin (**7b**): mp 84—87 °C. ^{1}H-NMR and IR: the same as those of **7a**. $[\alpha]_D^{34}-117.4°$ ($c=0.4$, chloroform). MS *m/z*: 387 (M^+). *Anal.* Calcd for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.50; N, 10.84. Found: C, 74.21; H, 6.71; N, 10.55.

(+)-8,9-Benzo-10-butyl-3-(*R*)-α-methylbenzyl-5-deazaflavin (IUPAC: 12-Butyl-3-(*R*)-α-methylbenzylbenzo[*h*]pyrimido[4,5-*b*]quinoline-8,10(9*H*, 12*H*)-dione) (**8a**): mp 203 °C, ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.97 (3H, t, $J=7.2$, CH_3), 1.42 (2H, sextet, $J=7.2$, CH_2), 1.82 (2H, quintet, $J=7.2$, CH_2), 1.96 (3H, d, $J=7.5$, CH_3), 4.92 (2H, br t, $J=7.2$, CH_2), 6.43 (1H, q, $J=7.5$, CH), 7.20—8.02 (10H, m, Ar), 8.47 (1H, d, $J=8$, Ar), 8.79 (1H, s, =CH–). IR ν_{max}cm^{-1}: 1693, 1638, 1599. $[\alpha]_D^{25}+205.6°$ ($c=0.2$, chloroform). MS *m/z*: 423 (M^+). *Anal.* Calcd for $C_{27}H_{25}N_3O_2$: C, 76.56; H, 5.95; N, 9.92. Found: C, 73.02; H, 5.70; N, 9.53.

1,5-Dihydro-5-deazaflavin Derivatives (9a, b and 10a, b): General Procedure——a) A large excess (3—4 eq) of sodium borohydride was added portionwise to a stirred solution of the optically active 5-deazaflavin derivative (**6a**, **b** or **7a**, **b**) (1 mmol) in 10 ml of a mixture of methanol and water (10 : 1) at 0 °C. The mixture was stirred for several minutes at the same temperature under an atmosphere of argon and then poured into an ice-cold aqueous solution of sodium sulfite. Extraction of the mixture with degassed methylene chloride and evaporation of the methylene chloride *in vacuo* under an atmosphere of argon in the dark afforded the 1,5-dihydro-5-deazaflavin quantitatively as a pale-yellow residue. In most cases, this sample was used directly for the asymmetric reduction without further purification due to the ready formation of oxidized 5-deazaflavins. In the cases of **9a**, **b**, a pure sample was obtained from the residue by careful and quick purification.

(+)-10-Butyl-3-(*R*)-α-methylbenzyl-1,5-dihydro-5-deazaflavin (**9a**): mp 83—84 °C (from ether–hexane). ^{1}H-

NMR (200 MHz, $CDCl_3$) δ: 0.87 (3H, t, $J=8$, CH_3), 1.90 (3H, d, $J=7$, CH_3), 3.66 (2H, m, CH_2), 3.77 (2H, s, CH_2), 6.34 (1H, q, $J=7$, CH), 6.82—7.42 (9H, m, Ar). IR $\nu_{max}cm^{-1}$: 3430, 1690, 1620. MS m/z: 375 (M^+). $[\alpha]_D^{25}+125°$ ($c=1.0$, ethanol).

(−)-10-Butyl-3-(*S*)-α-methylbenzyl-1,5-dihydro-5-deazaflavin (**9b**): mp 85 °C. ^{1}H-NMR and IR: the same as those of **9a**. MS m/z: 375 (M^+). $[\alpha]_D^{25}-127°$ ($c=2.0$, ethanol).

b) A mixture of optically active 5-deazaflavin (1 mmol) (**6a**, **b**), sodium dithionite (870 mg, 5 mmol) and 10% aqueous ammonia (5 ml) was heated on a water bath for 1 h. After cooling, the mixture was worked up in the same way as described in procedure a) to give the corresponding 1,5-dihydro-5-deazaflavin (**9a** or **9b**) in quantitative yield.

Asymmetric Reduction of Ethyl Benzoylformate with 1,5-Dihydro-5-deazaflavin Derivatives (9a, b and 10b): General Procedure——a) Ethyl benzoylformate, magnesium perchlorate and the above-mentioned residue of 1,5-dihydro-5-deazaflavin (**9a**, **b** or **10b**), each 1 mmol, were added to a mixture of acetonitrile and acetic acid (1 : 1). The reaction mixture was stirred at room temperature under an atmosphere of argon in the dark. The progress of the reaction was monitored by TLC or HPLC (μ-Porasil, hexane–ethyl acetate (8 : 1), UV 254 nm). After 7 d, the mixture was poured into ice-water and extracted with chloroform. The chloroform extract was washed with water, dried over magnesium sulfate and then evaporated to give a residue, which was subjected to p-TLC on silica gel with hexane–ethyl acetate (6 : 1). This separation procedure gave recovered ethyl benzoylformate, ethyl mandelate and 5-deazaflavin. Quantitative analysis of the residue by HPLC always showed a higher yield of ethyl mandelate than the isolated one. The optical purity of the resulting ethyl mandelate was determined by comparison of its value of specific rotation with the reported one[18] (see also Table II).

b) Asymmetric reduction of ethyl benzoylformate in the presence of metal catalysts other than magnesium perchlorate was undertaken in the same manner as described for procedure a) except that the solvent used was methylene chloride in place of acetonitrile–acetic acid, and the reaction was terminated when most of the 1,5-dihydro-5-deazaflavin derivatives had disappeared on the TLC plates (see also Table III).

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References and Notes

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