Radical Addition Reaction of Brominated Active Methylene Compounds to Enol Ethers Using 2,2′-Azobis(2,4-dimethyl-4-methoxyvaleronitrile) (V-70) as an Initiator

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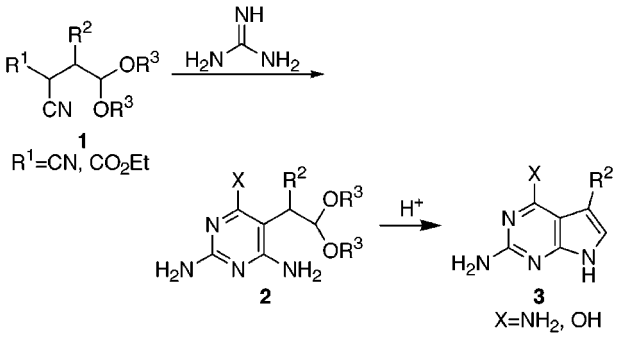
Pyrrolo[2,3-*d*]pyrimidine derivatives have been noted as 7-deaza analogues of naturally occurring purines or their nucleosides. A number of pyrrolo[2,3-*d*]pyrimidine compounds are being presented for potential biological activities, such as anticancer or antiviral.[1] Therefore, many synthetic methods for pyrrolo[2,3-*d*]pyrimidines have been developed.[2] Several pyrrolo[2,3-*d*]pyrimidine compounds such as 7-deazaguanine (**3**, X = NH_2, OH) are prepared starting from alkylated active methylene compounds (**1**) having an acetal moiety via pyrimidine intermediates (**2**)[3] (Scheme 1). Though this synthetic pathway has been used as the common and effective route, severe reaction conditions or multistep sequences are required to obtain the starting materials.[3a,b]

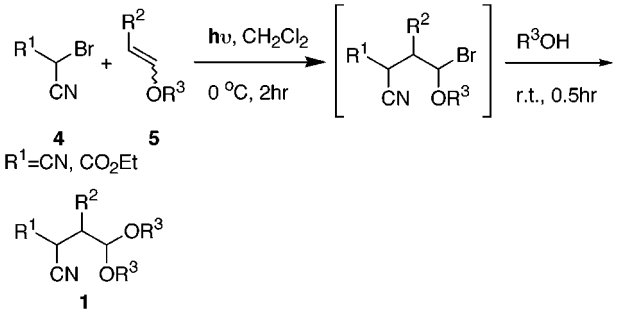
Recently, Miwa and co-workers[4] reported the syntheses of pyrrolo[2,3-*d*]pyrimidine antifolates,[5,6] a photoinduced radical addition reaction of brominated active methylene compounds (**4**) to enol ethers and subsequent alcoholysis (Scheme 2). This photoirradiation method is performed under mild conditions in high yields, but suffer from practical difficulties for a large-scale production.

The use of a radical initiator such as azobisisobutyronitrile (AIBN) is one effective and alternative means to avoid the use of a photochemical reaction. However, the applicability of AIBN in the radical addition reactions of halogenated active methylene compounds to enol ethers seems limited, as it was reported that a radical addition reaction of iodomethylmalononitrile to ethyl 1-propenyl ether in the presence of AIBN was unsuccessful.[7] The use of Lewis acid Et_3B, which is known to be an useful radical initiator at low temperature,[8] seems to be unsuitable for acid sensitive compounds.

Scheme 1



Scheme 2



Very recently, we reported that 2,2′-azobis(2,4-dimethyl-4-methoxyvaleronitrile) (V-70)[9] (Figure 1) serves as an effective initiator for the addition reactions of bromomalononitrile to various olefins including some enol ethers at room temperature.[10] In this paper, we report the results of our further investigation on the V-70-initiated radical addition reaction of brominated active methylene compounds (**4**) to enol ethers.

We first examined the addition reactions of bromomalononitrile to a β-substituted enol ethers using various radical initiators. The results are shown in Table 1. Treatment of **4a** (1 equiv) with methyl 4-(5-methoxy-4-pentenyl)benzoate (**5a**) (1 equiv) in the presence of V-70 (10 mol %) in CH_2Cl_2 at room temperature for 2 h and subsequent methanolysis afforded somewhat preferentially the desired acetal adduct (**1a**) (Table 1, entry 1).

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(9) 2,2′-Azobis(2,4-dimethyl-4-methoxyvaleronitrile) (V-70) is known as an effective initiator in the synthesis of polymers and is commercially available from Wako Pure Chemical Ind., Ltd., Japan. The abbreviation in parentheses is its trade name. This compound should be stored below −10 °C to prevent any decomposition. Half-life data indicates that V-70 is more unstable than AIBN in solvents. The temperature at which half of V-70 and AIBN is decomposed in 10 h in toluene: V-70, 30 °C; AIBN, 65 °C. V-70 is stable in a refrigerator for a few months in a solid state.

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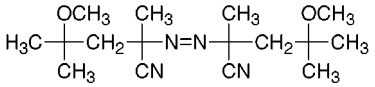
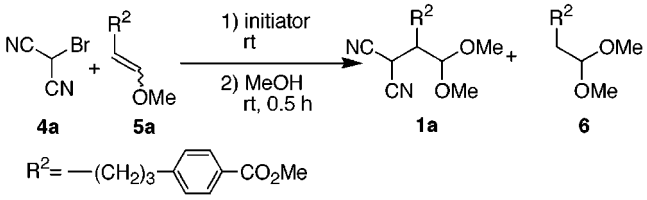


2,2'-azobis(2,4-dimethyl-4-methoxyvarelonitrile)
(V-70)

Figure 1.

Table 1. Radical Addition Reactions of 4a to 5a Using V-70 or V-70L as an Initiator



entry	initiator (mol %)	solvent	time (h)	yield (%)[a] 1a	6
1	V-70 (10)	CH_2Cl_2	2	44	36
2	V-70 (15)	CH_2Cl_2	12	55	30
3	V-70 (25)	CH_2Cl_2	12	76	18
4	V-70L (25)	CH_2Cl_2	12	80	11
5	V-70 (25)	toluene	12	83	9
6	V-70L (15)	toluene	24	88	3
7	V-70L (25)	MeOH	24	6	78
8	V-70L (25)	THF	24	56	39
9	V-70L (25)	IPE[b]	24	46	52
10	AIBN (25)	CH_2Cl_2	24	2	7
11	Et_3B (10)	CH_2Cl_2	6	0	79
12	none	CH_2Cl_2	12	0	89

[a] Product yields were determined by HPLC. [b] Isopropyl ether.

The yield of **1a** was improved to 76% by increasing the amount of V-70 and extending the reaction time (Table 1, entries 1−3). V-70 is a mixture of diastereomers (V-70L and V-70H),[11] and we previously reported that V-70L is a better initiator than V-70H.[10b] Therefore, we used V-70L in the addition reactions. By using V-70L, the yields of **1a** were increased (Table 1, entries 4 and 6). Thus, the reaction of **4a** and **5a** in toluene using 15 mol % of V-70L at room temperature for 24 h gave **1a** in 88% yield (Table 1, entry 6). The influence of the solvent in the reaction was then examined (Table 1, entries 7−9), and methylene chloride and toluene were found to be favorable solvents for the present radical reaction. The reaction in methanol afforded preferentially undesired product **6** (Table 1, entry 7), and the use of AIBN or Et_3B as initiator also gave **6** selectively (Table 1, entries 10 and 11). The reaction in the absence of an initiator afforded only **6** (Table 1, entry 12). The undesired **6** was obtained by methanolysis of unreacted **5a** in the second step of the reactions.

In addition, we investigated the V-70-induced radical addition reactions of ethyl bromocyanoacetate to β-substituted or β-unsubstituted enol ethers together with those for the reactions. The results are shown in Table 2. All of the addition reactions were carried out in toluene or methylene chloride at room temperature and were found to proceed smoothly, providing subsequent alcoholysis the corresponding acetal adducts (**1a**−**f**) in good yields.

These acetal adducts were easily purified by column chromatography on silica gel. Acetals **1a**−**d** were identified by their spectral data. The structures of **1e**,**f** were confirmed by comparison with the corresponding authentic samples.[3a,c]

Next, the conversion of **1a** into pyrrolo[2,3-*d*]pyrimidine **3b** was examined in order to obtain an intermediate for the synthesis of pyrrolo[2,3-*d*]pyrimidine antifolate TNP-351 (**3c**,[4] Scheme 3). The condensation of **1a** with guanidine hydrochloride in the presence of potassium *tert*-butoxide and subsequent cyclization with hydrochloric acid afforded methyl ester **3a** in 76% yield. Hydrolysis of **3a** with sodium hydroxide in aqueous methanol gave acid **3b**. Subsequent conversion of **3b** to TNP-351 has already been reported.[4] In conclusion, radical addition reactions of brominated active methylene compounds (**4a**,**b**) to enol ethers (**5a**−**c**) using V-70 or V-70L as initiator smoothly proceeded at room temperature, and acetal adducts (**1a**−**f**) were obtained in good yields by subsequent alcoholysis. Since these acetal adducts serve as starting materials for the synthesis of pyrrolo[2,3-*d*]-pyrimidine derivatives, such as the present method, affords a convenient and practical route to these derivatives compared with the use of a photochemical reaction.

Experimental Section

IR spectra were recorded using KBr disks. ^{1}H NMR spectra were measured in $CDCl_3$ on 270 MHz spectrometer with tetramethylsilane as the internal standard. Wakogel C-200 silica gel (Wako Pure Chemical Industries, Ltd.) was used for column chromatography. Wakosil 5C18 (4.6 mm × 150 mm) (Wako Pure Chemical) was used for a high-pressure liquid chromatography (HPLC). AIBN and V-70 were used after being dried. V-70L and V-70H were separated from commercial V-70 according to the procedure described in the literature.[11] Methylene chloride was used after being washed with water and dried with molecular sieves 4A overnight. Brominated active methylene compounds (**4a**,**b**) were prepared by the reported methods.[11,12]

Preparation of β-Substituted Enol Ethers (5a,b). The title compounds were obtained from methyl 4-formylbenzoate according to the method of Miwa.[4]

Methyl 4-(5-Methoxy-4-pentenyl)benzoate (5a): colorless oil; IR (KBr) 1716 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm) 7.94 (2H, d, J = 8 Hz), 7.24 (2H, d, J = 8 Hz), 6.28 and 5.90 (total 1H, each d, J = 13 and 6 Hz), 4.71 and 4.34 (total 1H, each m), 3.89 (3H, s), 3.58 and 3.50 (total 3H, each s), 2.67 (2H, m), 2.09 and 1.95 (total 2H, each m), 1.69 (2H, m). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.34; H, 7.38.

Methyl 4-(4-Methoxy-3-butenyl)benzoate (5b): colorless oil; IR (KBr) 1716 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm) 7.92 (2H, d, J = 8 Hz), 7.22 (2H, d, J = 8 Hz), 6.26 and 5.86 (total 1H, each d, J = 13 and 6 Hz), 4.68 and 4.30 (total 1H, each m), 3.78 (3H, s), 3.55 and 3.46 (total 3H, each s), 2.38 and 2.21 (total 2H, each m), 2.07 and 1.93 (total 2H, each m). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.64; H, 7.40.

Estimation of Product Yields of Radical Addition Reactions of 4a to 5a by HPLC Analysis. Typical Procedure. A mixture of **4a** (0.62 g, 4.27 mmol), **5a** (1.0 g, 4.27 mmol), and V-70 (0.33 g, 1.07 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature (25 °C) for 12 h under nitrogen atmosphere. The mixture was diluted with MeOH (2 mL), stirred for 30 min, and poured into cold water (10 mL) containing K_2CO_3 (1.26 g). The resulting organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was analyzed by HPLC [mobile phase, CH_3CN-H_2O containing 0.006 M sodium dodecyl sulfate and 0.02 M KH_2PO_4 (65:35, v/v); flow rate, 1 mL/min; detection, UV 254 nm]. The results are listed in Table 1.

(11) In this paper, the isomer melting at 58 °C corresponding to V-70L and the isomer melting at 107 °C corresponding to V-70H were designated. The separation of these epimers is readily possible through the difference of the solubility in diethyl ether.[12] V-70L is a racemic-form and V-70H is a meso-form.[10b,12c]

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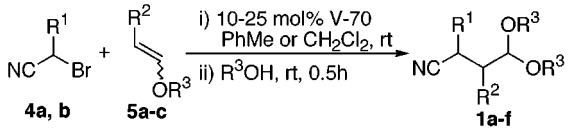
Table 2. Radical Addition Reactions of 4a,b to 5a−c

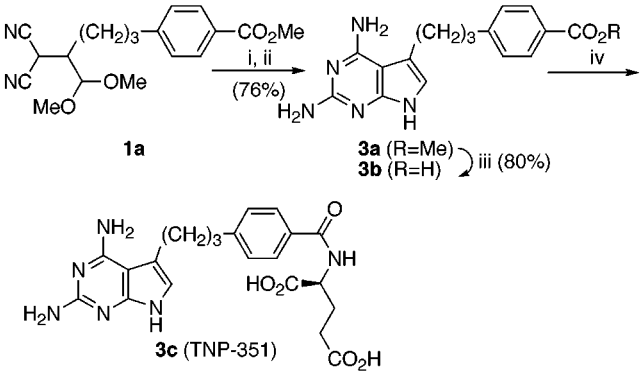


4a, b 5a-c 1a-f

	substrate					
	4	**5**				
entry	R^1	R^2	R^3	reaction conditions[b]	product **1**	yield[a] (%)
1	**4a** CN	**5a** $(CH_2)_3C_6H_4CO_2Me$ (*p*)	Me	A	**1a**	83
2	**4b** CO_2Et	**5a** $(CH_2)_3C_6H_4CO_2Me$ (*p*)	Me	A	**1b**	67
3	**4a** CN	**5b** $(CH_2)_2C_6H_4CO_2Me$ (*p*)	Me	A	**1c**	81
4	**4b** CO_2Et	**5b** $(CH_2)_2C_6H_4CO_2Me$ (*p*)	Me	A	**1d**	71
5	**4a** CN	**5c** H	Et	B	**1e**	71
6	**4b** CO_2Et	**5c** H	Et	B	**1f**	61

[a] Isolated yield. [b] (A) (i) 25 mol % V-70L, PhMe, rt, 24 h; (ii) MeOH, rt, 0.5 h. (B) (i) 10 mol% V-70, CH_2Cl_2, rt, 2 h; (ii) EtOH, rt, 0.5 h.

Scheme 3[a]



[a] Key: (i) $NH_2C(=NH)NH_2 \cdot HCl$, ^{t}BuOK, ^{t}BuOH, reflux, 2 h; (ii) HCl, reflux, 2 h; (iii) NaOH, aqueous MeOH (50%), reflux, 2 h; (iv) ref 4.

Preparation of Acetal Adducts (1a−d). Typical Procedure. A mixture of **4a** (0.62 g, 4.27 mmol), **5a** (1.0 g, 4.27 mmol), and V-70L (0.33 g, 1.07 mmol) in toluene (10 mL) was stirred at room temperature (25 °C) for 24 h under nitrogen atmosphere. The mixture was diluted with MeOH (2 mL), stirred for further 30 min, and poured into cold water (10 mL) containing K_2CO_3 (1.26 g). The resulting organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography [eluent; *n*-hexane−AcOEt (4:1, v/v)] to give **1a** (1.17 g) in 83% yield.

Methyl 4-[5,5-Dicyano-4-(dimethoxymethyl)pentyl]benzoate (1a): colorless oil; IR (KBr) 2255 (CN), 1719 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm) 7.96 (2H, d, J = 8 Hz), 7.25 (2H, d, J = 8 Hz), 4.31 (1H, d, J = 5 Hz), 4.13 (1H, d, J = 4 Hz), 3.90 (3H, s), 3.45 (3H, s), 3.39 (3H, s), 2.73 (2H, t, J = 8 Hz), 2.32−2.22 (1H, m), 1.95−1.60 (2H, m), 1.60−1.51 (2H, m). Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.78; H, 6.91; N, 8.12.

Ethyl 6-[4-(Methoxycarbonyl)phenyl]-2-cyano-3-(dimethoxymethyl) hexanoate (1b): 67% yield; diastereomeric mixture (1:1); colorless oil; IR (KBr) 2250 (CN), 1720 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm) 7.95 and 7.94 (total 2H, each d, J = 8 Hz), 7.24 and 7.23 (total 2H, each d, J = 8 Hz), 4.37 and 4.25 (total 1H, each d, J = 6 and 7 Hz), 4.26 and 4.25 (total 2H, each q, J = 7 Hz), 3.90 (3H, s), 3.94 and 3.56 (total 1H, each d, J = 3 Hz), 3.40 (3H, s), 3.37 and 3.36 (total 3H, each s), 2.76−2.68 (2H, m), 2.63−2.44 (1H, m), 1.81−1.56 (4H, m), 1.28 and 1.25 (total 3H, m). Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.78; H, 7.51; N, 3.65.

Methyl 4-[4,4-Dicyano-3-(dimethoxymethyl)butyl]benzoate (1c): 81% yield; colorless oil; IR (KBr) 2255 (CN), 1720 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm) 7.98 (2H, d, J = 8 Hz), 7.29 (2H, d, J = 8 Hz), 4.36 (1H, d, J = 5 Hz), 4.15 (1H, d, J = 4 Hz), 3.80 (3H, s), 3.46 (3H, s), 3.39 (3H, s), 2.88 (2H, t, J = 8 Hz), 2.36−2.20 (1H, m), 2.20−1.80 (2H, m). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.74; H, 6.61; N, 8.62.

Ethyl 5-[4-(Methoxycarbonyl)phenyl]-2-cyano-3-(dimethoxymethyl) pentanoate (1d): 71% yield; diastereomeric mixture (1:1); colorless oil; IR (KBr) 2250 (CN), 1720 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm) 7.94 and 7.93 (total 2H, each d, J = 8 Hz), 7.26 and 7.25 (total 2H, each d, J = 8 Hz), 4.41 and 4.31 (total 1H, each d, J = 6 and 7 Hz), 4.25 and 4.24 (total 2H, each q, J = 7 Hz), 3.81 (3H, s), 3.96 and 3.66 (total 1H, each d, J = 3 Hz), 3.40 and 3.36 (total 3H, each s), 3.37and 3.31 (total 3H, each s) 2.80−2.68 (2H, m), 2.62−2.42 (1H, m), 2.18−1.76 (2H, m), 1.31 and 1.28 (total 3H, each t, J = 7 Hz). Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.57; H, 6.61; N, 3.98.

Reaction of 4a to 5a in the Absence of Initiator. A mixture of **4a** (0.62 g, 4.27 mmol) and **5a** (1.0 g, 4.27 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature (25 °C) under nitrogen atmosphere for 12 h. The ^{1}H NMR analysis of the reaction mixture at 12 h showed that the unreacted **4a** was present in the reaction mixture (ca. 95%). The mixture was diluted MeOH (2 mL) and stirred further for 60 min at room temperature. Cold water (10 mL) containing K_2CO_3 (1.26 g) was poured into the mixture, and the resulting organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography [*n*-hexane−AcOEt (4:1, v/v)] to give methyl 4-(5,5-dimethoxypentyl)benzoate (**6**) (1.0 g) in 89% yield as colorless oil: IR (KBr) 1720 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm) 7.96 (2H, d, J = 8 Hz), 7.23 (2H, d, J = 8 Hz), 4.36 (1H, d, J = 5 Hz), 3.90 (3H, s), 3.30 (6H, s), 2.67 (2H, t, J = 8 Hz), 1.66−1.50 (6H, m). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.34, H, 8.26.

Preparation of Acetal Adducts (1e,f). Typical Procedure. A mixture of **4a** (1.45 g, 10 mmol), **5c** (1.45 g, 20 mmol), and V-70 (308 mg, 1 mmol) in CH_2Cl_2 (25 mL) was stirred at room temperature (25 °C) for 2 h under nitrogen atmosphere. The mixture was diluted with EtOH (5 mL) and stirred further for 30 min. Cold water (15 mL) containing K_2CO_3 (2.7 g) was poured into the mixture, and the resulting organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography [eluent, *n*-hexane−AcOEt (5:1, v/v)] to give **1e** (1.25 g) in 76% yield.

2-Cyano-4,4-diethoxybutyronitrile (1e): colorless oil; IR (KBr) 2220 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm) 4.63 (1H, t, J = 8 Hz), 3.94 (1H, t, J = 8 Hz), 3.65 (2H, m), 3.51 (2H, m), 2.21 (2H, m), 1.18 (6H, m).

Ethyl 2-Cyano-4,4-diethoxybutyrate (1f): 61% yield; colorless oil; IR (KBr) 2225 (CN), 1710 (CO_2Et) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm) 4.35 (1H, t, J = 8 Hz), 4.27 (2H, q, J = 8 Hz), 3.67 (4H, m), 3.47 (1H, m), 2.21 (2H, m), 1.34 (3H, t, J = 8 Hz), 1.22 (6H, t, J = 8 Hz).

Methyl Ester 3a. To a suspension of guanidine hydrochloride (3.04 g, 31.8 mmol) in *tert*-BuOH (30 mL) was added *tert*-BuOK (3.93 g, 35.0 mmol) under nitrogen atmosphere, and the mixture was stirred for 15 min at room temperature. A solution of **1a** (10.5 g, 31.8 mmol) in *tert*-BuOH (40 mL) was then added to

the mixture and refluxed for 2 h. After being cooled to room temperature, the mixture was poured into water (100 mL) and extracted with AcOEt (100 mL). The extract was acidified with concentrated HCl (3.82 g), refluxed for 2 h, and cooled to 10 °C. The resulting precipitate was collected by filtration and dried to give methyl 4-[3-(2,4-diamino-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)propyl]benzoate hydrochloride (**3a**) (8.8 g) in 76% yield as colorless needles: mp 272−275 °C; IR (KBr) 3181 (NH_2), 1718 (CO) cm^{-1}; ^1H NMR (CD_3OD, δ ppm) 7.93 (2H, d, J = 8 Hz), 7.30 (2H, d, J = 8 Hz), 6.66 (1H, s), 3.89 (3H, s), 2.77 (4H, m), 1.98 (2H, m). Anal. Calcd for $C_{17}H_{19}N_5O_2 \cdot HCl$: C, 56.43; H, 5.57; N, 19.36. Found: C, 56.39; H, 5.61, N, 19.21.

Acid 3b. A mixture of **3a** (11 g, 30 mmol) and NaOH (3.6 g, 90 mmol) in 50% aqueous MeOH (50 mL) was refluxed for 2 h. After being cooled to room temperature, the mixture was concentrated to a half volume in vacuo under 50 °C. The residual mixture was acidified to pH 2 with 6 N HCl (15 mL). The resulting precipitate was filtered off and dried to obtain 4-[3-(2,4-diamino-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)propyl]benzoic acid hydrochloride (**3b**) (8.9 g) in 80% yield as off-white crystalline powder: mp 315−317 °C (dec); IR (KBr) 3175 (NH_2), 1689 (CO) cm^{-1}; ^1H NMR (DMSO-d_6−D_2O, δ ppm) 7.86 (2H, d, J = 8 Hz), 7.33 (2H, d, J = 8 Hz), 6.71 (1H, s), 2.74 (4H, m), 1.86 (2H, m). Anal. Calcd for $C_{16}H_{17}N_5O_2 \cdot HCl \cdot H_2O$: C, 52.53; H, 5.51; N, 20.14. Found: C, 52.59; H, 5.56, N, 19.98.

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Additions and Corrections

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David A. Evans,* Gretchen S. Peterson, Jeffrey S. Johnson, David M. Barnes, Kevin R. Campos, and Keith A. Woerpel . An Improved Procedure for the Preparation of 2,2-Bis[2-[4(*S*)-*tert*-butyl-1,3-oxazolinyl]]propane ((*S*,*S*)-*tert*-Butylbis(oxazoline)) and Derived Copper(II) Complexes.

Page 4543, column 2. An error exists in the reported ^1H and ^{13}C NMR chemical shift data for 2,2-bis[2-[4(*S*)-*tert*-butyl-1,3-oxazolinyl]]propane (**1**). In the ^1H NMR spectrum, the resonance at δ 3.51 should be at δ 3.85. In the ^{13}C NMR spectrum, the peak at δ 26.8 should be at δ 75.4. All peak multiplicities and coupling constants are correct as originally reported. The authors wish to thank Dr. David W. C. MacMillan and Dr. Clayton H. Heathcock for bringing these errors to our attention.

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