α,β-Unsaturated Carboxylic Acid Derivatives. XIX. The Convenient Synthesis of α-Alkoxy-, α-Hydroxy-α-amino Acid, and Its Cyclic Dipeptide from α-Dehydroamino Acid[1]

Chung-gi SHIN,* Yoshiaki SATO, Hisao OHMATSU, and Juji YOSHIMURA†

Laboratory of Organic Chemistry, Faculty of Technology, Kanagawa University, Rokkakubashi, Kanagawa-ku, Yokohama 221

†*Laboratory of Chemistry for Natural Products, Faculty of Science, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 227*

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The facile conversion of α-dehydroamino acid into α-alkoxy-α-amino acid and its cyclic dipeptide is described. The reaction of *t*-butyl 2-acetylamino-2-alkenoate or 1-benzyl-3-ethylidene-2,5-piperazinedione with alcohol, water, or acetic acid in the presence of NBS or NCS, followed by reduction with 10% Pd-C, gives *t*-butyl 2-alkoxy-, 2-hydroxy-, and 2-acetoxy-2-(acetylamino)alkanoates, and 3-alkoxy-3-ethyl-2,5-piperazinedione respectively. All the new compounds were characterized by spectroscopic analysis.

Recently, increasing interest has been directed to the synthesis of ergot alkaloids and cyclic peptide antibiotics containing an α-alkoxy- or α-hydroxy-α-amino acid moiety as an very important constituent or precursor.[2-5]

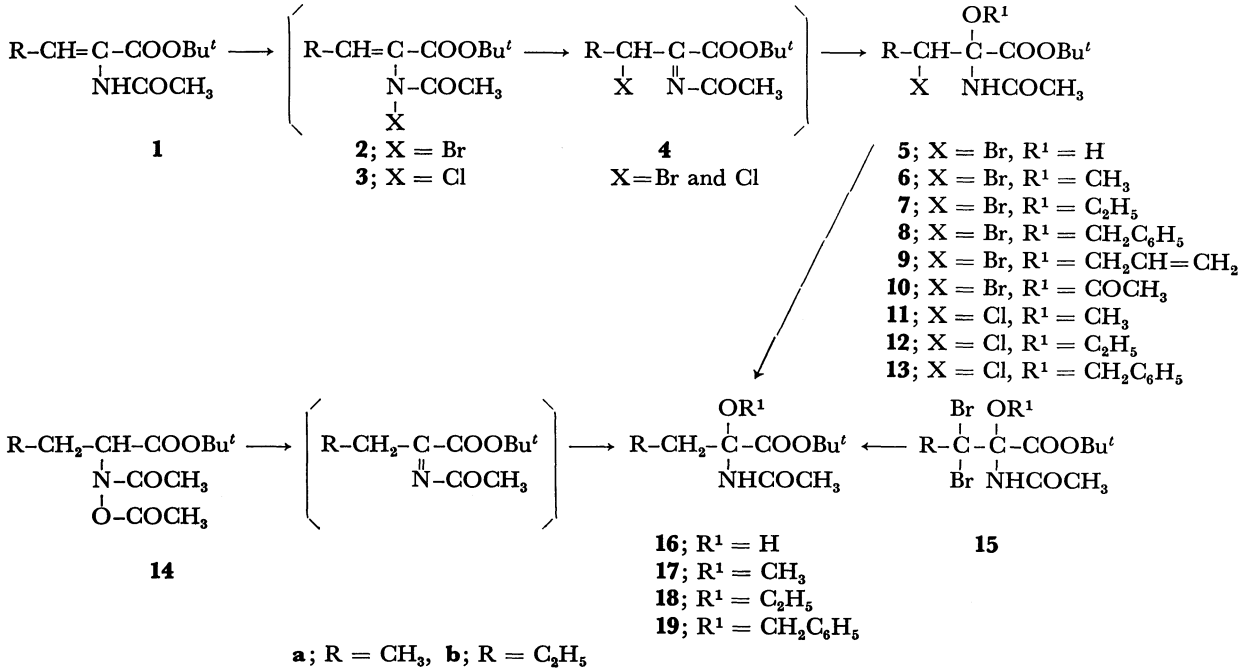
So far, several syntheses of α-alkoxy- and α-hydroxy-α-amino acids from α-amino acid[6-9] and from α-aminoacrylic acid,[10-13] as well as the semi-synthesis of 6-alkoxypenicillins and 7-alkoxycephalosporins,[14] have been reported. However, it seems that no facile and general synthetic method for α-alkoxy- and α-hydroxy-α-amino acids and their cyclic dipeptides has yet been achieved.

Previously, we reported briefly on the addition of alcohol to α,β-unsaturated α-amino acid (α-dehydroamino acid; DHA) in the presence of *N*-bromosuccinimide (NBS).[15] In order to apply and extend the addition reaction in a more versatile manner, various reactions of *t*-butyl 2-acetylamino-2-alkenoate (**1**) or 1-benzyl-3-ethylidene-2,5-piperazinedione (2,5-piperazinedione=PDO) (**21**) with several alcohols, acetic acid, or water in the presence of NBS or *N*-chlorosuccinimide (NCS) have here been studied thoroughly. As a result, the synthetic route for α-alkoxy- and α-hydroxy-α-amino acids and their cyclic dipeptides was established.

More recently, after the completion of our work,[16,17] Ottenheijm *et al.* reported a similar addition of methanol to acylimine intermediates.[18,19]

Results and Discussion

α-Alkoxy-α-amino Acid. A one-pot reaction of DHA (**1**: **a**; R=CH_3, **b**; R=C_2H_5) with an appropriate alcohol in the presence of NBS or NCS at room temperature gave directly the desired *t*-butyl 2-alkoxy-3-halo-2-(acetylamino)alkanoate (**6**—**13**) in an excellent yield. On the other hand, a similar reaction of *t*-butyl 2-acetylamino-2-butenoate (**1a**) with water in DMF barely proceeded to give *t*-butyl 2-hydroxy-3-bromo-2-(acetylamino)butanoate (**5a**) in a poor yield, whereas



Scheme 1.

the reaction of **1** with glacial acetic acid was worked-up similarly to give *t*-butyl 2-acetoxy-3-bromo-2-(acetylamino)alkanoate (**10**) in *ca.* a 51% yield.

Subsequently, an attempt at the catalytic reduction of bromine at the 3-position of the **5**—**8** thus obtained with 10% Pd-C and equimolar triethylamine in methanol was successful; the expected *t*-butyl 2-alkoxy-2-(acetylamino)alkanoate (**16**—**19**) was thus obtained as colorless crystals in a fairly good yield. A similar reduction was further applied to *t*-butyl 3,3-dibromo-2-alkoxy-2-(acetylamino)alkanoate (**15**), prepared and reported previously,[15] using 10% Pd-C and two molar triethylamine to give **16**—**19** in an almost quantitative yield.

Moreover, it was found that *t*-butyl 2-benzyloxy-2-(acetylamino)alkanoate (**19**) was hydrogenolyzed with 10% Pd-C in the absence of triethylamine to give **16** in *ca.* a 60% yield.

On the other hand, in order to prepare independently and to confirm the structure of **16**—**19**, *t*-butyl 2-(*N*,*O*-diacetyl-hydroxyamino)alkanoate (**14**)[20] was subjected to the elimination of acetic acid and the subsequent addition of alcohol to the acylimine thus formed as an intermediate. When a solution in an appropriate alcohol was treated with sodium alkoxide, the expected elimination-addition reaction was carried out to give α-alkoxy derivative, which was found to be completely identical with **17** and **18**. This method, however, was found to be ineffective for the preparation of an α-hydroxy- or α-benzyloxy-α-amino acid moiety, *e.g.*, *t*-butyl 2-hydroxy- and 2-benzyloxy-2-(acetylamino)-alkanoate (**16** and **19**), which were thought to be very

TABLE 1. *t*-BUTYL 2-SUBSTITUTED 3-BROMO-2-(ACETYLAMINO)ALKANOATES (**5**—**10**)

Compd No.	R[1]	Yield/%	Mp/°C	Formula	Found (Calcd), %			NMR spectrum, δ[f]		
					C	H	N	NH	(OH)	3-Proton
5a	H	18	99.5—100[a]	$C_{10}H_{18}NO_4Br$	40.77 (40.56	6.00 6.13	4.54 4.73)	6.66,	(5.10),	4.30
6a[g]	CH_3	89	90—91[b]	$C_{11}H_{20}NO_4Br$	42.48 (42.59	6.59 6.50	4.32 4.52)	6.46,	6.98,	4.48 5.30
6b		91	syrup[c]					6.49,	6.95,	4.21 4.98
7a	C_2H_5	86	85.5—86.5[b]	$C_{12}H_{22}NO_4Br$	44.40 (44.46	6.87 6.84	4.26 4.32)	6.42,	6.94,	4.43 5.29
7b		93	syrup[c]					6.50,	6.96,	4.20 4.98
8a[g]	$CH_2C_6H_5$	92	115—116[b]	$C_{17}H_{24}NO_4Br$	52.92 (52.86	6.30 6.26	3.58 3.63)	6.42,	7.02,	4.45 5.38
8b		62	86—87[d]	$C_{18}H_{26}NO_4Br$	53.79 (54.01	6.82 6.55	3.62 3.50)	6.50,	7.02,	4.27 5.14
9a	$CH_2CH=CH_2$	80	85—86[b]	$C_{13}H_{22}NO_4Br$	46.69 (46.44	6.54 6.59	3.97 4.13)	6.45,	6.96,	e)
9b		80	syrup[c]					6.53	6.95	
10a	$COCH_3$	53	77—78[b]	$C_{12}H_{20}NO_5Br$	42.68 (42.65	5.94 5.96	4.24 4.14)	7.06,	7.24	5.04 5.56
10b		49	82—83[b]	$C_{13}H_{22}NO_5Br$	44.63 (44.33	6.28 6.30	3.98 3.98)	7.11,	7.25	4.71 5.28

a) Colorless needles from methanol–water. b) Colorless needles from hexane. c) Unstable. d) Colorless needles from ethanol–water. e) Overlapped with allyl protons. f) Measured in $CDCl_3$. g) Ref. 15.

TABLE 2. *t*-BUTYL 2-SUBSTITUTED 3-CHLORO-2-(ACETYLAMINO)ALKANOATES (**11**—**13**)

Compd No.	R[1]	Yield/%	Mp/°C	Formula	Found (Calcd), %			NMR spectrum, δ[e]		
					C	H	N	NH		3-Proton
11a	CH_3	89	83—84[a]	$C_{11}H_{20}NO_4Cl$	49.53 (49.72	7.56 7.59	5.27 5.27)	6.45,	6.94,	4.40 5.18
11b		94	syrup[b]	$C_{12}H_{22}NO_4Cl$	51.56 (51.52	7.91 7.93	5.13 5.01)	6.52,	6.92,	4.12 4.85
12a	C_2H_5	90	66—69[b]	$C_{12}H_{22}NO_4Cl$	51.56 (51.52	7.96 7.93	5.19 5.01)	6.48,	6.94,	4.37 5.17
12b		89	syrup[b]	$C_{13}H_{24}NO_4Cl$	53.28 (53.15	8.09 8.23	4.62 4.77)	6.54,	6.96,	4.12 4.86
13a	$CH_2C_6H_5$	88	107—108[c]	$C_{17}H_{24}NO_4Cl$	59.53 (59.73	7.02 7.08	4.26 4.10)	6.42,	6.98,	4.40 5.23
13b		68	126—127[d]	$C_{18}H_{26}NO_4Cl$	60.74 (60.75	7.41 7.36	4.09 3.94)	7.02,	6.52,	4.17 4.95

a) Colorless needles from hexane. b) Colorless amorphous or colorless syrup purified on a silica-gel column using benzene–ethyl acetate (15 : 1 v/v). c) Colorless needles from ethanol–water. d) Colorless needles from dibutyl ether. e) Measured in $CDCl_3$.

TABLE 3. *t*-BUTYL 2-ALKOXY- AND 2-HYDROXY-2-(ACETYLAMINO)ALKANOATES (**16**—**19**)

Compd No.	Yield/% A[a]	B[b]	C[c]	D[d]	Mp/°C	Formula	Found (Calcd), % C	H	N	IR spectrum, cm^{-1} [e] NH (OH)	CO	NMR, δ[f] 3-Proton (J_{Hz})	NH (OH)
16a	62	65		66	78.5—79.5[g]	$C_{10}H_{19}NO_4$	55.31 (55.28)	8.91 (8.82)	6.44 (6.45)	(3420) 3340	1725 1655	1.82t (7.0)	(4.80) 6.95
16b				84	69—70[g]	$C_{11}H_{21}NO_4$	57.22 (57.12)	9.23 (9.15)	6.02 (6.06)	(3420) 3345	1725 1655	2.42m 1.75m	(4.83) 6.94
17a	87	97	56		137—138[h]	$C_{11}H_{21}NO_4$	57.36 (57.12)	9.44 (9.15)	6.03 (6.06)	3300	1745 1690	2.56m 1.90m	6.64
17b	83	99	62		109—110[i]	$C_{12}H_{23}NO_4$	58.78 (58.75)	9.63 (9.45)	5.53 (5.71)	3300	1745 1690	2.61m 1.86m	6.68
18a	84	96	21		144.5—145[i]	$C_{12}H_{23}NO_4$	58.80 (58.75)	9.34 (9.45)	5.70 (5.71)	3300	1745 1695	2.42m 1.85m	6.76
18b	86	93	22		110.5—111[i]	$C_{13}H_{25}NO_4$	60.31 (60.20)	9.81 (9.72)	5.32 (5.40)	3310	1750 1695	2.41m 1.87m	6.81
19a	92	96			90.5—91[i]	$C_{17}H_{25}NO_4$	66.17 (66.42)	8.32 (8.20)	4.56 (4.56)	3380	1730 1675	2.54m 1.87m	6.70
19b	94	93			71.5—72.5[i]	$C_{18}H_{27}NO_4$	67.34 (67.26)	8.50 (8.47)	4.22 (4.36)	3380	1740 1680	2.55m 1.86m	6.66

a) From **5**—**8**. b) From **15**. c) From **14**. d) From **19**. e) Recorded in KBr. f) Measured in $CDCl_3$. g) Colorless needles from dibutyl ether. h) Colorless needles from ethyl acetate. i) Colorless needles from hexane.

important segments in many of the natural products mentioned above.

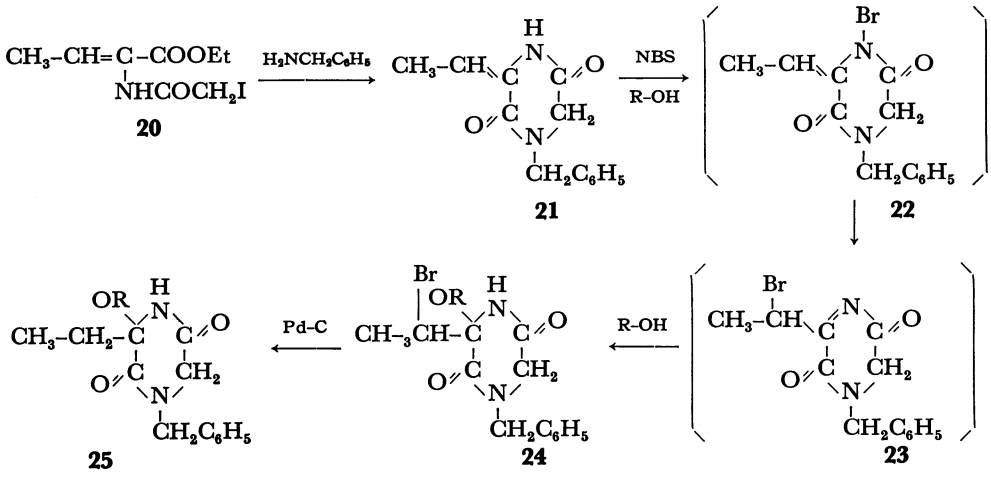
In consequence, a convenient synthetic method for α-alkoxy-α-amino acid in a 75% overall yield was established by only two steps from DHA (**1**).

As is shown in Scheme 1, a formation mechanism of **5**—**13** was deduced in which, at first, the substitution of halogen to the nitrogen atom of **1** yielded *t*-butyl 2-(*N*-haloacetylamino)-2-alkenoate (**2** and **3**), followed by the 1,3-shift of the halogen to form *t*-butyl 3-halo-2-(acetylimino)alkanoate (**4**) as an unstable intermediate, to which immediately the present protic solvent was added. This deduction has already been supported by the fact that, to the *t*-butyl 3,3-dibromo-2-(acetylimino)-alkanoate isolated stably, we added alcohols to give **15**.[15]

In the IR spectral data of **5**—**13** and **16**—**19**, the characteristic absorption bands of the NH, ester carbonyl, and secondary amide functions appeared in the 3260—3390, 1730—1760, and 1660—1700 cm^{-1} regions respectively. Moreover, from the NMR spectral data, the disappearance of the characteristic olefinic proton signals in the δ 6.59—7.13 region of **1** and the appearance of the C-3 proton signals of **5**—**13** and **16**—**19** in the δ 4.12—5.56 and δ 1.66—2.78 regions respectively, resonating in a considerably higher magnetic field, are consistent with the formation of the α-substituted-α-amino acid structure.

The yields, physical constants, and NMR spectral data of **5**—**13** and **16**—**19** are summarized in Tables 1, 2, and 3.

3-Alkoxy-2,5-piperazinedione. In order to apply extensively and generalize the protic reagent-addition utilizing the halogen migration, 3-alkylidene-PDO was for instance, employed. Exactly, according to the synthetic method for α-alkoxy-α-amino acid, the starting 1-benzyl-3-ethylidene-PDO (**21**), which has been prepared by the cyclization of ethyl 2-iodoacetyl-amino-2-butenoate (**20**)[21] with benzylamine in a good yield, was treated with an appropriate alcohol in the



Scheme 2.

TABLE 4. 1-BENZYL-3-ETHYLIDENE- AND 1-BENZYL-3-ALKOXY-3-ETHYL-PDO (**21**, **24**, **25**, AND **26**)

Compd No.	Yield %	Mp/°C	Formula	Found (Calcd), %			IR spectrum, cm^{-1} e)			NMR spectrum, δ f)		
				C	H	N	NH (OH)	CONH	C=C	-CH=	-CH- (-CH_2-)	NH (OH)
21	62	134—136 a)	$C_{13}H_{14}N_2O_2$	67.84 (67.81	6.39 6.13	12.24 12.17)	3180	1675	1635	6.29		9.60
24a	88	129—130 b)	$C_{14}H_{17}N_2O_3Br$	49.36 (49.28	5.09 5.02	8.38 8.21)	3170	1690 1670	—	—	4.72	8.27
24b	82	133—134 b)	$C_{15}H_{19}N_2O_3Br$	50.72 (50.72	5.45 5.39	7.72 7.88)	3180	1680 1655	—	—	4.73	8.16
24c	61	116—117 c)	$C_{20}H_{21}N_2O_3Br$	57.61 (57.56	5.12 5.07	6.78 6.71)	3200	1690 1660	—	—	4.78	8.45
25a	92	89—90 c)	$C_{14}H_{18}N_2O_3$	64.06 (64.10	6.88 6.92	10.60 10.68)	3210	1690 1645	—	—	(2.02)	8.06
25b	90	138—139 d)	$C_{15}H_{20}N_2O_3$	64.79 (65.19	7.24 7.30	10.08 10.14)	3220	1690 1640	—	—	(2.01)	7.72
25c	89	137—138 c)	$C_{20}H_{22}N_2O_3$	70.89 (70.98	6.50 6.55	8.22 8.28)	3180	1680	—	—	(2.08)	7.98
26	90	145—146 d)	$C_{13}H_{16}N_2O_3$	62.66 (62.89	6.47 6.50	11.09 11.28)	3210 (3260)	1680 1635	—	—	(1.96)	7.86 (4.8—5.6)

a) Colorless prisms from ethyl acetate–diethyl ether. b) Colorless needles from benzene–hexane. c) Colorless prisms from benzene–hexane. d) Colorless needles from benzene. e) Recorded in KBr. f) Measured in $CDCl_3$.

presence of NBS to give 1-benzyl-3-(1-bromoethyl)-3-alkoxy-PDO (**24**) as colorless crystals in *ca.* an 80% yield. The subsequent catalytic reduction of **24** with Pd–C and triethylamine was also carried out to give the desired 1-benzyl-3-alkoxy-3-ethyl-PDO (**25**) in a 90% yield.

Furthermore, the catalytic hydrogenolysis of **25** with 10% Pd–C was performed smoothly to give 1-benzyl-3-ethyl-3-hydroxy-PDO (**26**) in *ca.* a 90% yield.

From the above results, the yield of the each step from **21** to **26** was found to be excellent; the overall yield reached to *ca.* 50%.

As was illustrated in Scheme 2, the formation mechanism of **24** was also supposed that the initial substitution of bromine to the 4-position of **21** (**22**), followed by the immediate migration to the 2-position of exocyclic carbon, gave acylimine (**23**); finally, the addition reaction of alcohol to **23** occurred to give **24**.

Judging from the IR and NMR spectral data of **21** and **24**—**26**, the appearance of the carbon-carbon double bond at 1635 cm^{-1} and the olefinic proton signal at δ 6.29 in **21**, and the appearance of exocyclic 1-methine proton signals resonating at comparatively higher magnetic fields (at δ 4.72—4.78 in **24** and in the δ 1.96—2.08 region in **25** and **26**), indicate unambiguously the formation of 3-alkoxy- and 3-hydroxy-PDO structures.

All the new compounds thus obtained gave satisfactory results in their elemental analyses as well as in the spectroscopy.

The yields, physical constants, and NMR spectral data of **21**, **24**, **25**, and **26** are summarized in Table 4.

It is noteworthy that the addition reaction of protic reagent *via* the substitution and the subsequent migration in one pot is also applicable to linear and cyclic acylenamines, as is shown below (Fig. 1).

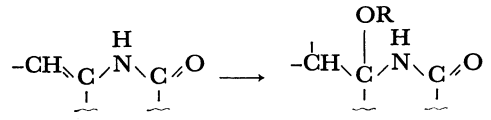


Fig. 1.

Experimental

All the melting points are uncorrected. The IR spectra were recorded with a Hitachi EPI-G3 Spectrometer. The NMR spectra were measured with a JNM-PS-100 Spectrometer (Japan Electron Optics Laboratory Co., Ltd.), using tetramethylsilane as the internal standard.

Preparation of ***5a***. Into a solution of **1a** (10.0 mmol) in water–DMF (15 ml, 1 : 9 v/v) we stirred NBS (11.0 mmol), portion by portion, at room temperature for 3 h. The reaction solution was poured into saturated aqueous NaCl (30 ml), and then the crystals deposited were collected by filtration. The recrystallization of the crystals from methanol–water gave colorless needles identified as *t*-butyl 3-bromo-2-hydroxy-2-(acetylamino)butanoate (**5a**).

Preparation of ***6***. Similarly, **1** and methanol (20 ml), in the presence of NBS, were worked-up for 2 h. The reaction solution was concentrated under reduced pressure to give a residue, which was subsequently dissolved in diethyl ether (30 ml). The resulting solution was washed twice with water and then dried over anhydrous Na_2SO_4. The evaporation of the ether gave colorless crystals or a syrup identified as *t*-butyl 3-bromo-2-methoxy-2-(acetylamino)alkanoate (**6**).

Preparation of ***7***. Similarly, a solution of **1** and NBS in ethanol (20 ml) was worked-up to give colorless crystals or a syrup identified as *t*-butyl 3-bromo-2-ethoxy-2-(acetylamino)-alkanoate (**7**).

Preparation of ***8***. A solution of **1a** in benzyl alcohol (6 ml) in the presence of NBS was similarly worked-up for 40 min to yield colorless crystals, which were then collected and washed with 50% ethanol. The crystals were identified as *t*-butyl 2-benzyloxy-3-bromo-2-(acetylamino)butanoate (**8a**).

Similarly, a solution of **1b** and NBS in benzyl alcohol was worked-up. The reaction solution was poured into water (250 ml), and then the aqueous solution was extracted three times with petroleum ether (180 ml). The combined extracts were washed three times with water, dried over anhydrous

Na_2SO_4, and then concentrated under reduced pressure to give colorless crystals identified as *t*-butyl 2-benzyloxy-3-bromo-2-(acetylamino)pentanoate (**8b**).

Preparation of ***9***. A solution of **1** in allyl alcohol (6 ml) in the presence of NBS was similarly worked-up for 10 h; to the reaction mixture we then added cyclohexane (60 ml). The resulting solution was washed twice with water and dried over anhydrous Na_2SO_4. The evaporation of the cyclohexane under reduced pressure gave colorless crystals or a syrup identified as *t*-butyl 2-allyloxy-3-bromo-2-(acetylamino)-alkanoate (**9**).

Preparation of ***10***. Into a solution of **1** (10.0 mmol) in acetic acid (5 ml) we stirred NBS (11.0 mmol), portion by portion, at room temperature for 3 h. To the reaction solution thus obtained we added hexane (100 ml). After the resulting solution had been washed twice with water, the crystals which separated out were collected by filtration. The filtrate was further washed twice with water and then dried over anhydrous $MgSO_4$. The removal of the hexane gave more of the crystals obtained above. The combined crystals were recrystallized from hexane to give colorless needles identified as *t*-butyl 3-bromo-2-acetoxy-2-(acetylamino)alkanoate (**10**).

Preparation of ***11***. A solution of **1a** in methanol (40 ml) in the presence of NCS (11.0 mmol) was similarly worked-up for 5 h to give colorless crystals identified as *t*-butyl 3-chloro-2-methoxy-2-(acetylamino)butanoate (**11a**).

In a similar manner, the reaction of **1b** with methanol and NCS for 24 h gave a syrupy residue, which was then purified on a silica gel column, using a mixture of benzene–ethyl acetate (15 : 1 v/v) as the eluent. The fraction thus obtained was concentrated under reduced pressure to give a colorless syrup identified as *t*-butyl 3-chloro-2-methoxy-2-(acetylamino)pentanoate (**11b**).

Preparation of ***12***. Similarly, a solution of **1** in ethanol (20 ml) in the presence of NCS was worked-up for 20 h to give a residual syrup. The crude syrup was purified on a silica gel column, using a mixture of benzene–ethyl acetate (15 : 1 v/v) as the eluent, to give a colorless amorphous substance or a syrup identified as *t*-butyl 3-chloro-2-ethoxy-2-(acetylamino)alkanoate (**12**).

Preparation of ***13***. Similarly, a solution of **1a** and NCS in benzyl alcohol (30 ml) was worked-up for 3 h to give colorless crystals identified as *t*-butyl 3-chloro-2-benzyloxy-2-(acetylamino)butanoate (**13a**).

In a similar manner, the treatment of **1b** with benzyl alcohol (10 ml) in the presence of NCS for 24 h gave a reaction solution which was then poured into water (400 ml). The resulting aqueous solution was extracted three times with petroleum ether (150 ml). The combined extracts were washed three times with water and then dried over anhydrous Na_2SO_4. The removal of the ether under reduced pressure gave colorless crystals identified as *t*-butyl 3-chloro-2-benzyloxy-2-(acetylamino)pentanoate (**13b**).

Preparation of ***16—19***. *a) From* ***5—8***: A solution of **5—8** (5.0 mmol) and triethylamine (5.5 mmol) in methanol (70 ml) was reduced in the presence of 10% Pd–C (500 mg). After 15 min, the catalyst was filtered off, and the reaction solution was concentrated under reduced pressure to give a residue, which was subsequently dissolved in chloroform (50 ml). The resulting solution was washed three times with water and then dried over anhydrous $MgSO_4$. The evaporation of the chloroform gave colorless crystals identified as *t*-butyl 2-alkoxy- and 2-hydroxy-2-(acetylamino)alkanoate (**16—19**).

b) From ***15***: A similar treatment of **15** (5.0 mmol) with triethylamine (10.5 mmol) in the presence of 10% Pd–C (500 mg) was worked-up to give the expected **16—19**.

c) From ***14***: Into a solution of **14** (10.0 mmol) in an appropriate alcohol (10 ml) we stirred sodium alkoxide (12.0 mmol) in alcohol (5 ml), drop by drop, below 10 °C. After the solution had been stirred for 2 h, the reaction solution was concentrated under reduced pressure to give a residue which was subsequently dissolved in chloroform (30 ml). The resulting solution was washed twice with water and then dried over anhydrous $MgSO_4$. The removal of the chloroform gave **17** and **18**.

Preparation of ***16*** *from* ***19***. A solution of **8** (3.8 mmol) in methanol (30 ml) was hydrogenolyzed in the presence of 10% Pd–C (100 mg) at room temperature for 1 h. After the removal of the catalyst, the resultant solution was concentrated to give a residual pale yellow syrup. The crude syrup was purified on a silica-gel column, using a mixture of benzene–ethyl acetate (5 : 2 v/v) as the eluent. The fraction was concentrated under reduced pressure to give colorless crystals, in agreement with the **16** prepared above.

Preparation of ***21***. Into a solution of **20** (6.73 mmol) in ethanol (20 ml) we stirred benzylamine (16.84 mmol), drop by drop, at room temperature. After the mixture had been stirred for 3 h, the reaction solution was concentrated under reduced pressure to give a residue, which was subsequently dissolved in 1 M HCl (50 ml). The aqueous solution was extracted three times with benzene (60 ml). The combined extracts were washed twice with saturated aqueous NaCl and then dried over anhydrous Na_2SO_4. The removal of the benzene under reduced pressure gave colorless crystals identified as 1-benzyl-3-ethylidene-PDO (**21**).

Preparation of ***24***. Into a solution of **21** (2.17 mmol) in an appropriate alcohol (5 ml) we stirred NBS (2.17 mmol), portion by portion, at room temperature. After the mixture had been stirred for 10 min, the reaction solution was concentrated under reduced pressure to give a residue, which was then dissolved in chloroform (20 ml). The resulting solution was washed twice with water and then dried over anhydrous Na_2SO_4. The removal of the chloroform gave colorless crystals identified as 1-benzyl-3-alkoxy-3-(1-bromoethyl)-PDO (**24**).

Preparation of ***25***. A solution of **24** (1.69 mmol) and triethylamine (2.03 mmol) in methanol (30 ml) was reduced in the presence of 10% Pd–C (170 mg) at room temperature for 1 h. After the removal of the catalyst, the reaction solution was concentrated under reduced pressure to give a residue, which was then dissolved in dichloromethane (20 ml). The resulting solution was washed twice with water and then dried over anhydrous Na_2SO_4. The evaporation of the dichlorome thane gave colorless crystals identified as 1-benzyl-3-alkoxy-3-ethyl-PDO (**25**).

Preparation of ***26***. A solution of 1-benzyl-3-benzyloxy-3-ethyl-PDO (**25c**; 2.07 mmol) in methanol (40 ml) was hydrogenolyzed in the presence of 10% Pd–C (500 mg) at room temperature for 24 h. After the removal of the catalyst, the resultant solution was concentrated under reduced pressure to give colorless crystals identified as 1-benzyl-3-ethyl-3-hydroxy-PDO (**26**).

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