Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 4581–4590

TETRAHEDRON

Stereoselective pyrroline-ring formation through the cyclization of conjugated azomethine ylides at the periphery of pyrido[1,2-*a*]pyrimidine system

Michihiko Noguchi,[a,*] Masashi Shirai,[a] Kuniko Nakashima,[a] Ichiro Arai,[a] Akiko Nishida,[a] Hidetoshi Yamamoto[a] and Akikazu Kakehi[b]

[a]*Department of Applied Chemistry, Faculty of Engineering, Yamaguchi University, Tokiwadai, Ube 755-8611, Japan*
[b]*Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380-8553, Japan*

Received 10 February 2003; accepted 18 April 2003

Abstract—The thermal reaction of *N*-benzyl-*N*-[3-(N-substituted imino)methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]amino acid esters, generated from aldehyde esters and primary amines, provides 2,3-dihydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidin-4(1*H*)-one derivatives effectively and stereoselectively. Therein, the stereoselective generation of conjugated azomethine ylides from the imine esters and their cyclization is essential for the pyrroline-ring formation.

1. Introduction

In previous papers, we reported the stereoselective azepine-ring formation through the thermal imine- and carbonyl-ene reaction at the periphery of heterocyclic systems[1] or at the acyclic ones.[2] The investigation on their mechanisms revealed that the azepine-ring formation consisted of two consecutive orbital-allowed reactions; the [1,6] sigmatropic shift of the allylic hydrogen, generating a conjugated azomethine ylide intermediate, and its [1,7] electrocyclic ring closure (Scheme 1). In the reaction utilizing a chiral substrate, the chirality at the alkenylamino moiety was conserved during the azepine-ring formation and transferred to the 4- and 5-positions of the azepine-ring.

In the course of our studies, we wanted to extend the cyclization chemistry of conjugated azomethine ylides to a pyrroline-ring formation. For the such cyclization process to pyrroline-ring, the term of '*tert*-amino effect'[3] has been used and more recently Viehe[4] proposed the more descriptive term 'α-cyclization of tertiary amines' and many investigation results have been accumulated. Among them, Reinhoudt and co-workers[5] investigated the reaction patterns and stereochemistry of this cyclization in structural variations and proposed reasonable mechanistic details; the [1,6] sigmatropic shift of the hydrogen on the carbon adjacent to the amino nitrogen, generating a conjugated azomethine ylide intermediate, and its [1,5] electrocyclic ring closure (Scheme 2).

In this paper, we describe here the thermal cyclization reaction of *N*-benzyl-[3-(N-substituted imino)methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]amino acid methyl esters leading to pyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine derivatives effectively and stereoselectively.

2. Results and discussion

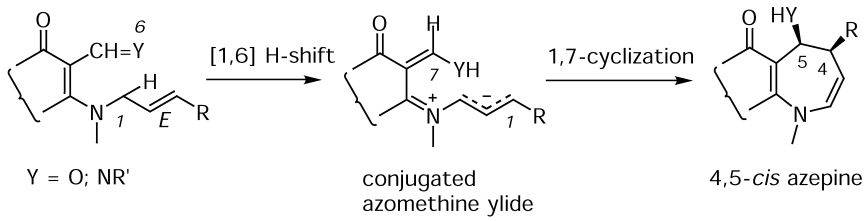
2.1. Thermal reaction of *N*-benzyl-*N*-[3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]amino acid esters 3 with primary amines 4 and 9

In order to elucidate the scope and features of the cyclization reaction, the starting amino acid methyl esters **3a**–**e** were prepared in moderate to good yields by the reaction of 2-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (**1**) with *N*-benzyl-glycine (**2a**), -DL-alanine (**2b**), -L-valine (**2c**), -L-leucine (**2d**), and -DL-phenylglycine methyl ester (**2e**) in refluxing acetonitrile or 1,4-dioxane (Scheme 3).

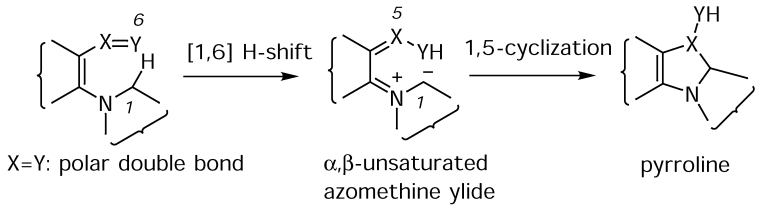
The reaction of **3a** with aniline (**4**) in refluxing benzene for 2 h gave the corresponding imine **5a**, but further heating (for 6 h) at the temperature did not give any changes. Similar reaction in refluxing toluene for 10 h gave pyrroline derivative **6a** and full-conjugated pyridopyrrolopyrimidine **7a** in 28 and 38% yields, respectively. The structure of **6a** was established on the basis of analytical and spectroscopic

Keywords: pyrroline-ring formation; conjugated azomethine ylide; cyclization; chirality transfer.
* Corresponding author. Tel.: +81-836-85-9261; fax: +81-836-85-9201; e-mail: noguchi@yamaguchi-u.ac.jp

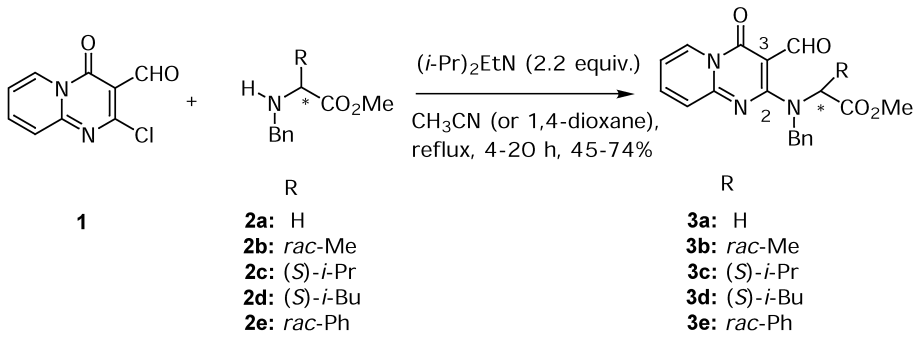
0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00657-4



Scheme 1.



Scheme 2.



Scheme 3.

data. The configuration between the 2- and 3-H was suggested to be *cis* from the coupling constant (9.2 Hz) and confirmed finally by the nuclear Overhauser effect (nOe) measurement; irradiation of the 3-H gave a considerable enhancement (14.7%) of the 2-H. On the other hand, the structure of **7a** was corresponded to the aniline-elimination product from **6a**; the treatment of **6a** with catalytic *p*-toluenesulfonic acid (PTSA) gave **7a** in 78% yield. The reaction of **3b** and **3c** with **4** in refluxing toluene for 3–10 h gave pyrroline derivatives **6b** and **6c** in good yields as sole products. On the other hand, similar reaction of **3d** with **4** for 12 h gave two diastereomeric pyrroline derivatives **6d** and **8d** as a 5:1 mixture in 75% total yield. A prolonged reaction time (22 h) at the same reaction conditions gave a 2:3 mixture of **6d** and **8d** in 75% total yield. Milder conditions, in acetonitrile or benzene under reflux for 48 h, gave **6d** in 84 and 82% yields, respectively, as a sole product. The reaction of **3e** with **4** in toluene at room temperature for 24 h gave pyrroline derivative **6e** in 67% yield. Similar reaction in refluxing acetonitrile or toluene gave a mixture of **6e** and **8e** depending on the conditions employed.

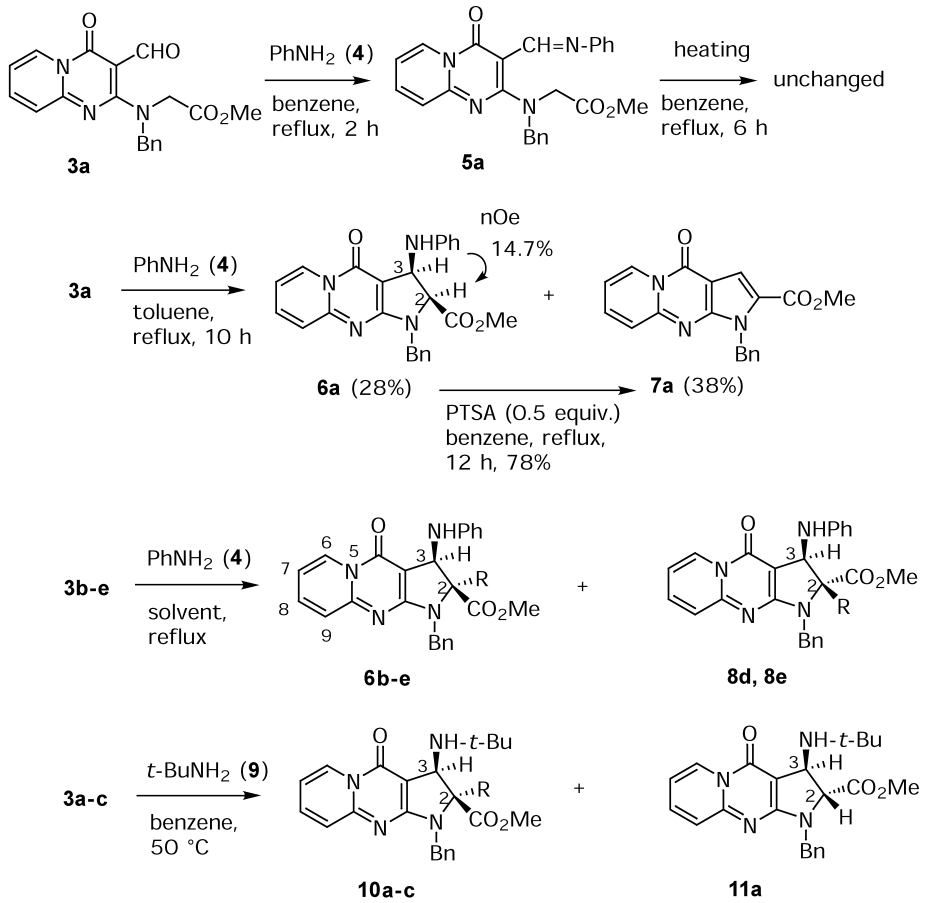
Reactions of amino acid esters **3** with *t*-butylamine (**9**) were also examined; the reaction of **3a** with **9** in benzene at 50°C for 84 h gave pyrroline derivatives **10a** and **11a** in 41 and 13% yields, respectively. The configurations between the 2- and 3-H of **10a** and **11a** were also deduced to be *cis* and *trans*, respectively, from their coupling constants; 9.2 Hz for **10a** and 1.2 Hz for **11a**. Single isomeric products **10b** and **10c** were obtained in moderate yields by similar reactions of **3b** and **3c**. Although the determination details of the configurations of these products will be discussed in later section, the configurations between the methyl ester moiety at the 2-position and the amino group at the 3-position are *cis* for **6** and **10**, and *trans* for **8** and **11**, respectively. These results are summarized in Table 1 (Scheme 4).

In order to obtain further information of the conversion between *cis* and *trans* pyrroline derivatives, the behaviors of

Table 1. Reaction of amino acid esters **3** with primary amines **4** and **9**

Run	R	Amine	Solvent[a]	Time (h)	Products (Yield, %)
1	H	Ph	Benzene	2	**5a** (80)
2	H	Ph	Toluene	10	**6a** (28), **7a** (38)
3	Me	Ph	Toluene	3	**6b** (86)
4	*i*-Pr	Ph	Toluene	10	**6c** (93)
5	*i*-Bu	Ph	Toluene	1	**6d** (8), **8d** (<1)
6	*i*-Bu	Ph	Toluene	12	**6d** (63), **8d** (12)
7	*i*-Bu	Ph	Toluene	22	**6d** (31), **8d** (44)
8	*i*-Bu	Ph	Toluene, 80°C	48	**6d** (84)
9	*i*-Bu	Ph	Acetonitrile	48	**6d** (82)
10	Ph	Ph	Toluene, rt	24	**6e** (67)
11	Ph	Ph	Toluene	12	**6e** (51), **8e** (10)
12	Ph	Ph	Acetonitrile	20	**6e** (25), **8e** (37)
13	H	*t*-Bu	Benzene, 50°C	84	**10a** (43), **11a** (14)
14	Me	*t*-Bu	Benzene, 50°C	64	**10b** (89)
15	*i*-Pr	*t*-Bu	Benzene, 50°C	96	**10c** (54)

[a] Under reflux unless otherwise stated.

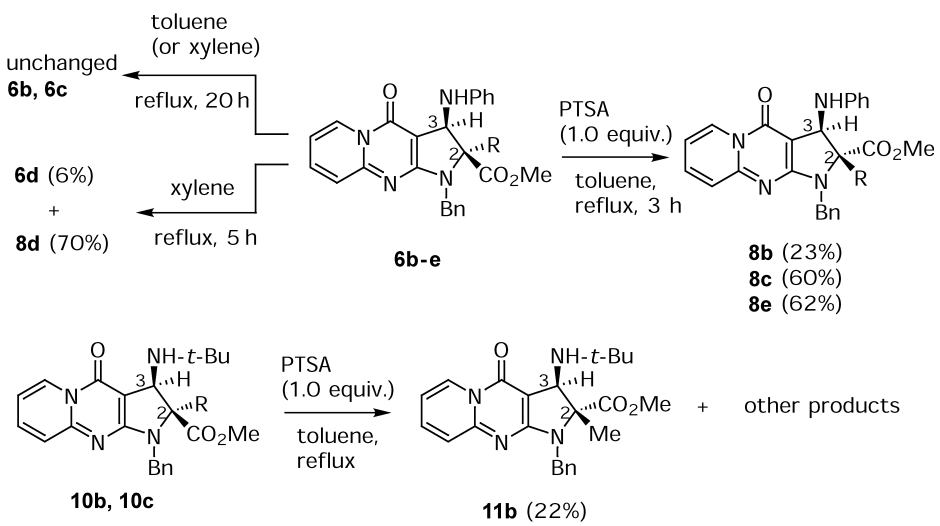


Scheme 4.

the isolated sole products **6** and **10** under thermal and acidic conditions were examined; the reaction of the isolated **6b** and **6c** in refluxing toluene or xylene for 20 h gave no changes and recovered **6b** and **6c** in more than 90% yields. The thermal reaction of **6d** in refluxing xylene for 5 h gave a 1:9 mixture of **6d** and **8d** in total 76% yield. The treatment of **6b**, **6c** and **6e** with PTSA (1.0 equiv.) in refluxing toluene for 3 h gave **8b**,**8c** and **8e** in 23, 60, and 62% yields, respectively. These results suggest that a protic acid should also accelerate the isomerization to *trans*-isomers. The conversion of **10b** and **10c** to **11b** and **11c** by the treatment with PTSA was also examined, but disappointing results were obtained except for the case of **10b** (Scheme 5).

2.2. Determination of the configurations of 2-pyrroline derivatives 6 and 8 (10 and 11)

The diastereomeric products **6** and **8** were easily distinguished to each other by the spectroscopic features as below; in the ^{1}H NMR spectra of **6** and **8**, the benzyl



Scheme 5.

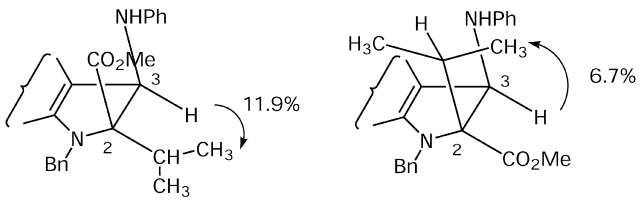


Figure 1. Selected nOe signal enhancements of **6c** and **8c**.

methylene protons of minor isomer **8** were observed as typical AB quartets with more largely differential chemical shifts than those of another isomer **6**. In the ^{13}C NMR spectra of **6** and **8**, the carbon signals assigned to the 3-position of **8** were observed at the upper fields ($\Delta\delta$=more than 5.1 ppm) than those of **6**. On the other hand, the carbon signals of **11a** and **11b** were observed at only little upper field shifts ($\Delta\delta$=0.4 and 4.6 ppm, respectively) than those of **10a** and **10b**.

While the alkyl groups at the 2-position in **8b** and **8d** were shielded probably by the anilino groups, the methyl protons of the ester moiety in **6b** and **6d** were shielded by the anilino ones. This suggests that the configuration between the methyl ester moiety at the 2-position and the anilino group at the 3-position are *cis* for **6** and *trans* for **8**. On the other hand, nOe measurement of **6c** and **8c** elucidated that the configuration of **6c** and **8c** were *cis* and *trans*, respectively; irradiation of the 3-H provided enhancements of the methyl signal of the isopropyl group at the 2-position by 11.9% for **6c** and 6.7% for **8c**, respectively (Fig. 1). The *trans*-configuration of **8e** was also confirmed unambiguously by its X-ray crystallographic analysis.

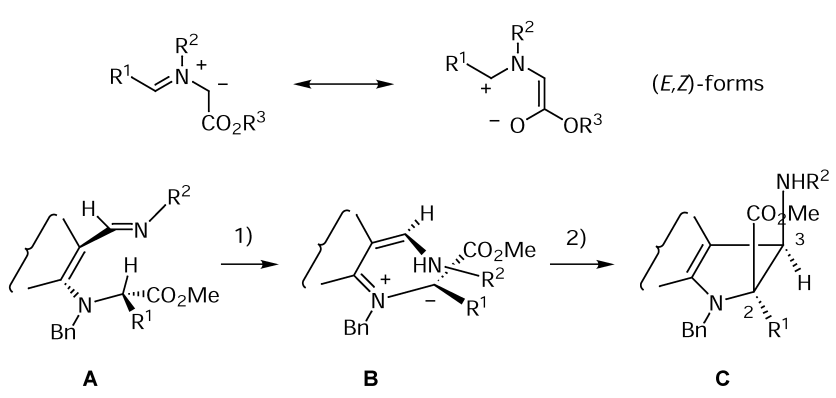
2.3. Reaction features

Although this pyrroline-ring formation through the thermal reaction of *N*-benzyl-*N*-[3-(N-substituted imino)methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]amino acid esters belongs to a category of '*tert*-amino effect', it has some characteristics; it proceeded smoothly under mild conditions even in less polar solvents and in a highly stereoselective manner. The stereoselective features are explainable by assuming that the [1,6] shift of the hydrogen proceeds in the course for generating a more stable azomethine ylide intermediate and the two consecutive reactions, the hydrogen shift and the cyclization of the resultant azomethine ylide, behave as an almost one step process as well as the azepine-ring formation reported by our group.[1,2] Kanemasa and co-workers[6] elucidated that the N-substituted azomethine ylides of carbonyl-stabilized types existed with *anti*-configurations [(*E*,*Z*)-forms] due to the stabilization through a proximate interaction of both termini of the extended dipole. As demonstrated in Scheme 6, the [1,6] H-shift with antarafacial mode **A** for generating the more stable azomethine ylide **B** and the 1,5-electrocyclization of the azomethine ylide **B** with disrotatory mode gave 2,3-*cis* pyrroline derivatives **C** exclusively.

We first examined the chirality transfer through reaction of **3c** with aniline (**4**). The **6c** obtained had an optical purity in more than 94% by a chiral column HPLC method using racemic **6c**. Stimulated by these findings, we examined the reaction of **3c** with chiral primary amines, (*R*)-(+)-1-phenylethylamine (**12**) and (*S*)-(−)-1-(1-naphthyl)ethylamine (**13**), in refluxing toluene. The desired pyridopyrrolopyrimidines **14c** and **15c** were also formed as single diastereomers in 72 and 68% yields, respectively. However, these were obtained as pastes with low melting points at room temperature and, therefore, unavailable to a crystallographic analysis. Although the information on the absolute configuration of the pyrroline-ring formed has been open, we believe that chirality transfer in the pyrroline-ring formation could be also attained in similar other systems (Scheme 7).

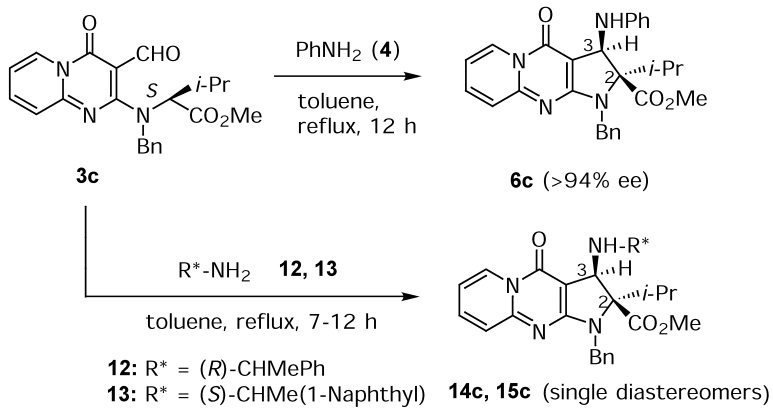
3. Conclusions

We have reported the stereoselective pyrroline-ring formation through the thermal reaction of *N*-benzyl-*N*-[3-(N-substituted imino)methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]amino acid esters. This provides an efficient approach toward functionalized 2,3-dihydro-1*H*-pyrroles fused by heterocyclic systems. Further details on the mechanistic aspects of the pyrroline-ring formation and investigations on the effect of the heterocyclic systems are in progress and will be reported elsewhere.



Reaction modes: 1) *antarafacial*; 2) *disrotatory*

Scheme 6.



Scheme 7.

4. Experimental

4.1. General

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured on a JASCO IR-Report-100 spectrophotometer from samples as KBr pellets or NaCl discs. ^{1}H NMR spectra were measured on JEOL EX-270 and/or EX-400 spectrometers (270 and 400 MHz, respectively) and ^{13}C NMR spectra were measured on a JEOL EX-270 spectrometer (67.8 MHz) in deuterated-chloroform ($CDCl_3$) solutions unless otherwise stated. Tetramethylsilane was used as internal standard, and *J* values are given in Hz. Splitting patterns are indicated as: s, singlet; d, doublet; t, triplet; q, quadruplet, m, mutiplet; br, broad signal; and ov, overlapping signals. Mass spectra were determined on a JEOL JMS-SX102A spectrometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Elemental analyses were performed on a Yanagimoto MT-5 CHN analyzer. All non-aqueous reactions were run under positive pressure of argon or nitrogen. All solvents were dried by standard methods before use. The progress of reactions was monitored by TLC (silica gel 60F-254, Merck). Chromatographic purification was performed with Wakogel C-200 (100–200 mesh, Wako Pure Chemical Industries) and/or silica gel 60 (230–400 mesh, Merck).

4.2. Typical procedures for the preparation of *N*-benzyl-*N*-[3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]-amino acid esters 3

A solution of 2-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (**1**:[7] 0.50 g, 2.4 mmol), *rac*-*N*-benzylalanine methyl ester (**2b**: 0.47 g, 2.6 mmol), and diisopropylethylamine (0.50 mL, 2.9 mmol) in 1,4-dioxane was heated at reflux for 4 h. The resultant precipitates were filtered off and the filtrate was evaporated to dryness. The residue was subjected to a column chromatography on silica gel with hexane/ethyl acetate (EtOAc) (3:1) as an eluent to afford *N*-benzyl-*N*-[3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]alanine methyl ester (**3b**: 0.63 g, 72%).

4.2.1. *N*-Benzyl-*N*-(3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)alanine methyl ester (3b). Yellow needles from EtOAc–hexane; mp 138–139°C; ^{1}H NMR ($CDCl_3$): 1.68 (3H, d, *J*=6.9 Hz, 2-Me), 3.69 (3H, s, OMe), 4.55 (1H, q, *J*=6.9 Hz, 2-H), 4.60, 5.15 (each 1H, each d, *J*=15.5 Hz, CH_2Ph), 6.94 (1H, dt, *J*=1.3, 6.9 Hz, 7′-H), 7.18–7.38 (6H, ov, Ph–H and 9′-H), 7.68 (1H, ddd, *J*=1.0, 6.9, 8.5 Hz, 8′-H), 8.84 (1H, dd, *J*=1.0, 6.9 Hz, 6′-H), 10.15 (1H, s, 3′-CHO); ^{13}C NMR ($CDCl_3$): 16.0 (2-Me), 52.1 (OMe), 52.5 (*C*H_2Ph), 59.8 (2-C), 97.5 (3′-C), 113.7 (7′-C), 124.8 (9-C), 127.0, 127.4, 128.1, 128.2, 137.5 (Ph–C and 6′-C), 139.4 (8′-C), 150.4 (4′-C), 160.2 (2′-C), 161.6 (9a′-C), 172.7 (*C*O_2Me), 186.8 (3′-CHO). Anal. calcd for $C_{20}H_{19}N_3O_4$ (365.4): C, 65.74; H, 5.24; N, 11.50. Found: C, 65.71; H, 5.23; N, 11.50.

Similarly, amino acid esters **3a** (1,4-dioxane, reflux, 5 h, 74%), **3c** [acetonitrile (MeCN), reflux, 8 h, 62%], **3d** (MeCN, reflux, 20 h, 66%), and **3e** (MeCN, reflux, 12 h, 45%) were obtained.

4.2.2. *N*-Benzyl-*N*-(3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)glycine methyl ester (3a). Colorless needles from EtOAc–hexane; mp 137°C; ^{1}H NMR ($CDCl_3$): 3.75 (3H, s, OMe), 4.17 (2H, s, 2-H_2), 5.08 (2H, s, CH_2Ph), 6.97 (1H, dt, *J*=1.3, 6.9 Hz, 7′-H), 7.25–7.33 (6H, ov, Ph–H and 9′-H), 7.72 (1H, ddd, *J*=1.6, 6.9, 7.6 Hz, 8′-H), 8.88 (1H, ddd, *J*=0.7, 1.6, 7.6 Hz, 6′-H), 10.19 (1H, s, 3′-CHO); ^{13}C NMR ($CDCl_3$): 51.8 (2′-C), 52.1 (OMe), 54.5 (*C*H_2Ph), 96.6 (3′-C), 113.7 (7′-C), 124.9 (9′-C), 127.6, 128.0, 128.3, 128.6, 136.4 (Ph–C and 6′-C), 139.5 (8′-C), 150.9 (4′-C), 160.9 (2′-C), 161.7 (9a′-C), 170.1 (*C*O_2Me), 186.9 (3′-CHO). Anal. calcd for $C_{19}H_{17}N_3O_4$ (351.4): C, 64.95; H, 4.88; N, 11.96. Found: C, 64.84; H, 4.98; N, 12.03.

4.2.3. *N*-Benzyl-*N*-(3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)valine methyl ester (3c). Yellow prisms from EtOAc–hexane; mp 143–144°C; ^{1}H NMR ($CDCl_3$): 0.99, 1.05 (each 3H, each d, *J*=6.6 Hz, CH*Me*$_2$), 2.47 (1H, m, C*H*Me$_2$), 3.74 (3H, s, OMe), 4.46 (1H, d, *J*=9.6 Hz, 2-H), 4.98 (2H, s, CH_2Ph), 6.91 (1H, dt, *J*=1.3, 6.9 Hz, 7′-H), 7.14–7.23 (6H, ov, Ph–H and 9′-H), 7.66 (1H, ddd, *J*=1.0, 6.9, 9.6 Hz, 8′-H), 8.78 (1H, dd, *J*=1.0, 6.9 Hz, 6′-H), 10.04 (1H, s, 3′-CHO); ^{13}C NMR ($CDCl_3$): 20.5, 20.7 (CH*Me*$_2$), 30.9 (*C*HMe$_2$), 52.1 (*C*H_2Ph), 70.5 (2-C), 98.5 (3′-C), 114.0 (7′-C), 125.4 (9′-C), 127.3, 128.1, 128.3, 128.5, 137.6 (Ph–C and 6′-C), 139.5 (8′-C), 150.9, (4′-C), 160.8 (2′-C), 161.9 (9a′-C), 172.4, (*C*O_2Me), 186.8 (3′-CHO). Anal. calcd

for $C_{22}H_{23}N_3O_4$ (393.4): C, 67.16; H, 5.89; N, 10.68. Found: C, 67.16; H, 5.87; N, 10.65.

4.2.4. *N*-Benzyl-*N*-(3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)leucine methyl ester (3d). Yellow prisms from EtOAc–hexane; mp 148°C; ^{1}H NMR ($CDCl_3$): 0.82, 0.89 (each 3H, each d, J=6.6 Hz, CHMe_2), 1.67 (1H, m, CHMe$_2$), 1.93 (2H, m, 3-H$_2$), 3.74 (3H, s, OMe), 4.62 (1H, dd, J=5.6, 8.9 Hz, 2-H), 4.83 (2H, s, CH_2Ph), 6.92 (1H, ddd, J=1.3, 5.9, 7.3 Hz, 7′-H), 7.15–7.38 (6H, ov, Ph–H and 9′-H), 7.66 (1H, ddd, J=1.6, 6.6, 7.3 Hz, 8′-H), 8.79 (1H, dd, J=1.6, 5.9 Hz, 6′-H), 10.08 (1H, s, 3′-CHO); ^{13}C NMR ($CDCl_3$): 22.5, 22.7 (CHMe_2), 24.9 (CHMe$_2$), 29.4 (3-C), 52.2 (CH_2Ph), 70.3 (2-C), 98.5 (3′-C), 113.8 (7′-C), 125.7 (9′-C), 127.3, 128.1, 128.4, 128.5, 137.9 (Ph–C and 6′-C), 139.5 (8′-C), 150.9 (4′-C), 160.8 (2′-C), 161.9 (9a′-C), 172.6 (CO_2Me), 186.9 (3′-CHO). Anal. calcd for $C_{23}H_{25}N_3O_4$ (407.5): C, 67.79; H, 6.18; N, 10.31. Found: C, 67.56; H, 5.81; N, 10.73.

4.2.5. *N*-Benzyl-*N*-(3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)phenylglycine methyl ester (3e). Colorless needles from EtOAc–hexane; mp 180–181°C; ^{1}H NMR ($CDCl_3$): 3.83 (3H, s, OMe), 4.46, 4.74 (each 1H, each d, J=15.5 Hz, CH_2Ph), 5.77 (1H, s, 2-H), 6.99 (1H, dt, J=1.3, 6.9 Hz, 7′-H), 7.11–7.40 (11H, ov, Ph–H and 9′-H), 7.71 (1H, ddd, J=1.0, 6.9, 8.6 Hz, 8′-H), 8.89 (1H, dd, J=1.0, 6.9 Hz, 6′-H), 10.19 (1H, s, 3′-CHO); ^{13}C NMR ($CDCl_3$): 52.2 (OMe), 53.0 (CH_2Ph), 68.1 (2-C), 98.0 (3′-C), 114.1 (7′-C), 125.0 (9′-C), 126.7, 127.8, 128.0, 128.1, 128.6, 128.8, 128.9, 134.7, 137.6 (Ph–C and 6′-C), 139.5 (8′-C), 150.8 (4′-C), 159.1 (9a-C), 161.4 (2′-C), 171.2 (CO_2Me), 186.5 (3′-CHO). Anal. calcd for $C_{25}H_{21}N_3O_4$ (427.4): C, 70.25; H, 4.95; N, 9.83. Found: C, 70.19; H, 5.01; N, 9.80.

4.3. Reaction of *N*-benzyl-*N*-(3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)amino acid esters 3 with primary amines

4.3.1. Reaction of *N*-benzyl-*N*-(3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)glycine methyl ester (3a) with aniline (4). A solution of **3a** (0.21 g, 0.60 mmol) and aniline (**4**: 0.070 mL, 0.72 mmol) in benzene (20 mL) was heated at reflux for 2 h. The solvent was evaporated to dryness and the residue was subjected to the ^{1}H NMR analysis. The formation of the corresponding *N*-phenyl imine **5a** (80% by the NMR) was elucidated by the following ^{1}H NMR spectroscopic data: **5a**: 3.52 (3H, s, OMe), 4.23 (2H, s, 2-H$_2$), 5.15 (2H, s, CH_2Ph), 8.97 (1H, s, –CH=N–). Further heating for 6 h the mixture in benzene did not give any change on TLC.

Similar reaction of **3a** with **4** (1.2 equiv.) in toluene at reflux for 10 h and usual work-up with silica-gel chromatography gave **6a** (28%) and **7a** (38%) with hexane/EtOAc (2:1) as an eluent.

4.3.2. Methyl 3-anilino-1-benzyl-4-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (6a). Colorless needles from EtOAc–hexane; mp 221–222°C; IR (KBr): 3300 (NH), 1740, 1680 (CO); ^{1}H NMR ($CDCl_3$): 3.39 (3H, s, OMe), 4.06, 5.46 (each 1H, each d, J=15.2 Hz, CH_2Ph), 4.33 (1H, d, J=6.6 Hz, 3-NH–Ph, exchanged with D_2O), 4.46 [1H, d, J=9.2 Hz (*cis*), 2-H], 5.43 [1H, dd, J=6.6, 9.2 Hz (*cis*), 3-H], 6.69–7.38 (10H, Ph–H), 7.00 (1H, dt, J=1.3, 6.9 Hz, 7-H), 7.48 (1H, dd, J=1.3, 8.6 Hz, 9-H), 7.71 (1H, ddd, J=1.0, 6.9, 8.6 Hz, 8-H), 9.02 (1H, dd, J=1.0, 6.9 Hz); ^{13}C NMR ($CDCl_3$): 46.7 (CH_2Ph), 51.7 (OMe), 55.3 (3-C), 66.5 (2-C), 91.1 (3a-C), 113.5 (7-C), 114.0, 118.3, 124.4, 127.8, 128.3, 128.5, 128.8, 128.9, 136.1, 147.1 (Ph–C and 6- and 9-C), 137.5 (8-C), 153.7, 153.8 (4-C and 10a-C), 164.3 (9a-C), 169.0 (CO_2Me). Anal. calcd for $C_{25}H_{22}N_4O_3$ (426.5): C, 70.41; H, 5.20; N, 13.14. Found: C, 70.43; H, 5.32; N, 13.17.

4.3.3. Methyl 3-anilino-1-benzyl-4-oxo-1,4-dihydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (7a). Yellow prisms from benzene–hexane; mp 204–205°C; IR (KBr): 1715, 1690 (CO); ^{1}H NMR ($CDCl_3$): 3.84 (3H, s, OMe), 5.90 (2H, s, CH_2Ph), 6.90–7.60 (9H, ov, Ph–H and 3-, 7-, 8-, and 9-H), 9.02 (1H, ddd, J=0.8, 1.6, 6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 46.5 (CH_2Ph), 51.7 (OMe), 102.2 (3a-C), 112.4 (7-C), 112.5 (3-C), 124.7, 125.8, 127.3, 127.4, 128.1, 128.4, 138.2 (Ph–C and 6-, 7-, 8-, and 9-C), 149.2 (2-C), 150.4 (10a-C), 155.1 (4-C), 161.2 (9a-C), 168.4 (CO_2Me). Anal. calcd for $C_{19}H_{15}N_3O_3$ (333.3): C, 68.46; H, 4.54; N, 12.61. Found: C, 68.32; H, 4.63; N, 12.39.

The solution of **6a** (0.10 g, 0.23 mmol) and PTSA monohydrate (0.045 g, 0.24 mmol) in toluene (5 mL) was heated at reflux for 12 h. The toluene was evaporated to dryness to give a residue, which was subjected to silica-gel column chromatography to afford **7a** (0.061 g, 78%).

4.4. General procedures for the reaction of *N*-benzyl-*N*-(3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)amino acid methyl esters 3b–e with aniline (4)

A solution of **3b** (0.20 g, 0.56 mmol) and aniline (**4**: 0.060 mL, 0.60 mmol) in toluene (20 mL) was heated at reflux for 3 h. The solvent was evaporated to dryness to give a residue, which was subjected to a column chromatography on silica gel with hexane/EtOAc (3:1) as an eluent to afford **6a** (0.20 g, 86%).

4.4.1. Methyl 3-anilino-1-benzyl-2-methyl-4-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (6b). Colorless prisms from EtOAc–hexane; mp 213°C; IR (KBr): 3300 (NH), 1740, 1690 (CO); ^{1}H NMR ($CDCl_3$): 1.55 (3H, s. 2-Me), 3.39 (3H, s, OMe), 4.03 (1H, d, J=7.9 Hz, NHPh, exchanged with D_2O), 4.29, 5.11 (each 1H, each d, J=15.8 Hz, CH_2Ph), 5.09 (1H, d, J=7.9 Hz, 3-H), 6.95 (1H, t, J=6.9 Hz, 7-H), 7.13–7.42 (11H, ov, Ph–H and 9-H), 7.65 (1H, dd, J=6.9, 8.6 Hz, 8-H), 9.02 (1H, d, J=6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 22.6 (2-Me), 46.3 (CH_2Ph), 52.0 (CO_2*Me*), 64.3 (3-C), 75.3 (2-C), 90.6 (3a-C), 113.2 (7-C), 114.1, 118.4, 124.5, 127.2, 128.1, 128.2, 128.4, 129.0, 138.6, 147.3 (Ph–C and 6- and 9-C), 137.2 (8-C), 153.7, 153.8 (4- and 10a-C), 163.7 (9a-C), 171.0 (CO_2Me). Anal. calcd for $C_{26}H_{24}N_4O_3$ (440.5): C, 70.89; H, 5.49; N, 12.72. Found: C, 71.11; H, 5.60; N, 12.65.

While the reaction of **3c** with **4** in refluxing toluene also gave **6c** in 93% yield, those of **3d** and **3e** with **4** gave mixtures of (**6d** and **8d**) and (**6e** and **8e**), respectively, depending on the conditions.

4.4.2. Methyl 3-anilino-1-benzyl-2-isopropyl-4-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (6c). Colorless prisms from benzene–hexane; mp 111–113°C; IR (KBr): 3300 (NH), 1735, 1690 (CO); ^{1}H NMR ($CDCl_3$): 0.89, 1.00 (each 3H, each d, J=6.9 Hz, CHMe_2), 2.76 (1H, m, CHMe$_2$), 3.32 (3H, s, OMe), 4.06 (1H, d, J=9.2 Hz, NHPh, exchanged with D_2O), 4.61, 4.78 (each 1H, each d, J=15.8 Hz, CH_2Ph), 5.28 (1H, d, J=9.2 Hz, 3-H), 6.71–7.44 (11H, ov, Ph–H and 9-H), 6.95 (1H, dt, J=1.3, 6.9 Hz, 7-H), 7.64 (1H, ddd, J=1.0, 6.9, 8.6 Hz, 8-H), 9.02 (1H, dd, J=1.0, 6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 16.6, 18.5 (CHMe_2), 32.8 (*C*HMe$_2$), 47.8 (*C*H$_2$Ph), 51.4 (OMe), 58.3 (3-C), 81.3 (2-C), 92.0 (3a-C), 113.1 (7-C), 113.9, 118.4, 124.4, 127.1, 128.1, 128.4, 128.6, 129.1, 138.1, 147.2 (Ph–C and 6- and 9-C), 137.0 (8-C), 153.4, 153.5 (4- and 10a-C), 164.6 (9a-C), 170.5 (*C*O$_2$Me). Anal. calcd for $C_{28}H_{28}N_4O_3$ (468.5): C, 71.77; H, 6.02; N, 11.96. Found: C, 71.48; H, 6.01; N, 11.90.

4.4.3. Methyl 3-anilino-1-benzyl-2-isobutyl-4-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (6d). Pale yellow prisms from EtOAc–hexane; mp 115–117°C; IR (KBr): 3300 (NH), 1735, 1690 (CO); ^{1}H NMR ($CDCl_3$): 0.67, 1.02 (each 3H, each d, J=6.6 Hz, CHMe_2), 1.66 (1H, m, CH$_2$CHMe$_2$), 2.04 (1H, dd, J=5.9, 15.1 Hz, 2-CHHCHMe$_2$), 2.27 (1H, dd, J=6.6, 15.1 Hz, 2-CHHCHMe$_2$), 3.21 (3H, s, OMe), 3.89 (1H, d, J=8.2 Hz, NHPh, exchanged with D_2O), 4.67 (2H, br s, CH_2Ph), 5.34 (1H, d, J=8.2 Hz, 3-H), 6.68–7.58 (12H, ov, Ph–H and 7- and 9-H), 7.64 (1H, ddd, J=0.6, 6.9, 8.6 Hz, 8-H), 9.01 (1H, dd, J=0.6, 6.2 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 23.5, 24.2, 24.5 (CHMe_2 and 2-*C*H$_2$CHMe$_2$), 39.2 (2-CH$_2$*C*HMe$_2$), 46.2 (*C*H$_2$Ph), 52.3 (OMe), 65.6 (3-C), 75.8 (2-C), 91.9 (3a-C), 113.2 (7-C), 113.3, 117.9, 124.2, 137.0, 127.1, 128.4, 128.9, 129.2, 139.1, 147.6 (Ph–C and 6- and 9-C), 137.1 (8-C), 153.5, 153.6 (4- and 10a-C), 163.7 (9a-C), 174.0 (*C*O$_2$Me). Anal. calcd for $C_{29}H_{30}N_4O_3$ (482.6): C, 72.18; H, 6.27; N, 11.61. Found: C, 71.93; H, 6.32; N, 11.50.

4.4.4. Methyl 3-anilino-1-benzyl-2-isobutyl-4-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (8d). Pale yellow prisms from benzene–hexane; mp 118–119°C; IR (KBr): 3300 (NH), 1740, 1690 (CO); ^{1}H NMR ($CDCl_3$): 0.69, 0.77 (each 3H, each d, J=6.3 Hz, 2-CH$_2$CHMe_2), 1.80–2.06 (3H, ov, 2-CH_2-CHMe$_2$), 3.53 (3H, s, OMe), 3.99 (1H, d, J=7.6 Hz, NHPh, exchanged with D_2O), 4.82, 4.98 (each 1H, each d, J=16.5 Hz, CH_2Ph), 5.60 (1H, d, J=7.6 Hz, 3-H), 7.14-7.40 (12H, ov, Ph–H and 7- and 9-H), 7.66 (1H, ddd, J=1.0, 6.1, 7.4 Hz, 8-H), 9.01 (1H, dd, J=1.0, 6.5 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 23.5, 24.2, 24.5 (2-CH$_2$CHMe_2 and 2-*C*H$_2$-CHMe$_2$), 39.2 (2-CH$_2$*C*HMe$_2$), 46.2 (*C*H$_2$Ph), 52.3 (OMe), 59.6 (3-C), 75.8 (2-C), 91.9 (3a-C), 113.2 (7-C), 113.3, 117.9, 124.2, 127.0, 127.1, 128.4, 128.9, 129.2, 139.1, 147.6 (Ph–C and 6- and 9-C), 137.1 (8-C), 153.5, 153.6 (4- and 10a-C), 163.7 (9a-C), 174.0 (*C*O$_2$Me). Anal. calcd for $C_{29}H_{30}N_4O_3$ (482.6): C, 72.18; H, 6.27; N, 11.61. Found: C, 71.89; H, 6.32; N, 11.53.

4.4.5. Methyl 3-anilino-1-benzyl-2-phenyl-4-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (6e). Yellow prisms from benzene–hexane; mp 129–130°C; IR (KBr): 3300 (NH), 1740, 1690 (CO); ^{1}H NMR ($CDCl_3$): 3.33 (3H, s, OMe), 4.23 (1H, d, J=7.6 Hz, NHPh, exchanged with D_2O), 4.61 (2H, br s, CH_2Ph), 5.62 (1H, d, J=7.6 Hz, 3-H), 6.54 (2H, br d, J=7.6 Hz, Ph–H), 6.68 (1H, br t, J=7.3 Hz, Ph–H), 6.97–7.48 (14H, ov, Ph–H and 7- and 9-H), 7.68 (1H, ddd, J=1.6, 5.9, 7.4 Hz, 8-H), 9.04 (1H, dd, J=1.6, 6.3 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 47.2 (*C*H$_2$Ph), 51.6 (OMe), 66.3 (3-C), 81.0 (2-C), 91.1 (3a-C), 114.2 (7-C), 118.3, 121.6, 124.6, 126.6, 127.5, 127.8, 128.0, 128.2, 128.4, 128.6, 128.8, 137.3, 137.8, 147.2 (Ph–C and 6- and 9-C), 138.8 (8-C), 153.5, 153.8 (4- and 10a-C), 163.9 (9a-C), 169.6 (*C*O$_2$Me). Anal. calcd for $C_{31}H_{26}N_4O_3$ (502.6): C, 74.08; H, 5.22; N, 11.15. Found: C, 73.88; H, 5.41; N, 11.27.

4.4.6. Methyl 3-anilino-1-benzyl-2-phenyl-4-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (8e). Yellow prisms from benzene–hexane; mp 128–129°C; IR (KBr): 3360 (NH), 1720, 1690 (CO); ^{1}H NMR ($CDCl_3$): 3.28 (3H, s, OMe), 3.46 (1H, d, J=9.6 Hz, NHPh, exchanged with D_2O), 4.39, 5.20 (each 1H, each d, J=16.5 Hz, CH_2Ph), 6.26 (1H, d, J=9.6 Hz, 3-H), 6.44 (2H, br d, J=7.9 Hz, Ph–H), 6.57 (1H, br t, J=7.9 Hz, Ph–H), 6.95–7.49 (14H, ov, Ph–H and 7- and 9-H), 7.71 (1H, ddd, J=1.6, 5.9, 7.4 Hz, 8-H), 9.01 (1H, br d, J=6.7 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 47.1 (*C*H$_2$Ph), 52.4 (OMe), 60.0 (3-C), 81.3 (2-C), 95.0 (3a-C), 113.5 (7-C), 117.4, 124.6, 126.7, 127.0, 127.7, 128.0, 128.1, 128.2, 128.3, 128.4, 128.7, 133.4, 137.3, 146.8 (Ph–C and 6- and 9-C), 138.5 (8-C), 154.1, 154.3 (4- and 10a-C), 163.8 (9a-C), 171.4 (*C*O$_2$Me). Anal. calcd for $C_{31}H_{26}N_4O_3$ (502.6): C, 74.08; H, 5.22; N, 11.15. Found: C, 73.71; H, 5.22; N, 11.07. The structure of **8e** was confirmed by X-ray crystal structure analysis.

4.5. Typical procedures for the reaction of *N*-benzyl-*N*-(3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)glycine methyl esters 3a–c with *t*-butylamine (9)

A solution of **3a** (0.16 g, 0.46 mmol) and *t*-butylamine (**9**: 0.30 mL, 2.8 mmol) in benzene (20 mL) was heated at 50°C for 84 h. The solvent was evaporated to dryness to give a residue, which was subjected to a usual work-up with a silica-gel column chromatography to afford **10a** (0.080 g, 43%) and **11a** (0.025 g, 14%) with an eluent of hexane/EtOAc (2:1), respectively.

4.5.1. Methyl 1-benzyl-3-(*t*-butylamino)-4-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (10a). Colorless needles from hexane; 108–109°C; IR (KBr): 3400 (NH), 1740, 1680 (CO); ^{1}H NMR ($CDCl_3$): 1.16 (9H, s, 3-NHCMe_3), 1.63 (1H, br, 3-NHCMe$_3$), 3.70 (3H, s, OMe), 3.90, 5.37 (each 1H, each d, J=15.2 Hz, CH_2Ph), 4.19 [1H, d, J=9.2 Hz (*cis*), 2-H], 4.86 [1H, d, J=9.2 Hz (*cis*), 3-H], 6.98 (1H, dt, J=1.3, 6.9 Hz, 7-H), 7.23–7.37 (5H, ov, Ph–H), 7.42 (1H, d, J=8.6 Hz, 9-H), 7.66 (1H, ddd, J=1.0, 6.9, 8.6 Hz, 8-H), 9.01 (1H, d, J=6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 29.4 (CMe_3), 47.1 (*C*H$_2$Ph), 50.9 (*C*Me$_3$), 51.3 (OMe), 54.0 (3-C), 69.6 (2-C), 92.8 (3a-C), 113.2 (7-C), 124.3 (9-C), 127.6, 127.9, 128.4, 128.6, 136.6, 136.8 (Ph–C and 6- and 8-C), 153.3, 153.4 (4- and 10a-C), 164.3 (9a-C), 169.8 (*C*O$_2$Me). Anal. calcd for $C_{23}H_{26}N_4O_3$ (406.5): C, 67.96; H, 6.45; N, 13.78. Found: C, 67.88; H, 6.71; N, 13.81.

4.5.2. Methyl 1-benzyl-3-(*t*-butylamino)-4-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (11a). Colorless needles from hexane; mp 89–91°C; IR (KBr): 3400 (NH), 1740, 1690 (CO); ^{1}H NMR ($CDCl_3$): 1.20 (9H, s, NHC*Me*$_3$), 3.56 (3H, s, OMe), 4.11 [1H, d, *J*=1.2 Hz (*trans*), 2-H], 4.50, 5.04 (each 1H, each d, *J*=15.2 Hz, C*H*$_2$Ph), 4.62 [1H, d, *J*=1.2 Hz (*trans*), 3-H], 6.97 (1H, dt, *J*=1.3, 6.9 Hz, 7-H), 7.23–7.34 (5H, ov, Ph–H), 7.41 (1H, dd, *J*=1.3, 8.6 Hz, 9-H), 7.65 (1H, ddd, *J*=1.0, 6.9, 8.6 Hz, 8-H), 9.01 (1H, d, *J*=6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 30.0 (3-NHC*Me*$_3$), 47.4 (*C*H$_2$Ph), 51.9 (3-NH*C*Me$_3$), 52.5 (OMe), 53.6 (3-C), 69.0 (2-C), 94.0 (3a-C), 113.7 (7-C), 124.9 (9-C), 127.9, 128.45, 128.8, 129.0, 137.1, 137.4 (Ph–C and 6- and 8-C), 154.1, 154.2 (4- and 10a-C), 164.4 (9a-C), 171.8 (*C*O$_2$Me). Anal. calcd for $C_{23}H_{26}N_4O_3$ (406.5): C, 67.96; H, 6.45; N, 13.78. Found: C, 68.18; H, 6.33; N, 13.88.

Similar reaction of **3b** and **3c** with **9** gave **10b** and **10c** as single isomers, respectively.

4.5.3. Methyl 1-benzyl-3-(*t*-butylamino)-4-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (10b). Pale yellow prisms from benzene–hexane; mp 132–133°C; IR (KBr): 3400 (NH), 1740, 1690 (CO); ^{1}H NMR ($CDCl_3$): 1.20 (10H, ov 3-N*HC*Me$_3$), 1.45 (3H, s, 2-Me), 3.58 (3H, s, OMe), 4.05, 5.10 (each 1H, each d, *J*=15.8 Hz, C*H*$_2$Ph), 4.44 (1H, s, 3-H), 6.94 (1H, dt, *J*=1.3, 6.9 Hz, 7-H), 7.20–7.38 (6H, ov, Ph–H and 9-H), 7.62 (1H, ddd, *J*=1.0, 6.9, 8.6 Hz, 8-H), 9.02 (1H, dd, *J*=1.0, 6.9 Hz); ^{13}C NMR ($CDCl_3$): 21.6 (2-Me), 30.2 (3-NHC*Me*$_3$), 46.8 (*C*H$_2$Ph), 51.0 (3-NH*C*Me$_3$), 51.4 (OMe), 58.1 (3-C), 73.5 (2-C), 92.7 (3a-C), 113.0 (7-C), 124.4 (9-C), 127.0, 127.7, 127.9, 128.3, 136.7 (Ph–C and 6-C), 138.9 (8-C), 153.3, 153.4 (4- and 10a-C), 164.1 (9a-C), 171.8 (*C*O$_2$Me). Anal. calcd for $C_{24}H_{28}N_4O_3$ (420.5): C, 68.55; H, 6.71; N, 13.32. Found: C, 68.59; H, 6.84; N, 13.33.

4.5.4. Methyl 1-benzyl-3-(*t*-butylamino)-2-isopropyl-4-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (10c). Pale yellow needles from benzene–hexane; mp 128–130°C; IR (KBr): 3300 (NH), 1740, 1690 (CO); ^{1}H NMR ($CDCl_3$): 0.84, 0.90 (each 3H, each d, *J*=6.6 Hz, 2-CH*Me*$_2$), 1.22 (9H, s, 3-NHC*Me*$_3$), 1.50 (1H, br, 3-N*H*CMe$_3$), 2.57 (1H, m, 2-C*H*Me$_2$), 3.68 (3H, s, OMe), 4.12, 5.10 (each 1H, each d, *J*=16.5 Hz, C*H*$_2$Ph), 4.53 (1H, s, 3-H), 6.93 (1H, dt, *J*=1.7, 6.9 Hz, 7-H), 7.20–7.36 (6H, ov, Ph–H and 9-H), 7.60 (1H, ddd, *J*=1.7, 6.9, 8.6 Hz, 8-H), 9.03 (1H, dd, *J*=1.7, 6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 16.4, 19.7 (2-CH*Me*$_2$), 30.4 (3-NHC*Me*$_3$), 31.5 (3-NH*C*Me$_3$), 33.0 (2-*C*HMe$_2$), 50.7 (*C*H$_2$Ph), 51.1 (OMe), 59.6 (3-C), 85.9 (2-C), 93.6 (3a-C), 112.8 (7-C), 124.5 (9-C), 126.5, 127.7, 127.8, 128.2, 139.2 (Ph–C and 6-C), 136.4 (8-C), 153.0, 153.1 (4- and 10a-C), 165.3 (9a-C), 171.1 (*C*O$_2$Me). Anal. calcd for $C_{26}H_{32}N_4O_3$ (448.6): C, 69.62; H, 7.19; N, 12.49. Found: C, 69.28; H, 7.47; N, 12.15.

4.6. Conversion of pyrido[1,2-*a*]pyrrolo[2,3-*d*]-pyrimidine-2-carboxylates 6

4.6.1. Thermal isomerization of 6d to 8d. A solution of **6d** (0.080 g, 0.21 mmol) in xylene (5 mL) was heated at reflux for 5 h and a usual work-up with a silica-gel column chromatography to give **8d** (0.56 g, 70%) and the recovered **6d** (0.005 g, 6%).

4.7. General procedures for the treatment of 6 with PTSA

A solution of **6b** (0.27 g, 0.60 mmol) and PTSA monohydrate (0.11 g, 0.60 mmol) in toluene (15 mL) was heated at reflux for 3 h and a usual work-up with a silica-gel column chromatography gave **8b** (0.063 g, 23%) together with an intractable mixture of products.

4.7.1. Methyl 3-anilino-1-benzyl-2-methyl-4-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (8b). Colorless needles from benzene–hexane; mp 284°C; IR (KBr): 3360 (NH), 1720, 1690 (CO); ^{1}H NMR ($CDCl_3$): 1.02 (3H, s, 2-Me), 3.59 (1H, br, 3-N*H*Ph, exchanged with D_2O), 3.65 (3H, s, OMe), 4.30, 5.17 (each 1H, each d, *J*=15.8 Hz, C*H*$_2$Ph), 4.57 (1H, s, 3-H), 6.57–7.33 (11H, ov, Ph–H and 7-H), 7.43 (1H, br d, *J*=8.6 Hz, 9-H), 7.64 (1H, ddd, *J*=1.0, 6.9, 8.6 Hz, 8-H), 9.00 (1H, dd, *J*=1.0, 6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 19.1 (2-Me), 45.8 (*C*H$_2$Ph), 50.8 (3-C), 52.6 (OMe), 75.2 (2-C), 94.3 (3a-C), 113.1 (7-C), 115.2, 124.5, 126.9, 127.3, 127.4, 128.1, 128.3, 129.7, 129.8, 139.2, 145.6 (Ph–C and 6- and 7-C), 136.8 (8-C), 152.3, 153.5 (4- and 10a-C), 165.1 (9a-C), 175.2 (*C*O$_2$Me). Anal. calcd for $C_{26}H_{24}N_4O_3$ (440.5): C, 70.89; H, 5.49; N, 12.72. Found: C, 70.58; H, 5.71; N, 12.53.

Similar reactions of **6c** and **6e** with PTSA monohydrate (1.0 equiv.) gave **8c** and **8e** in 60 and 62% yields, respectively.

4.7.2. Methyl 3-anilino-1-benzyl-2-isopropyl-4-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (8c). Pale yellow needles from ethanol as a 1:1 molecular complex of **8c** and ethanol; mp 118°C; IR (KBr): 3480 (OH), 3400 (NH), 1740, 1680 (CO); ^{1}H NMR ($CDCl_3$): 0.92, 1.07 (each 3H, each d, *J*=6.9 Hz, 2-CH*Me*$_2$), 2.54 (1H, m, 2-C*H*Me$_2$), 3.04 (1H, s, OMe), 3.55 (1H, br, 3-N*H*Ph), 4.43, 4.97 (each 1H, each d, *J*=15.8 Hz, C*H*$_2$Ph), 4.56 (1H, s, 3-H), 6.55 (2H, br d, *J*=7.1 Hz, Ph–H), 6.83–7.01, 7.22–7.47 (total 10H, ov, Ph–H and 7- and 9-H), 7.62 (1H, ddd, *J*=1.0, 6.9, 8.6 Hz, 6-H), 8.98 (1H, br d, *J*=6.9 Hz, 6-H), [CH_3CH_2OH: 1.18 (3H, t, *J*=7.2 Hz, Me), 3.64 (2H, q, *J*=7.2 Hz, MeC*H*$_2$-OH), 3.4–3.8 (br, OH)]; ^{13}C NMR ($CDCl_3$): 16.8, 19.2 (2-CH*Me*$_2$), 35.5 (2-C*H*Me$_2$), 49.0 (C*H*$_2$Ph), 51.1, 51.2 (OMe and 3-C), 82.8 (2-C), 93.5 (31-C), 113.2 (7-C), 114.6, 124.3, 126.6, 127.6, 128.0, 128.1, 128.3, 129.7, 138.8, 145.5 (Ph–C and 6- and 9-C), 136.3 (8-C), 152.9 (4- and 10a-C), 165.4 (9a-C), 170.9 (*C*O$_2$Me), [CH_3CH_2OH: 18.2 (Me), 58.0 (MeC*H*$_2$OH)]; MS (EI) *m*/*z*: 468 (M^+). Anal. calcd for $C_{28}H_{28}N_4O_3$+C_2H_5OH (546.6): C, 70.02; H, 6.66; N, 10.89. Found: C, 70.22; H, 6.47; N, 11.19.

Similar reactions of **10b** and **10c** with PTSA monohydrate (0.3–1.0 equiv.) were also examined, but in every case, mixtures of intractable products were obtained except for **11b** (22%).

4.7.3. Methyl 1-benzyl-3-(*t*-butylamino)-2-methyl-4-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (11b). Colorless needles from hexane;

mp 134–135°C; IR (KBr): 3400 (NH), 1720, 1680 (CO); ^{1}H NMR ($CDCl_3$): 1.20 (10H, ov 3-NH*CMe*$_3$), 1.48 (3H, s, 2-Me), 3.51 (3H, s, OMe), 4.51, 4.90 (each 1H, each d, J=15.8 Hz, C*H*$_2$Ph), 4.44 (1H, s, 3-H), 6.94 (1H, dt, J=1.3, 6.9 Hz, 7-H), 7.20–7.38 (6H, ov, Ph–H and 9-H), 7.62 (1H, ddd, J=1.0, 6.9, 8.6 Hz, 8-H), 9.02 (1H, dd, J=1.0, 6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 17.0 (2-Me), 30.2 (NHC*Me*$_3$), 45.5 (*C*H$_2$Ph), 50.1 (NH*C*Me$_3$), 52.3 (OMe), 58.1 (3-C), 74.3 (2-C), 93.7 (3a-C), 113.0 (7-C), 124.8 (9-C), 126.9, 127.6, 128.1, 128.3, 136.6 (Ph–C and 6-C), 138.9 (8-C), 153.3, 153.5 (4- and 10a-C), 163.8 (9a-C), 175.2 (*C*O$_2$Me). Anal. calcd for $C_{24}H_{28}N_4O_3$ (420.5): C, 68.55; H, 6.71; N, 13.32. Found: C, 68.59; H, 6.84; N, 13.33.

4.8. General procedures for the reaction of *N*-benzyl-*N*-(3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)valine methyl ester (3c) with chiral primary amines 12 and 13

A solution of **3c** (0.67 g, 1.7 mmol) and (*R*)-(+)-1-phenylethylamine (**12**: 0.24 mL, 1.9 mmol) in toluene (3 mL) was heated under reflux for 7 h and a usual work-up with a silica-gel column chromatography (hexane/EtOAc=4:1) to give **14c** (0.61 g, 72%).

4.8.1. Methyl 1-benzyl-2-isopropyl-3-(1-phenylethyl)-amino-4-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (14c). Pale yellow oil; IR (NaCl): 3400 (NH), 1730, 1680 (CO); ^{1}H NMR ($CDCl_3$): 0.51 (3H, d, J=6.6 Hz, 2-CH*Me*Me), 0.58 (3H, d, J=6.3 Hz, 2-CHMe*Me*), 1.31 (3H, d, J=6.1 Hz, 3-NHCH*Me*Ph), 2.25 (1H, m, 2-C*H*Me$_2$), 3.41 (3H, s, OMe), 4.20 (1H, s, 3-H), 4.49, 4.60 (each 1H, each d, J=15.5 Hz, C*H*$_2$Ph), 4.86 (1H, q, J=6.1 Hz, 3-NHC*H*MePh), 6.97 (1H, ddd, J=1.3, 6.9, 8.3 Hz, 8-H), 7.19–7.66 (12H, ov, Ph–H and 7- and 9-H), 9.13 (1H, dd, J=1.3, 6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 16.4, 17.9 (2-CHMe2), 25.1 (3-NHCH*Me*Ph), 32.0 (2-*C*HMe$_2$), 47.5 (*C*H$_2$Ph), 51.0 (OMe), 57.1 (3-NH*C*HMePh), 59.0 (3-C), 80.8 (2-C), 95.0 (3a-C), 113.0 (7-C), 124.4, 126.7, 127.0, 127.9, 128.0, 128.1, 128.3, 128.7, 136.6, 138.1, 141.9 (Ph–C and 6-, 8-, and 9-C), 153.0, 154.0 (4- and 10a-C), 164.6 (9a-C), 171.0 (*C*O$_2$Me); $[\alpha]_D$ (22°C)=−157.3° (*c* 2.0, $CHCl_3$). Anal. calcd for $C_{30}H_{32}N_4O_3$ (496.6): C, 72.55; H, 6.50; N, 11.28. Found: C, 72.14; H, 6.59; N, 11.08.

4.8.2. Methyl 1-benzyl-2-isopropyl-3-[1-(1-naphthyl)-ethyl]amino-4-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-2-carboxylate (15c). Pale yellow oil; IR (NaCl): 3400 (NH), 1740, 1680 (CO); ^{1}H NMR ($CDCl_3$): 0.69 (3H, d, J=6.9 Hz, 2-CH*Me*Me), 0.75 (3H, d, J=6.6 Hz, 2-CHMe*Me*), 1.46 [3H, d, J=6.3 Hz, 3-NHCH*Me*(1-Naphthyl)], 2.36 [1H, br, 3-N*H*CHMe(1-Naphthyl)], 2.56 (1H, m, 2-C*H*Me$_2$), 3.41 (3H, s, OMe), 4.49, 4.70 (each 1H, each d, J=15.8 Hz, C*H*$_2$Ph), 4.65 (1H, s, 3-H), 5.31 [1H, q, 3-NHC*H*Me(1-Naphthyl)], 6.99 (1H, ddd, J=1.3, 6.9, 8.0 Hz, 8-H), 7.19–8.29 (14H, ov, Ar-H and 7- and 9-H), 9.11 (1H, ddd, J=1.0, 1.3, 6.2 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 17.0, 18.2 (2-CH*Me*$_2$), 23.7 [3-NHCH*Me*(1-Naphthyl)], 32.5 (2-*C*HMe$_2$), 47.7 (C*H*$_2$Ph), 51.4 (OMe), 58.8, 59.1 [3-NH*C*HMe(1-Naphthyl) and 2-C], 81.1 (2-C), 93.8 (3a-C), 113.0 (7-C), 123.6, 124.4, 125.1, 125.6, 125.9, 127.0, 127.4, 128.0 128.1, 128.3, 128.6, 128.7, 131.1, 133.9, 136.7, 138.2, 141.8 (Ar-C and 6-, 8-, and 9-C), 153.1, 154.1 (4- and 10a-C), 164.1 (9a-C), 171.3 (*C*O$_2$Me); $[\alpha]_D$ (23°C)=−77.5° (*c* 2.0, $CHCl_3$). Anal. calcd for $C_{34}H_{34}N_4O_3$ (546.6): C, 74.70; H, 6.27; N, 10.25. Found: C, 74.99; H, 6.39; N, 10.18.

4.9. Single-crystal X-ray structure determination of 8e[8]

Single crystals (prisms) of compound **8e** for X-ray diffraction studies were recrystallized from 2-propanol. A crystal of approximate dimensions 0.20×0.30×0.62 mm was used for data collection. All measurements were made on a Rigaku AFC55 diffractometer by employing graphite-monochromated Mo Kα radiation. The unit-cell dimensions were obtained by least-squares analysis of 25 reflections within the range of $20.10<2\theta<24.01°$. The crystal data for **8e** are given: crystal system: monoclinic; space group: $P2_1/n$ (#14); cell constants: a: 11.268(4) Å, b: 15.068(2) Å, c: 15.644(3) Å, V: 2508.2(9) Å^3, β: 109.22(2)°; Z value: 4; Dc: 1.331 g cm^{-3}. The $\omega-2\theta$ scan technique to a maximum 2θ-value of 55.0° was used and scans of $(1.00+0.30 \tan\theta)°$ were made at a speed of 16° min^{-1} for **8e**. A total of 6204 observed reflections (unique: 5999; R_{int}=0.059) was collected. All calculations were performed using TEXAN program.[9] Atoms other than hydrogen were refined anisotropically. The structure of compound **8e** was solved by direct method (SIR92)[10] and refined by least-squares to R 0.055 (R_w 0.042).

4.10. Optical purity of 6c in the reaction of *N*-benzyl-*N*-(3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)valine methyl ester (3c) with aniline (4)

HPLC measurements were performed with a Hitachi L-6200 (equipmented with L-4000 UV detector and D-2500 data processor) and a Dicel Chiralcel OD-H (id 4.6×250 mm) column; pressure: 12 kgf cm^{-2}; flow rate: 0.3 mL min^{-1}; temperature: 21°C. Crude (*rac*)-**6c** and **6c** were used without recrystallization. For (*rac*)-**6c**, two peaks (retention time: 66.0 and 74.4 min). The enantiomer excess (ee) of **6c** was determined by the area of the two peaks [retention time: 60.3 min (91.2) and 73.2 min (3.0)].

Acknowledgements

The present work was partially supported by Grant-in-Aid for Scientific Researchs on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' (13029082 and 14044073) and Grant-in-Aid for Scientific Research (C-13650905) from the Ministry of Education, Science, Sports and Culture, Japan.

References

1. (a) Noguchi, M.; Mizukoshi, T.; Kakehi, A. *Tetrahedron* **1996**, *52*, 13081. (b) Noguchi, M.; Mizukoshi, T.; Uchida, T.; Kuroki, Y. *Tetrahedron* **1996**, *52*, 13097. (c) Noguchi, M.; Mizukoshi, T.; Nakagawa, S.; Kakehi, A. *Tetrahedron* **1996**, *52*, 13111.
2. (a) Noguchi, M.; Yamada, H.; Takamura, S.; Uchida, T.; Hironaka, M.; Kakehi, A.; Yamamoto, H. *Eur. J. Org. Chem.* **2000**, 1489. (b) Noguchi, M.; Yamada, H.; Tamamura, S.;

Okada, K.; Kakehi, A.; Yamamoto, H. *Tetrahedron* **2000**, *56*, 1299. (c) Noguchi, M.; Matsushita, R.; Takamura, S.; Uchida, T.; Kakehi, A.; Shiro, M.; Yamamoto, H. *Tetrahedron Lett.* **2000**, *41*, 8489.

3. For reviews: (a) Suschitzky, H.; Meth-Cohn, O. *Adv. Heterocycl. Chem.* **1972**, *13*, 211. (b) Meth-Cohn, O. *Adv. Heterocycl. Chem.* **1996**, *65*, 1.
4. (a) Jiang, S.; Janousek, Z.; Viehe, H. G. *Bull. Soc. Chim. Belg.* **1993**, *102*, 663. (b) Jiang, S.; Janousek, Z.; Viehe, H. G. *Tetrahedron Lett.* **1994**, *35*, 1185. (c) De Boeck, B.; Jiang, S.; Janousek, Z.; Viehe, H. G. *Tetrahedron* **1994**, *50*, 7075. (d) De Boeck, B.; Janousek, Z.; Viehe, H. G. *Tetrahedron* **1995**, *51*, 13239.
5. For a review: Verboom, W.; Reinhoudt, D. R. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 311.
6. (a) Tsuge, O.; Kanemasa, S.; Takenaka, S. *Chem. Lett.* **1985**, 355. (b) Tsuge, O.; Kanemasa, S.; Takenaka, S. *Bull. Chem. Soc. Jpn* **1985**, *58*, 3137. (c) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K. *Chem. Lett.* **1986**, 1271. (d) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K.; Takenaka, S.; Ueno, K. *Bull. Chem. Soc. Jpn* **1987**, *60*, 4067.
7. George, T.; Mehta, D. V.; Dabholkar, D. A. *J. Org. Chem.* **1971**, *36*, 2192.
8. Crystallographic data for **8e** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 202 241. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: 144-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
9. TEXANE-TEXRAY, Crystal Structure Analysis Package, Molecular Structures Corporation, 1997–1999.
10. Altomare, A.; Cascarano, M.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Cryst.* **1994**, *26*, 343.