# Synthesis of *O*-(α-Aminoacyl)glycolic and -lactic Amides from 2-Bromoacetamides or -propanamides with *N*-Protected Amino Acids

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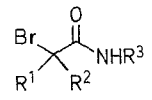
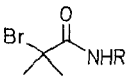
2-Bromocarboxamides carrying a primary, secondary or tertiary halide and a primary or secondary amide function react with *N*-protected amino acids in the presence of silver oxide to afford the desired depsipeptide analogs in high yields. Some racemization was observed in the synthesis of a lactoylamide derivative.

Previous research in our laboratory have shown that 2-bromocarboxamides **1** undergo cyclocondensation reactions in the presence of a strong base (sodium hydride), to yield heterocyclic derivatives whose structures and properties depend upon the substitution pattern at both the $sp^3$ carbon and nitrogen atoms of **1**. However, substitution products at the tertiary carbon atom, e.g. **3, 4** were obtained when the 2-bromoisobutyramides **2** were allowed to react with amines in the presence of sodium hydroxide,[1] or with *N*-protected aminoacids in the presence of silver oxide.[2]



**1**



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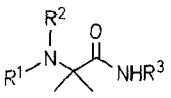

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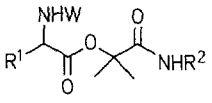
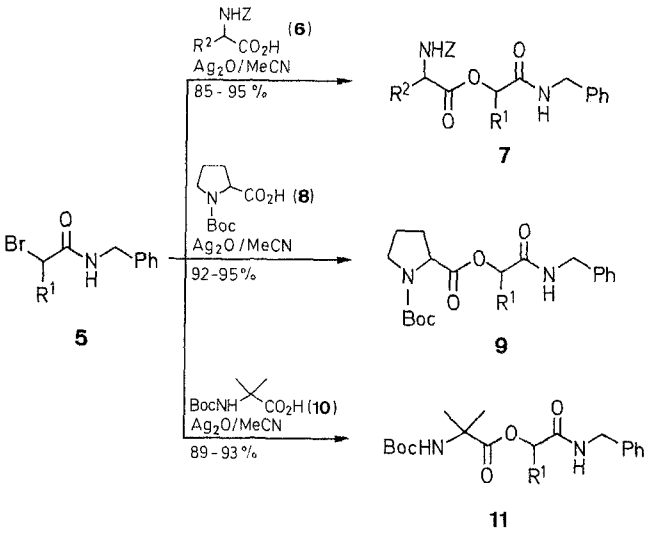


**4** W = protecting group

The mild conditions and high yields involved in the formation of the ester derivatives of 2-hydroxyisobutyric acid, which represent interesting depsipeptide models **4**,[3] prompted us to study analogous reactions of 2-bromoacetamide **5a** or -propanamide **5b** with *N*-protected amino acids **6, 8** and **10**.




| 5 | $R^1$ | 6 | $R^2$ | 7 | $R^1$ | $R^2$ | 9, 11 | $R^1$ |
|---|---|---|---|---|---|---|---|---|
| **a** | H | **a** | $CH_3$ | **aa** | H | $CH_3$ | **a** | H |
| **b** | $CH_3$ | **b** | $PhCH_2$ | **ab** | H | $PhCH_2$ | **b** | $CH_3$ |
| | | | | **ba** | $CH_3$ | $CH_3$ | | |
| | | | | **bb** | $CH_3$ | $PhCH_2$ | | |

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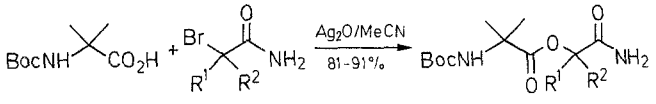
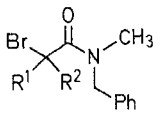
As shown in the Table, 2-bromo-*N*-benzylacetamide (**5a**) or -propanamide (**5b**) react with representative *N*-protected aminoacids **6, 8, 10** in the presence of silver oxide in acetonitrile, slowly at room temperature (one day), faster at reflux (one hour), to yield the corresponding *O*-(*N*-protected 2-aminoacyl)glycolamides **7aa, 7ab, 9a** and **11a** and lactamides **7ba, 7bb, 9b** and **11b** in high yields. When the reflux conditions were applied to a 2-bromoisobutyramide **2**, high yields of compounds of general type **4** were obtained in 10–15 minutes. The influence of the substitution pattern both at the halogenated carbon and nitrogen atoms was further evaluated by allowing 2-bromoacetamide, -propanamide, and -isobutyramide **12a–c** as well as 2-bromo-*N*-benzyl-*N*-methylacetamide, -propanamide, and -isobutyramide **14a–c** to react with *N*-Boc-aminoisobutyric acid (**10**).




**8** **12** **13**




**14**

| 12–14 | $R^1$ | $R^2$ |
|---|---|---|
| **a** | H | H |
| **b** | H | $CH_3$ |
| **c** | $CH_3$ | $CH_3$ |

The 2-bromoprimary amides **12a–c** gave the expected ester derivatives **13a–c** within a few hours at room temperature, with the more hindered **12c** reacting faster, and more so at reflux (0.5 h) (Table). However, the 2-bromotertiary amides **14a–c** failed to give any ester formation even after reacting up to three weeks at room temperature or refluxing up to ten hours. This result points to the importance of the presence of at least one hydrogen atom at the nitrogen of the 2-bromocarboxamide, in the reaction promoted by silver oxide.

Whereas the formation of *O*-acyloxyisobutyramides **4, 13c** and *O*-acylglycolamides **7aa, 7ab, 9a, 11a, 13a** does not rise stereochemical problems, the formation of *O*-acyllactamides **7ba, 7bb, 9b, 11b, 13b** may, in principle, be accompanied by racemization at the chiral atom of the 2-bromopropanamides **5b, 12b**. In previous reactions of two *S*(−)-2-bromopropananilides with alkoxides at room temperature, only one substitution product, namely 2-methoxypropananilide was obtained, with low optical purity.[4] On the other hand, chiral 2-halocarboxylic esters were reported to react stereoselectively with the

**Table.** Compounds **7, 9, 11, 13, 17, 19** Prepared[a]

| Product | Reaction Time (h) at | | Yield (%) | mp (°C)[b] | $R_F$ | Molecular Formula[c] | $^1$H-NMR ($CDCl_3$/TMS)[d] $\delta$, $J$(Hz) |
|---|---|---|---|---|---|---|---|
| | Room Temp. | Reflux | | | | | |
| **7aa** | 25 | 1 | 92 | 131–133 | 0.19 | $C_{20}H_{22}N_2O_5$ (370.4) | 1.4 (d, 3H, $J$ = 7); 4.2–5.0 (4m, 7H); 5.2 (s, 1H) |
| **7ab** | 26 | 1 | 87 | 116–118 | 0.28 | $C_{26}H_{26}N_2O_5$ (446.5) | 3.1 (d, 2H, $J$ = 6.8); 4.3–4.5 (2m, 3H); 4.6 (AB, 2H, $J$ = 15.7); 4.8 (d, 2H, $J$ = 12.2); 5.2 (d, 1H, $J$ = 5.4); 7.0 (br, 1H) |
| **7ba** | 25 | 1 | 85 | 84–86[e] | 0.11 | $C_{21}H_{24}N_2O_5$ (384.5) | 1.41, 1.44 (2d, 3H, $J$ = 3.6); 1.49, 1.51 (2d, 3H, $J$ = 7); 4.40, 4.43 (2m, 1H); 4.45 (d, 2H, $J$ = 5.8); 4.87, 4.90 (2s, 2H); 5.00, 5.27 |
| **7bb** | 31 | 1.1 | 93 | oil[e] | 0.20 | $C_{27}H_{28}N_2O_5$ (460.5) | 1.29, 1.41 (2d, 3H, $J$ = 7); 3.0, 3.1 (2d, 2H, $J$ = 6.4, 7.6); 4.21 (part of ABx, 2H, $J$ = 5.2); 4.39 (d, 2H, $J$ = 5.8); 4.47–4.58 (2m, 1H); 4.83 (AB, $\Delta\nu$ = 32 Hz, 2H, $J$ = 12.2); 4.8 (s, 2H); 5.16–5.28 (m, 1H); 5.44 (d, 1H, $J$ = 4.6); 6.73 (unresolved × of ABx, 1H) |
| **9a** | 24 | 1 | 95 | oil | 0.22 | $C_{19}H_{26}N_2O_5$ (362.5) | 1.3 (s, 9H); 1.5 (s, 6H); 4.5 (d, 2H, $J$ = 5.9); 4.7 (s, 2H); 5.0 (s, 1H); 7.9 (s, 1H) |
| **9b** | 25 | 1 | 92 | oil[e] | 0.20 | $C_{20}H_{28}N_2O_5$ (376.5) | 1.3 (s, 9H); 1.45 (s, 3H); 1.5 (s, 3H); 1.55 (d, 3H, $J$ = 6.7); 4.45 (AB of ABx, 2H, $J_{Ax}$ = 16, $J_{Bx}$ = 14, $J_{AB}$ = 6); 4.9 (s, 1H); 5.2 (q, 1H, $J$ = 6.7); 7.7 (br, 1H) |
| **11a** | 24 | 1 | 93 | 118–120 | 0.23 | $C_{18}H_{26}N_2O_5$ (350.5) | 1.3 (s, 9H); 1.8–2.25 (2m, 4H); 3.4 (m, 2H); 4.3 (X of ABx, 1H, $J_{Ax}$ = 8, $J_{Bx}$ = 5); 4.45 (AB of ABx, 2H, $J_{Ax}$ = 15.1, $J_{Bx}$ = 15, $J_{AB}$ = 6); 4.7 (AB, 2H, $J$ = 15.4); 8.0 (br, 1H) |
| **11b** | 25 | 1 | 89 | 126–128[e] | 0.24 | $C_{19}H_{28}N_2O_5$ (364.5) | 1.31, 1.32 (s, 9H); 1.5, 1.53 (d, 3H, $J$ = 6.8); 1.8–2.25 (2m, 2H); 3.43 (m, 2H); 4.0–4.65 (m, 3H); 5.23, 5.36 (q, 1H, $J$ = 6.8) |
| **13a** | 4 | 0.20 | 86 | 112–114 | 0.23 | $C_{12}H_{20}N_2O_5$ (260.3) | 1.43 (s, 9H); 4.65 (s, 2H); 5.0 (br, 1H); 5.45 (br, 1H); 7.5 (br, 1H) |
| **13b** | 6 | 0.30 | 91 | oil[e] | 0.28 | $C_{13}H_{22}N_2O_5$ (274.3) | 1.45 (s, 9H); 1.5 (d, 3H, $J$ = 7.3); 1.55 (s, 6H); 5.0 (br, 1H); 5.18 (m, 1H); 5.3 (br, 1H); 7.4 (br, 1H) |
| **13c** | 1 | 0.10 | 81 | 151–153 | 0.10 | $C_{14}H_{24}N_2O_5$ (288.3) | 1.45 (s, 6H); 1.47 (s, 9H); 1.6 (s, 6H); 5.0 (br, 1H); 5.2 (br, 1H); 7.25 (br, 1H) |
| **17** | – | – | 32 | 69–70 | 0.48 | $C_{14}H_{18}BrNO_3$ (328.2) | 1.26 (t, 3H, $J$ = 7.6); 1.85 (d, 3H, $J$ = 6.8); 3.15 (d, 2H, $J$ = 5.9); 4.19 (q, 2H, $J$ = 7.6); 4.36 (q, 1H, $J$ = 6.8); 4.8 (m, 1H); 6.77 (d, 1H, $J$ = 7.9) |
| **17′** | – | – | 19 | 71–72 | 0.41 | $C_{14}H_{18}BrNO_3$ (328.2) | 1.26 (t, 3H, $J$ = 6.9); 1.81 (d, 3H, $J$ = 7.5); 3.17 (t, 2H, $J$ = 5.3); 4.2 (q, 2H, $J$ = 7.6); 4.36 (q, 1H, $J$ = 6.8); 4.83 (m, 1H); 6.73 (d, 1H, $J$ = 6.9) |
| **19′** | 24 | 1 | 84 | oil | 0.27 | $C_{27}H_{34}N_2O_7$ (498.6) | 0.83, 0.86 (2d, 6H, $J$ = 6.7); 1.23 (t, 3H, $J$ = 7); 1.44 (d, 3H, $J$ = 6.8); 2.1 (m, 1H); 3.14 (d, 2H, $J$ = 5.8); 4.18 (q, 2H, $J$ = 7); 4.29 (m, 1H); 4.84 (q, 2H, $J$ = 6.7); 5.2 (m, 3H); 6.61 (d, 1H, $J$ = 7.6) |

[a] Abbreviations: Z = *N*-Benzyloxycarbonyl ($PhCH_2OCO$); Boc = *N*-*tert*-Butyloxycarbonyl (*t*-BuOCO); Glyco = *O*-glycolyl; Lac = *O*-lactoyl; Hib = *O*-isobutyryl.

[b] Melting points were determined on a Reichert-Kofler block and are uncorrected.

[c] Satisfactory microanalyses obtained for H and N: H ±0.22, N ±0.22. The values for C varied from ±0.00 to 1.00.

[d] The $^1$H-NMR spectra were recorded on a Bruker AC200 spectrometer at 200 MHz. Aromatic protons are always omitted.

[e] Diastereoisomeric mixture.

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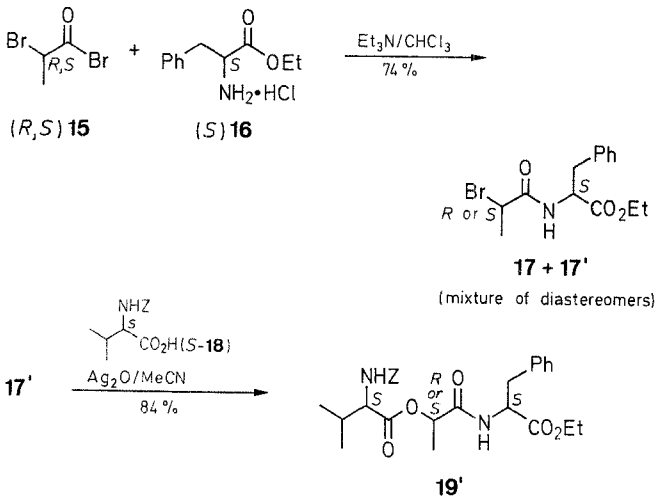
caesium salts of *N*-protected aminoacids, in dimethylformamide.[5]

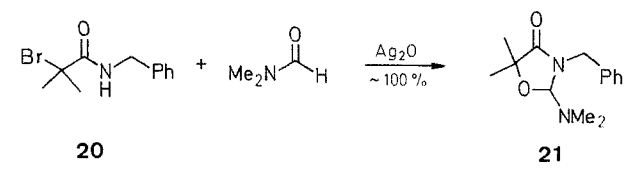
To check the stereochemistry of lactamide formation in the presence of silver oxide, we decided to use, instead of the racemic **5**, an enantiomerically pure substrate. Accordingly, ethyl (*R,S*)-2-bromopropanoyl-*S*-phenylalanate **17, 17′** was obtained as a diastereomeric mixture from (*R,S*)-2-bromopropanoyl bromide **(15)** and ethyl(*S*)-alanate **(16)**. Part of the mixture was resolved by column chromatography yielding **17** and **17′**, having almost superimposable $^1$H-NMR spectra. The slowly moving ethyl (*R*) or (*S*)-2-bromopropanoyl-*S*-phenylalanate **(17′)** was allowed to react with Z-*S*-valine **(18)** to yield the expected derivative ethyl Z-*S*-valyl-*O*-lactoyl-*S*-phenylalanate **(19′)**.




In a parallel experiment, a sample of the diastereomeric mixture **17** + **17′** was allowed to react with **18**, under the same conditions used for **17′**. HPLC of the reaction products showed the two expected diastereoisomers **19** + **19′** as two peaks of comparable area, starting from **17** + **17′** and a major diastereoisomer **19′**, with a small peak for **19**, starting from **17′**: area integration indicated that about 7% of racemization had occurred. Accordingly, the $^1$H-NMR spectrum of **19′** (Table) showed a major NH lactamide signal at $\delta = 6.61$ accompanied by a minor one at 6.89 ppm (about 5%). The $^1$H-NMR spectrum of the diastereomeric mixture **19** + **19′** (not reported) showed two almost identical diastereoisomers **19** + **19′** except for the presence of the two NH signals ($\delta = 6.61$ and 6.89).

The *S*-valyl-(*R* or *S*)-lactoyl unit is related to the *R*-valyl-*S*-lactoyl unit of the cyclic depsipeptide valinomicine, bearing twelve alternating *S* or *R* aminoacids and hydroxyacids.[6]

In order to ascertain whether dimethylformamide must be excluded as a solvent in the above reactions, due to its reactivity with some 2-bromocarboxamides, we allowed 2-bromo-*N*-benzylisobutyramide **(20)**, as well as 2-bromo-*N*-benzylpropanamide **(5b)** or 2-bromoacetanilide, to react with dimethylformamide in the presence of silver oxide. A quantitative yield of 3-benzyl-5,5-dimethyl-2-dimethylaminooxazolidine-4-one **(21)** was obtained from **20**.[7] Compound **5b** and 2-bromoacetanilide gave definite indication of undergoing similar reactions.[8] Accordingly, dimethylformamide is ruled out as a solvent for the present type of silver oxide promoted reactions.




Preliminary studies on the role of silver oxide established the following facts:

- silver oxide does not act as a catalyst, since the condensation requires equimolecular amounts; and
- other compounds, as silver acetate, sodium hydride, barium or copper oxide, failed to give the expected products; instead, starting materials were recovered.

As a conclusion from the previous and present study, the depsipeptide analogs **4, 7, 9, 11, 13,** and **19** can be obtained in high yields from a 2-bromoamide bearing one or two hydrogen atoms at the nitrogen. Reaction times become longer when passing from hydroxyisobutyryl derivatives **4** to the lactoyl **7ba, 7bb, 9b, 11b, 19** and glycolyl derivatives **7aa, 7ab, 9a, 11a**. Reaction times are greatly improved by working at reflux, one hour being sufficient to complete all reactions. No side reactions were observed, noteworthy with the fastest reacting tertiary halides. The results suggest that steric hindrance at C-2 atom may be overcome by a developing positive charge at the tertiary carbon. On the other hand, the small racemization of the secondary halide function of the model **17′** suggests that inversion of configuration represents the main stereochemical outcome in this case. Further study to shed more light on the reaction mechanism and the role of silver oxide is under way.

Chromatographic columns were filled with activated neutral $Al_2O_3$ (95%, Merck), covered with Celite 577 (Fluka).

MeCN and DMF were distilled prior to use. *S*-α-aminoacids were received from Fluka. 2-Bromoacetamides and racemic -propionamides were prepared as previously described.[1]

**Depsipeptides 7, 9, 11, and 13;[1] General Procedure:**
$Ag_2O$ (348 mg, 1.5 mmol) is added to a solution of *N*-Boc- or *N*-Z-aminoacid **6, 8, 10** or **12** (1.5 mmol) and 2-bromo-*N*-benzylisobutyramide **(20)**, -propanamide or -acetamide **5** (1.5 mmol) in MeCN (5 mL). The mixture is stirred at room temperature or at reflux for the time indicated in the Table. The progress of the reaction is monitored by TLC using 0.25 mm silica gel plates (Merck), and EtOAc/toluene (1:4) as solvent; the spots are detected by exposure to iodine vapour.

Silver salts are removed by passing the solution through a short column of $Al_2O_3$ (10 g), covered with Celite (1 g), using a little MeCN as eluent; the filtrate is evaporated and dried over $P_2O_5$ *in vacuo* until constant weight. Crystallization of the crude oils is effected with ether/light petroleum (bp 40–70 °C) (Table).

**Ethyl (*R*)- and (*S*)-*N*-(2-Bromopropanoyl)phenylalanate (17 + 17′):**
$Et_3N$ (1.16 mL, 8.3 mmol) is added to a suspension of the hydrochloride of ethyl phenylalanate (1.908 g, 8.3 mmol) in $CHCl_3$ (35 mL). After stirring until complete dissolution, the solution is cooled to 0 °C, and (*R,S*)-2-bromopropionyl bromide (0.88 mL, 8.3 mmol) dissolved in $CHCl_3$ (15 mL) is added dropwise in 30 min, under stirring, and the reaction temperature is allowed to rise to about 20 °C. The solution is washed with water (3 × 20 mL), dried ($Na_2SO_4$), and concentrated to dryness. A part (1.034 g) of the pale yellow crude oil (2.011 g, 74%), $R_f$ 0.48 and 0.41 using EtOAc/toluene (1:8) as eluent, is fractionated by flash chromatography on a column filled with silica gel using the same (1:4) eluent. The faster moving product **17** (328 mg, 32%), mp 69–70 °C, the slower moving product **17′** (198 mg, 19%), mp 71–72 °C, and some unresolved mixture (508 mg, 49%) are obtained (Table).

**Z-Val-Lac-Phe-OEt (19′):**
This is prepared following the general procedure given above for the depsipeptides from Z-Val (**6**, $R^2$ = *i*-Pr; 150.8 mg, 0.6 mmol), **17′** (197 mg, 0.6 mmol), and $Ag_2O$ (140 mg, 0.6 mmol); oil; $R_f$ 0.27; yield: 250 mg (84%). Resolution of the diastereomeric mixture is achieved by reverse phase HPLC on a Brucker LC-21-B equipped with Rheodine injection valve, revelation with UV spectrometer LC 313 at 220 nm, using as a stationary less polar phase IB01 c-18 (250 × 4.5 mm, particles 5.0 μm) column with the eluting system (a) 10% MeCN in water, (b)

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80% MeCN in water, each containing 0.1% $CF_3CO_2H$. The two diastereoisomers **19** and **19'** are eluted in 25 min via a linear gradient of the solvent (ab), from 1:1 to 1:4. Retention times: **19'**: 20'51''; **19**: 21'21''. Percentage of **19**: 7.8%.

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