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Gold-Catalyzed Amide/Carbamate-Linked *N,O*-Acetal Formation with Bulky Amides and Alcohols

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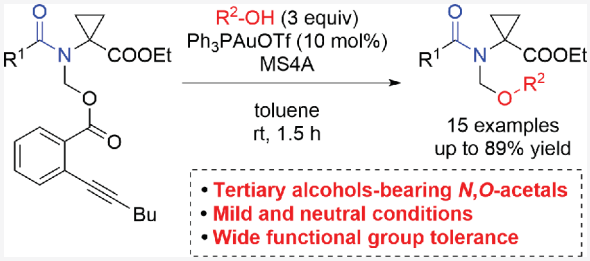
ABSTRACT: A gold-catalyzed *N,O*-acetal formation was established to construct an amide/carbamate-linked *N,O*-acetal substructure with bulky alcohols. The acyliminium cation species generated from *o*-alkynylbenzoic acid ester in the presence of a gold catalyst is highly reactive and underwent nucleophilic attack of various bulky alcohols and phenols at room temperature under neutral conditions, leading to the corresponding *N,O*-acetals in yields of 34−89% with good functional group tolerance.



The *N,O*-acetal moiety has been well-known as an important precursor of active iminium cation species in Mannich and Pictet−Spengler reactions.[1] Among these species, amide/peptide-linked *N,O*-acetals have been recently noticed as an important substructure for use in various fields in biologically active natural products,[2] in backbone *NH*-protecting groups during peptide synthesis,[3] as stable linkers in antibody−drug conjugates,[4] and as prodrugs.[5]

There have been several reports of acyclic carbonyl-linked *N,O*-acetal formation by Mannich-type reactions using amides and aldehydes/acetals[6] and oxidative fragmentation of amino acids/amino alcohols.[7] However, these applications to produce tertiary amide/carbamate-containing *N,O*-acetals are limited. One of the procedures generally used is the alkylation of chloromethyl adducts. For example, *N*-chloromethylated amides, prepared from corresponding secondary amides, reacted with alcohols including antitumor compounds, such as SN-38 and auristatin E, under mildly basic conditions to provide the desired *N,O*-acetals (Scheme 1a).[3−5] Ellman et al. conducted the *N*-alkylation of a secondary amide with potassium hexamethyldisilazide (KHMDS) and chloromethyl 3-methylbutanoate during the total synthesis of tubulysin D (Scheme 1b).[8] A relatively stable *N*-trialkylsilylmethyl group has also been employed as a latent form of peptide-linked *N,O*-acetals. Additionally, the electrochemical oxidation in the presence of TBAF or Tamao-type oxidation affords the *N,O*-acetal functionality (Scheme 1c).[9]

Nonetheless, carbonyl-linked *N,O*-acetal formation at a sterically hindered position is still a difficult task. Our goal is synthetic studies on branched-peptide antibiotics, named stalobacin I (Figure 1).[2g] A *N,O*-acetal substructure in stalobacin I is composed of two non-proteinogenic amino acids, α,α'-disubstituted carnosadine lactam and 3-hydroxyisoleucine, linked via a methylene group. A key challenge for the total synthesis is the incorporation of a tertiary-alcohol-installed *N,O*-acetal moiety on an amide nitrogen of a backbone peptide, which has rarely been found in natural and unnatural products. Disappointingly, our initial attempts based on S_N2-type *N*- and *O*-alkylation with corresponding chloromethyl adducts were fruitless owing to the bulkiness of the tertiary alcohol. To overcome the steric issue, we focused on *o*-alkynylbenzoic acid esters as effective alkylation agents in the presence of cationic gold(I) catalyst, as reported by Asao et al.[10] This substructure has also been known as a precursor of highly reactive oxonium and carbenium cation species in the glycosidation[11] and the propargylation,[12] respectively. Based on these reports, we envisioned that an acyliminium cation species, generated from the corresponding *o*-alkynylbenzoic acid ester in the presence of a catalytic amount of cationic gold(I), can work as a sterically less-hindered electrophile to react with bulky alcohols via S_N1-type *O*-alkylation (Scheme 1d). Herein, we report an amide/carbamate-linked *N,O*-acetal formation method that uses a highly reactive acyliminium cation generated in situ by the $Ph_3PAuOTf$ catalyst.

Our study began from the preparation of the acyliminium cation precursors **3** from 1-aminocyclopropanecarboxylic acid derivatives **1** as a structurally simplified surrogate of carnosadine lactam. The initial attempt for the *N*-chloromethylation of **1a** was carried out using $TMSCl/(CH_2O)_n$ according to the reported procedure.[3b,4,5c] Although substrate **1a** was not fully consumed within 24 h, the resulting *N*-chloromethyl adduct reacted by subsequent addition of *o*-

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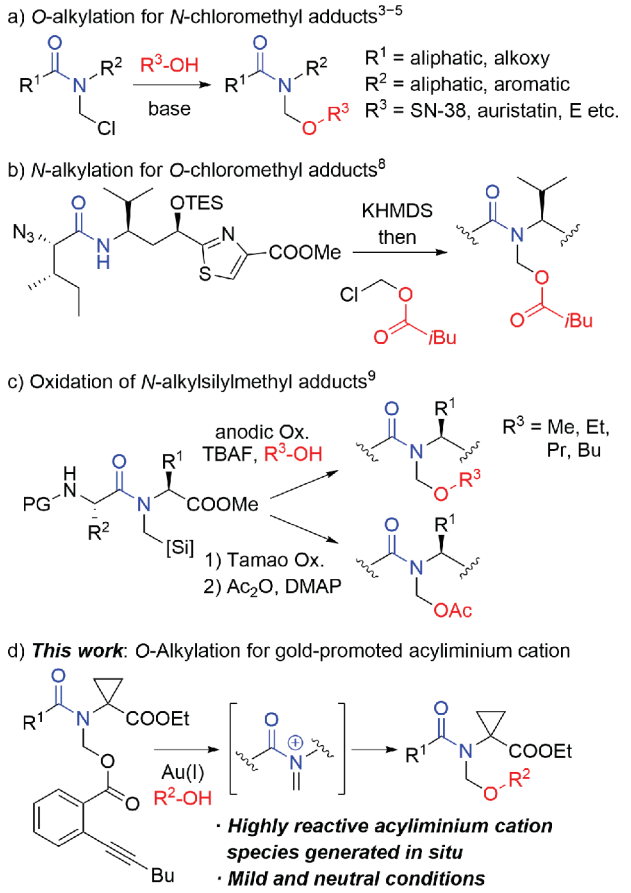
Scheme 1. Synthetic Strategy for Tertiary Amide/Carbamate-Linked *N,O*-Acetals



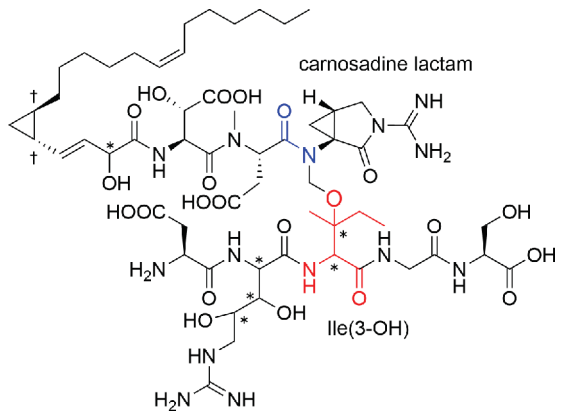
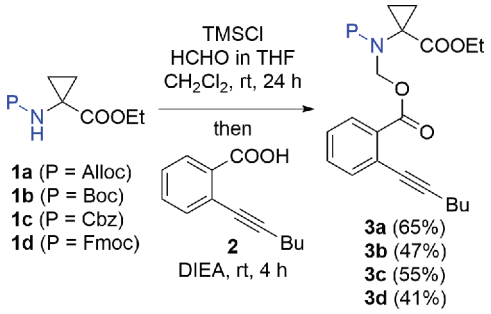


Figure 1. Chemical structure of stalobacin I. The absolute configuration of the asymmetric carbons with an asterisk was not determined. The relative configuration of the *trans*-cyclopropane carbons marked by a dagger was clarified, whereas the absolute configuration of them was unclear.

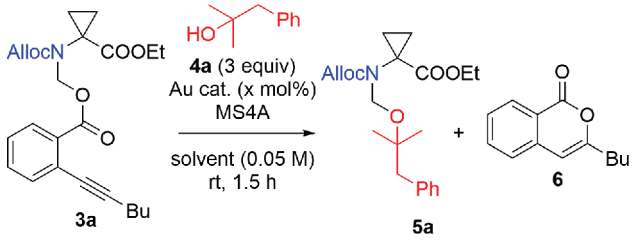
hexynylbenzoic acid **2** and DIEA in an one-pot operation, providing the desired *o*-hexynylbenzoic acid ester **3a** in a 36% yield. After investigation of the HCHO source, solvent, and base, the *N*-chloromethylation step was found to be dramatically improved when using a solution of monomeric HCHO[13] instead of polymeric $(CH_2O)_n$, and the subsequent addition of **2** and DIEA afforded **3a**−**3d**, bearing Alloc, Boc, Cbz, and Fmoc groups, in moderate yields (Scheme 2).

Scheme 2. Preparation of the Acyliminium Cation Precursor 3



With the desired acyliminium cation precursor in hand, we next surveyed a gold-catalyzed *N,O*-acetal formation of *N*-Alloc-protected **3a** with a bulky alcohol. The reaction conditions were optimized using 2-methyl-1-phenylpropan-2-ol (**4a**) as a substrate, and the results are shown in Table 1.

Table 1. Gold-Catalyzed *N,O*-Acetal Formation of 4 with 5a via Acyliminium Cation Species



entry	Au cat.[a] (*x* mol %)	solvents	yield of **5a**[b,c] (%)
1	$Ph_3PAuOTf$ (30)	CH_2Cl_2	63
2	$Ph_3PAuOTf$ (10)	CH_2Cl_2	37
3	$Ph_3PAuOTf$ (10)	toluene	73
4	$Ph_3PAuOTf$ (10)	toluene/CH_2Cl_2 (7:1)	73
5	$Ph_3PAuOTf$ (5)	toluene	69
6	$Ph_3PAuOTf$ (2)	toluene	17
7[d]	$Ph_3PAuOTf$ (10)	toluene	57
8	$Ph_3PAuNTf_2$ (10)	toluene	59

[a]The Au catalyst was prepared in situ from Ph_3PAuCl and the corresponding Ag salt. [b]Isolated yield. [c]The isocoumarin **6** was isolated in 84−99% yields. [d]Performed at 50 °C.

According to the gold-catalyzed glycosidation procedure reported by Yu,[11] **3a** was activated using a catalytic amount of $Ph_3PAuOTf$ (30 mol %) prepared in situ in the presence of MS4A. The generated acyliminium cation species was immediately captured by the alcohol **4a** to provide the desired *N,O*-acetal **5a** in a 63% yield with the isocoumarin **6** in a 98% yield (entry 1). Compared with a one-pot approach from **1a** via the *N*-chloromethyl adduct, the yield of **5a** was dramatically improved,[14] suggesting usefulness of our procedure for bulky substrates. We next tried to reduce the amounts of the Au catalyst. However, the *N,O*-acetal formation led to a significant decrease in yield when the amount of the Au catalyst was reduced to 10 mol % (37%, entry 2). After several experiments, the choice of solvent was found to be important. Using toluene or mixed toluene/CH_2Cl_2 (7:1) as a solvent improved the yield up to 73% (entries 3 and 4). Toluene could stabilize the generated acyliminium cation species through π-stacking interactions.[15] The *N,O*-acetal formation led to a slight decrease in yield when the amount of the Au catalyst was

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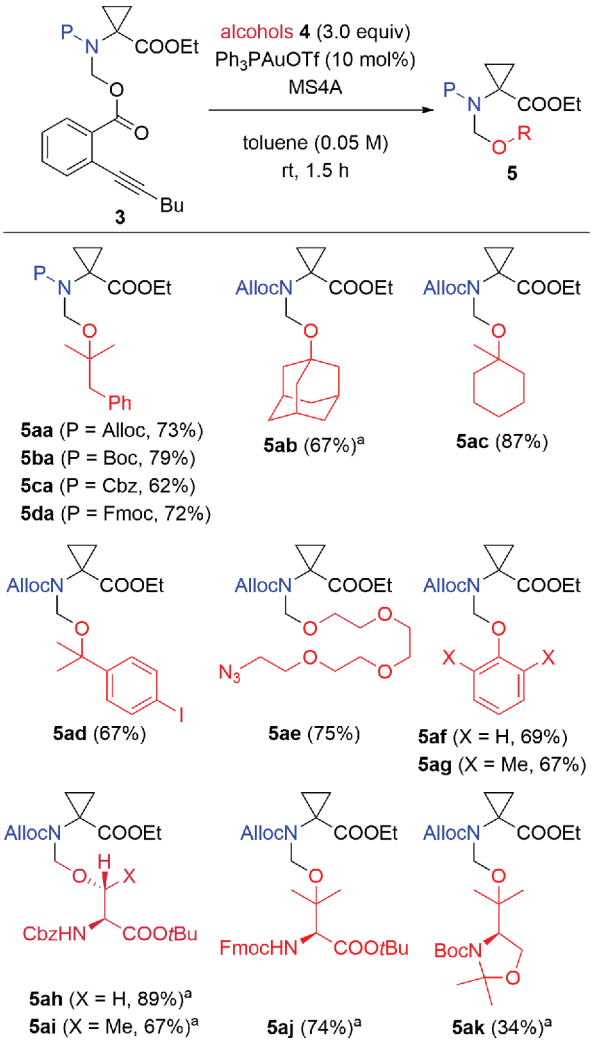
reduced to 5 mol % (69%, entry 5), whereas further reduction to 2 mol % resulted in a significant decrease in yield (17%, entry 6). Upon increasing the reaction temperature, the yield decreased owing to the decomposition of substrate **3a** (entry 7). Other cationic Au(I) species, such as $Ph_3PAuNTf_2$, resulted in a moderate yield (59%, entry 8). Thus, we determined that the optimized condition is shown in entries 3 and 4.

The substrate scope for our developed *N,O*-acetal methodology is depicted in Scheme 3. When alcohols were not

Scheme 3. Scope of Alcohols 4 in the *N,O*-Acetal Formation of 3[b]

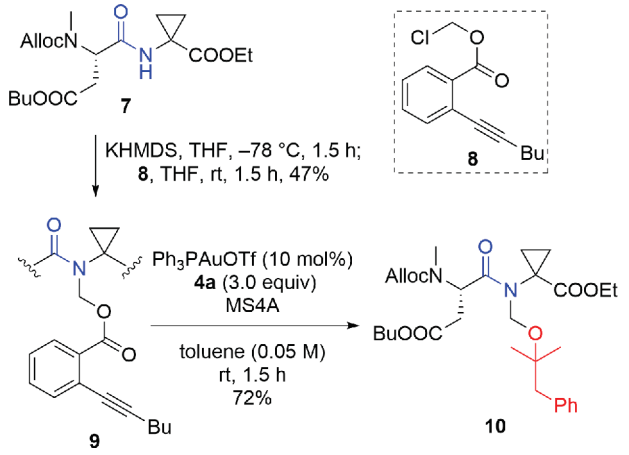


[a]Toluene/CH_2Cl_2 (7:1) was used as a mixed solvent. [b]Yields refer to isolated yield.

dissolved in toluene, toluene/CH_2Cl_2 (7:1) was used as a mixed solvent. The precursors **3a**–**3d** bearing carbamate-type protecting groups, such as Alloc, Boc, Cbz, and Fmoc groups, readily reacted with the alcohol **4a** under optimized conditions, providing the corresponding *N,O*-acetals **5aa**–**5da** in moderate to good yields (69–79%). Cyclic tertiary alcohols, such as 1-adamantanol (**4b**) and 1-methylcyclohexanol (**4c**), were transformed into the corresponding products of **5ab** (67%) and **5ac** (87%). 4-Iodophenyl and azide groups, which are effective for transition-metal-catalyzed coupling reactions and Huisgen cycloaddition, were found to be tolerant under the reaction conditions. Products **5ad** and **5ae** were afforded in 67 and 75% yields, respectively. Phenols, including sterically hindered 2,6-disubstituents, also reacted to provide *N,O*-acetals **5af** (69%) and **5ag** (67%). Next, we examined the *N,O*-acetal formation using hydroxy-bearing amino acids: serine, threonine, and 3-hydroxyvaline. Primary, secondary, and tertiary alcohols on the side chains of these amino acids reacted to produce *N,O*-acetal-linked dipeptides **5ah**–**5aj** in moderate to good yields (67–89%). Additionally, a tertiary alcohol having a *N,O*-acetonide moiety was applied, affording **5ak** in a 34% yield. Of note, protecting groups, such as Alloc, Boc, Cbz, Fmoc, and *t*Bu ester, which are used widely in peptide synthesis, are tolerated under our *N,O*-acetal formation protocols.

We next shifted our attention to the synthesis of the amide-linked *N,O*-acetal substructure, as presented in stalobacin I, and the reaction using the dipeptide **7** is illustrated in Scheme 4. Because a *N,N*-dialkylamine bearing a bulky substituent is

Scheme 4. Gold-Catalyzed *N,O*-Acetal Formation of the Dipeptide 9 with 4a



often poorly reactive for activated acylating reagents, such as acid chlorides and mixed acid anhydrides,[9c] installing a *N,O*-acetal substructure for an amide compound is also worthwhile. Preparation of the acyliminium cation precursor **9** was conducted using the established protocol in Scheme 2; however, the *N*-chloromethylation of **7** with TMSCl/monomeric HCHO did not proceed, recovering the substrate. Given the poorer nucleophilicity of the amide nitrogen than that of the carbamate nitrogen, we planned the *N*-alkylation of **7** with the *O*-chloromethyl adduct **8** according to Ellman's report.[8] The amide anion of **7**, generated with KHMDS at −78 °C, readily reacted with **8**, providing **9** in a 47% yield. The *N,O*-acetal formation of **9** with **4a** was successful under the optimized conditions, and the desired **10** was obtained in a 72% yield. This result indicates the possibility of our procedure for application to the synthesis of structurally complex *N,O*-acetal compounds.

Based on the gold-catalyzed glycosidation,[11] a plausible mechanism of gold-catalyzed *N,O*-acetal formation is shown in Scheme 5. The triple bond in precursor **I** is initially activated by gold(I). Subsequent intramolecular nucleophilic attack of the proximal carbonyl oxygen in **II** results in the removal of isocoumarin **IV**, providing the acyliminium cation species **III**. The resulting **III** is readily captured by an alcohol to produce the desired *N,O*-acetal **V**. Because an acidic proton derived

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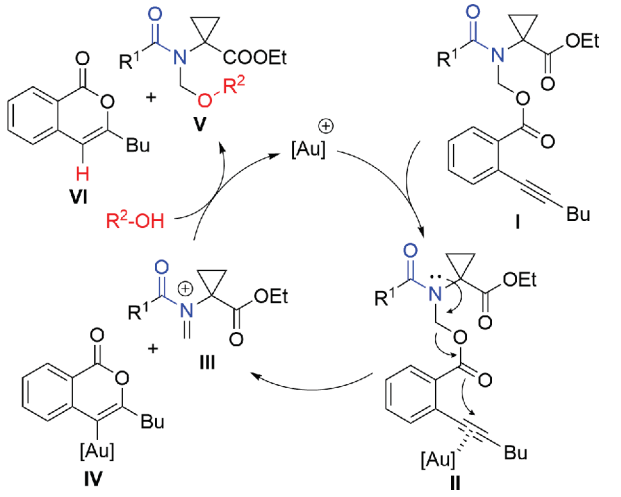
Scheme 5. Plausible Mechanism of Au-Catalyzed *N,O*-Acetal Formation



from the alcohol is consumed by proto-demetalation of **IV** to afford isocoumarin **VI**, the reaction proceeds under neutral conditions with the regeneration of the gold(I) catalyst.

In summary, we have demonstrated the carbamate/amide-linked *N,O*-acetal formation using cyclopropaneamino acid derivatives. An acyliminium cation species generated from *o*-ethynylbenzoic acid ester **3** in the presence of 10 mol % of $Ph_3PAuOTf$ is highly reactive, and nucleophilic attack of alcohols **4**, especially even sterically hindered 2,6-disubstituted phenols and tertiary alcohols, proceeded at room temperature, leading to the corresponding *N,O*-acetals **5** in moderate to good yields. Functional group tolerance for not only iodophenyl and azido groups but also various protecting groups, such as Alloc, Cbz, Fmoc, Boc, and the *t*Bu ester, suggests the effectiveness of the reaction in the synthesis of highly functionalized peptide compounds. Furthermore, our procedure was applied to dipeptide-containing precursor **9** to produce the *N,O*-acetal **10**. This reaction could be widely useful for the formation of tertiary-alcohol-containing *N,O*-acetals, and the synthesis of stalobacin I and its *N,O*-acetal-containing analogues is underway.

EXPERIMENTAL SECTION

General Techniques. All commercially available reagents were purchased from commercial suppliers and used as received. Dry tetrahydrofuran (THF) and CH_2Cl_2 (Kanto Chemical Co.) were obtained by passing commercially available predried, oxygen-free formulations through an activated alumina column. All reactions in the solution phase were monitored by TLC carried out on Merck silica gel plates (0.2 mm, 60F-254) with UV light and visualized by *p*-anisaldehyde/H_2SO_4/EtOH solution, phosphomolybdic acid/EtOH solution, or ninhydrin/AcOH/1-BuOH solution. Column chromatography was carried out with silica gel 60 N (Kanto Chemical Co. 100−210 μm). Preparative TLC was performed on 0.75 mm Wakogel B-5F PLC plates. ^{1}H NMR spectra (400 and 600 MHz) and ^{13}C NMR spectra (100 and 150 MHz) were recorded on JEOL JNMAL400 and JEOL JNM-ECA600 spectrometers in the indicated solvent. Chemical shifts (δ) are reported in units of parts per million (ppm) relative to the signal for internal TMS (0.00 ppm for ^{1}H) for solutions in $CDCl_3$. NMR spectral data are reported as follows: $CHCl_3$ (7.26 ppm for ^{1}H), $CDCl_3$ (77.0 ppm for ^{13}C), CH_3CN (1.94 ppm for ^{1}H), CD_3CN (118.26 ppm for ^{13}C), when internal standard is not indicated. Multiplicities are reported by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet), td (triple doublet), brs (broad singlet), brd (broad doublet), brt (broad triplet), brq (broad quartet), and *J* (coupling constants in hertz). High-resolution mass spectra were measured on a Thermo Scientific Exactive Plus Orbitrap Mass Spectrometer (for ESI). IR spectra were recorded on a JASCO FTIR-4100 instrument. Only the strongest and/or structurally important absorptions are reported as the IR data afforded in wavenumbers (cm^{-1}). Optical rotations were measured on a JASCO P-1010 polarimeter. Melting points were measured with a Round Science Inc. RFS-10 instrument and are not corrected.

*Ethyl 1-(((Allyloxy)carbonyl)amino)cyclopropane-1-carbo-xylate (**1a**).* To a solution of 1-(ethoxycarbonyl)cyclopropane-1-carboxylic acid[16] (1.27 g, 8.03 mmol) in dry $(CH_2Cl)_2$ (50 mL) were added NEt_3 (1.5 mL, 10.4 mmol) and DPPA (1.9 mL, 8.83 mmol) at room temperature under an argon atmosphere, and the mixture was stirred at the same temperature for 30 min. After being stirred at reflux for 2 h in an oil bath, the reaction mixture was cooled to room temperature, and allyl alcohol (1.1 mL, 16.1 mmol) was added to the above mixture. After being stirred at reflux for 3 h in an oil bath, the reaction mixture was cooled to room temperature, concentrated in vacuo, and diluted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and filtrated. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 7:1) to afford the *N*-Alloc amine **1a** (1.58 g, 7.41 mmol, 92%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83−5.92 (m, 1H), 5.50 (brs, 1H), 5.27 (dd, 1H, *J* = 17.2, 1.3 Hz), 5.17 (dd, 1H, *J* = 10.5, 1.3 Hz), 4.55 (brd, 2H, *J* = 4.2 Hz), 4.11 (q, 2H, *J* = 7.2 Hz), 1.50 (dd, 2H, *J* = 7.9, 4.5 Hz), 1.20 (t, 3H, *J* = 7.2 Hz), 1.15 (brs, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.7, 156.3, 132.6, 117.6, 65.6, 61.3, 34.4, 17.6, 14.0; IR (neat) 3340, 2984, 1727, 1519, 1298, 1304, 1242, 1161, 1079 cm^{-1}; HRMS[ESI] *m/z* calcd for $C_{10}H_{16}NO_4$ $[M + H]^+$ 214.1074, found 214.1073.

*Ethyl 1-((tert-Butoxycarbonyl)amino)cyclopropane-1-carbo-xylate (**1b**).* Compound **1b** was prepared using the reported procedure.[17] To a solution of 1-(ethoxycarbonyl)cyclopropane-1-carboxylic acid[16] (1.38 g, 8.74 mmol) in dry *t*BuOH (25 mL) were added NEt_3 (1.5 mL, 10.5 mmol) and DPPA (2.1 mL, 9.62 mmol) at room temperature under an argon atmosphere. After being stirred at 100 °C for 21 h in an oil bath, the reaction mixture was cooled to room temperature, quenched with water, and concentrated in vacuo to remove *t*BuOH. The aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtrated. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 7:1) to afford the *N*-Boc amine **1b** (1.52 g, 6.81 mmol, 76%) as a colorless oil. The spectral data of synthetic **1b** were in good agreement with those reported.[17] ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.13 (brs, 1H), 4.15 (q, 2H, *J* = 7.1 Hz), 1.50 (brs, 2H), 1.45 (s, 9H), 1.24 (t, 3H, *J* = 7.1 Hz), 1.15 (brs, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 173.1, 156.0, 79.9, 61.3, 34.3, 28.3, 17.5, 14.1; IR (neat) 3357, 2979, 17525, 1509, 1368, 1251, 1183, 1073 cm^{-1}; HRMS[ESI] *m/z* calcd for $C_{11}H_{19}NO_4Na$ $[M + Na]^+$ 252.1206, found 252.1204.

Ethyl 1-Aminocyclopropane-1-carboxylate Hydrochloride. To a solution of the *N*-Boc amine **1b** (678 mg, 2.96 mmol) in dry 1,4-dioxane (3.0 mL) was added 4 M HCl/1,4-dioxane (7.4 mL, 29.6 mmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 5 h, the reaction mixture was concentrated in vacuo to afford the amine (489 mg, 2.95 mmol, quant.) as a yellowish oil, which was solidified during refrigerated storage. mp 118−119 °C [lit. 108−110 °C];[18] ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.07 (brs, 3H), 4.25 (q, 2H, *J* = 7.1 Hz), 1.76 (dd, 2H, *J* = 7.9, 5.8 Hz), 1.53 (dd, 2H, *J* = 7.9, 5.8 Hz), 1.30 (t, 3H, *J* = 7.1 Hz); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 169.2, 62.6, 34.6, 14.2, 14.0; IR (neat) 3416, 2912, 1737, 1594, 1531, 1381, 1210 cm^{-1}; HRMS[ESI] *m/z* calcd for $C_6H_{12}NO_2$ $[M + H]^+$ 130.0863, found 130.0861.

*Ethyl 1-(((Benzyloxy)carbonyl)amino)cyclopropane-1-carboxy-late (**1c**).* To a solution of ethyl 1-aminocyclopropane-1-carboxylate hydrochloride (56.9 mg, 344 μmmol) in dry 1,4-dioxane (0.7 mL)

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and water (0.7 mL) were added Na_2CO_3 (130 mg, 1.24 mmol) and CbzCl (58.6 μL, 412 μmol) at 0 °C. After being stirred at room temperature for 9 h, the reaction mixture was diluted with EtOAc and quenched with 1 M aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 4:1) to afford the *N*-Cbz amine **1c** (85.4 mg, 324 μmol, 94%) as a colorless oil. The spectral data of synthetic **1c** were in good agreement with those reported.[18] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30−7.36 (m, 5H), 5.38 (brs, 1H), 5.13 (brs, 2H), 4.13−4.14 (m, 2H, 1.55 (brs, 2H), 1.20−1.24 (m, 5H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 172.7, 156.5, 136.4, 128.5, 128.1, 66.8, 61.4, 34.6, 17.7, 14.1; IR (neat) 3335, 2981, 1741, 1517, 1246, 1183, 1028 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{14}H_{18}NO_4$ $[M + H]^+$ 264.1230, found 264.1227.

*Ethyl 1-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-cyclopropane-1-carboxylate (**1d**).* To a solution of ethyl 1-aminocyclopropane-1-carboxylate hydrochloride (52.4 mg, 316 μmmol) in dry 1,4-dioxane (0.6 mL) and water (0.6 mL) were added Na_2CO_3 (121 mg, 948 μmol) and FmocOSu (128 mg, 380 μmol) at 0 °C. After being stirred at room temperature for 9 h, the reaction mixture was diluted with EtOAc and quenched with 1 M aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 4:1) to afford the *N*-Fmoc amine **1d** (76.1 mg, 217 μmol, 68%) as a white solid. mp 136−137 °C; ^{1}H NMR (600 MHz, $CDCl_3$, 3:1 rotamer mixture) δ 7.76 (d, 2H, *J* = 7.4 Hz), 7.60−7.61 (m, 2H), 7.40 (t, 2H, *J* = 7.4 Hz), 7.31 (t, 2H, *J* = 7.4 Hz), 5.37 (brs, 0.7H), 5.04 (brs, 0.3H), 4.41−4.51 (m, 2H), 4.00−4.26 (m, 3H), 1.57 (brs, 2H), 1.22−1.25 (m, 5H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, 3:1 rotamer mixture) δ 176.6, 143.9, 141.3, 127.7, 127.0, 125.1, 120.0, 67.0, 61.4, 47.1, 29.7, 17.7, 14.2; IR (neat) 3319, 2980, 1714, 1518, 1337, 1247, 1181, 739 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{21}H_{21}NO_4Na$ $[M + Na]^+$ 374.1363, found 374.1356.

*2-(Hex-1-yn-1-yl)benzoic Acid (**2**).* Compound **2** was prepared using the reported procedure.[19] To a solution of methyl 2-iodobenzoate (524 mg, 2.00 mmol) in NEt_3 (6.0 mL) were added hex-1-yne (274 μL, 2.40 mmol), $PdCl_2(PPh_3)_2$ (28.1 mg, 40.0 μmol), and CuI (9.1 mg, 48.0 μmol) at room temperature under an argon atmosphere. After being stirred at the same temperature for 16 h, the reaction mixture was concentrated in vacuo, and the resulting residue was diluted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and filtrated. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 70:1) to afford the ethynylbenzene (394 mg, 1.82 mmol, 91%) as a pale yellow oil. The spectral data of synthetic ethynylbenzene were in good agreement with those reported.[19]

To a solution of the ethynylbenzene (398 mg, 1.84 mmol) in dry THF (7.3 mL) was added a solution of NaOH (147 mg, 3.68 mmol) in water (15 mL) at 0 °C. After being stirred at 50 °C for 12 h in an oil bath, the reaction mixture was diluted with water and concentrated in vacuo to remove THF. The aqueous layer was washed twice with CH_2Cl_2, acidified with 10% aqueous citric acid to pH 4, and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to afford the carboxylic acid **2** (336 mg, 1.66 mmol, 90%) as a colorless oil. Because the corresponding isocoumarine **6** was formed during the process of purification by column chromatography on silica gel, the crude **2** was immediately used for the next reaction. The spectral data of synthetic **2** were in good agreement with those reported.[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, 1H, *J* = 7.5 Hz), 7.51 (d, 1H, *J* = 7.5 Hz), 7.42 (t, 1H, *J* = 7.5 Hz), 7.31 (t, 1H, *J* = 7.5 Hz), 3.92 (s, 3H), 2.48 (t, 2H, *J* = 7.1 Hz), 1.48−1.66 (m, 4H), 0.96 (t, 3H, *J* = 7.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.0, 134.2, 131.9, 131.5, 130.1, 127.1, 124.5, 96.0, 79.2, 52.0, 30.7, 22.0, 19.5, 13.6; IR (neat) 2955, 2871, 2311, 1731, 1485, 1432, 1294, 1130, 1083, 701 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{14}H_{16}O_2$ $[M + H]^+$ 217.1123, found 217.1122.

General Procedure for the Synthesis of Acyliminium Cation Precursors 3 (GP-1). To a solution of the carbamates **1** (1.0 equiv) in dry CH_2Cl_2 (6.0 mL/mmol) were added TMSCl (3.0 equiv) and monomeric formaldehyde (ca. 0.5−0.6 M in THF solution,[13] 3.0 equiv) at room temperature under an argon atmosphere, and the mixture was stirred at the same temperature for 24 h. DIEA (3.0 equiv) and benzoic acid **2** (1.5 equiv) were then added to the above mixture at room temperature. After being stirred at the same temperature for 4 h, the reaction mixture was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc) to afford the acyliminium cation precursors **3**.

*The Precursor **3a**.* Compound **3a** was prepared from the *N*-Alloc amine **1a** (70.0 mg, 328 μmol) according to GP-1 and was obtained in a 65% yield (92.0 mg, 215 μmol) as a colorless oil after purification by column chromatography on silica gel (eluted with hexane/EtOAc = 8:1). ^{1}H NMR (400 MHz, $CDCl_3$, rotamer mixture) δ 7.88 (brd, 1H, *J* = 7.1 Hz), 7.50 (brd, 1H, *J* = 7.1 Hz), 7.42 (brt, 1H, *J* = 7.1 Hz), 7.27−7.31 (m, 1H), 5.57−5.94 (m, 3H), 5.29−5.33 (m, 1H), 5.22 (dd, 1H, *J* = 10.6, 1.1 Hz), 4.67−4.68 (m, 2H), 4.04−4.11 (m, 2H), 2.46 (t, 2H, *J* = 7.1 Hz), 1.29−1.73 (m, 8H), 1.14 (brt, 3H, *J* = 6.8 Hz), 0.95 (t, 3H, *J* = 7.3 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamer mixture) δ 172.2, 171.9, 165.6, 165.5, 156.5, 155.5, 141.4, 134.4, 134.3, 132.8, 132.1, 131.6, 131.2, 130.3, 130.2, 129.8, 127.9, 127.0, 124.8, 117.5, 96.4, 74.2, 74.1, 66.8, 66.7, 61.5, 41.6, 41.1, 36.7, 22.0, 20.7, 19.5, 17.2, 14.0, 13.6; IR (neat) 2962, 1728, 1308, 1273, 1238, 1187, 1122 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{24}H_{29}NO_6Na$ $[M + Na]^+$ 450.1887, found 450.1882.

*Larger Scale Synthesis of **3a**.* The *N*-chloromethylation followed by the *O*-alkylation with **2** for the *N*-Alloc amine **1a** (263 mg, 1.23 mmol) was carried out according to GP-1. The *N*,*O*-acetal **3a** was obtained in a 47% yield (91% brsm, 248 mg, 581 μmol), and the substrate **1a** was recovered in a 49% yield (128 mg, 60.0 μmol).

*The Precursor **3b**.* Compound **3b** was prepared from the *N*-Boc amine **1b** (60.3 mg, 263 μmol) according to GP-1 and was obtained in a 47% yield (55.2 mg, 124 μmol) as a colorless oil after purification by column chromatography on silica gel (eluted with hexane/EtOAc = 10:1). ^{1}H NMR (600 MHz, $CDCl_3$, rotamer mixture) δ 7.88 (brd, 1H, *J* = 7.3 Hz), 7.49 (brd, 1H, *J* = 7.6 Hz), 7.41−7.42 (m, 1H), 7.27−7.30 (m, 1H), 5.52−5.80 (m, 2H), 5.29−5.33 (m, 1H), 4.05−4.13 (m, 2H), 2.47 (t, 2H, *J* = 7.3 Hz), 1.21−1.69 (m, 17H), 1.16 (t, 3H, *J* = 7.2 Hz), 0.95 (t, 3H, *J* = 7.4 Hz); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, rotamer mixture) δ 172.6, 172.3, 165.8, 165.4, 155.5, 154.7, 1134.5, 134.3, 131.5, 130.3, 130.0, 127.03, 126.98, 124.84, 124.77, 96.3, 81.6, 91.2, 79.1, 74.7, 73.9, 61.4, 41.2, 30.7, 28.2, 22.0, 20.9, 19.5, 17.4, 14.1, 13.6; IR (neat) 2975, 2933, 1722, 1368, 1310, 1283, 1241, 1186, 1122, 756 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{25}H_{33}NO_6Na$ $[M + Na]^+$ 466.2200, found 466.2188.

*The Precursor **3c**.* Compound **3c** was prepared from the *N*-CBz amine **1c** (62.4 mg, 237 μmol) according to GP-1 and was obtained in a 55% yield (62.7 mg, 131 μmol) as a colorless oil after purification by column chromatography on silica gel (eluted with hexane/EtOAc = 10:1). ^{1}H NMR (600 MHz, $CDCl_3$, rotamer mixture) δ 7.78−7.89 (m, 1H), 7.29−7.50 (m, 8H), 5.57−7.84 (m, 2H), 5.20−5.24 (m, 2H), 3.99−4.07 (m, 2H), 2.44−2.45 (m, 2H), 0.93−1.59 (m, 17H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, rotamer mixture) δ 172.2, 171.9, 165.7, 165.5, 156.7, 136.04, 136.01, 134.5, 134.4, 131.7, 131.2, 131.1, 130.4, 130.2, 128.5, 128.3, 128.1, 127.7, 127.0, 124.9, 94.4, 79.1, 74.2, 67.9, 67.7, 61.6, 41.7, 41.1, 30.7, 22.0, 20.8, 19.5, 17.3, 13.9, 13.6; IR (neat) 2958, 2931, 1726, 1307, 1279, 1239, 1187 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{28}H_{31}NO_6Na$ $[M + Na]^+$ 500.2044, found 500.2034.

*The Precursor **3d**.* Compound **3d** was prepared from the *N*-Fmoc amine **1d** (62.2 mg, 177 μmol) according to GP-1 and was obtained in a 41% yield (41.1 mg, 72.7 μmol) as a colorless oil after purification by column chromatography on silica gel (eluted with hexane/EtOAc = 10:1). ^{1}H NMR (600 MHz, $CDCl_3$, 2:1 rotamer mixture) δ 7.14−

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7.29 (m, 12H), 5.74 (d, 1H, J = 10.6 Hz), 5,46 (d, 1H, J = 10.6 Hz), 4.11−4.66 (m, 4.6H), 3.82−3.83 (m, 1.4H), 2.43−2.45 (m, 2H), 1.15−1.61 (m, 9H), 0.92−1.01 (m, 4.3H), 0.76 (brs, 0.7H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, 2:1 rotamer mixture) δ 171.8, 169.8, 165.6, 156.7, 155.8, 143.8, 143.6, 141.5, 141.2, 134.6, 134.3, 131.9, 131.7, 131.2, 130.4, 127.7, 127.1, 127.0, 125.1, 124.8, 124.5, 124.3, 120.0, 96.4, 79.1, 74.5, 74.0, 68.5, 67.6, 61.6, 61.5, 47.1, 46.9, 40.8, 30.7, 29.7, 22.0, 20.4, 19.5, 17.2, 14.1, 13.9, 13.6; IR (neat) 2957, 2932, 1726, 1451, 1271, 1239, 1188 cm^{-1}; HRMS[ESI] m/z calcd for $C_{35}H_{35}NO_6Na$ $[M + Na]^+$ 588.2357, found 588.2348.

*2-(4-Iodophenyl)propan-2-ol (**4d**).* To a solution of the methyl 4-iodobenzoate (340 mg, 1.30 mmol) in dry THF (10 mL) was added MeMgBr (3.00 M in Et_2O, 1.3 mL, 3.90 mmol) dropwise at 0 °C under an argon atmosphere. After being stirred at the same temperature for 3 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 5:1) to afford the alcohol **4d** (303 mg, 1.16 mmol, 89%) as a pale yellow oil. The spectral data of synthetic **4d** were in good agreement with those reported.[20]

*11-Azido-3,6,9-trioxaundecan-1-ol (**4e**).* To a solution of HO-PEG_3-OH (1.00 g, 5.15 mmol) in dry CH_2Cl_2 (30 mL) were added Ag_2O (1.79 g, 7.22 mmol), NaI (849 mg, 5.66 mmol), and TsCl (1.03 g, 5.41 mmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 1 h, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 1:4 to EtOAc) to afford the ditosylate (632 mg, 1.26 mmol, 24%) as a colorless oil and the monotosylate (1.14 g, 3.28 mmol, 64%) as a colorless oil. The spectral data of synthetic monotosylate were in good agreement with those reported.[21]

To a solution of the monotosylate (1.00 g, 2.87 mmol) in dry MeCN (20 mL) was added NaN_3 (224 mg, 3.44 mmol) at room temperature under an argon atmosphere. After being stirred at reflux for 21 h in an oil bath, the reaction mixture was concentrated in vacuo to remove MeCN. The resulting residue was dissolved in EtOAc. The organic layer was washed with water, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 1:4) to afford the azide **4e** (348 mg, 1.59 mmol, 55%) as a colorless oil. The spectral data of synthetic **4e** were in good agreement with those reported.[21]

*Cbz-Ser-OtBu (**4h**).* To a solution of Cbz-Ser-OH (502 mg, 2.10 mmol, 1.0 equiv) in dry CH_2Cl_2 (21 mL) was added *t*-butyl 2,2,2-trichloroacetimidate (917 mg, 4.20 mmol, 2.0 equiv) at room temperature under an argon atmosphere. After being stirred at the same temperature for 4 h, the reaction mixture was diluted with EtOAc. The organic layer was washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 4:1) to afford the *tert*-butyl ester **4h** (484 mg, 1.57 mmol, 74%) as a white solid. The spectral data of synthetic **4h** were in good agreement with those reported.[22] Mp 93−94 °C [lit. 89−90 °C]; $[\alpha]^{22}_D$ −15 (c 1.0, EtOH) [lit. $[\alpha]^{22}_D$ −13.7 (c 1.03, EtOH)].

*Cbz-Thr-OtBu (**4i**).* Compound **4i** was prepared from Cbz-Thr-OH (772 mg, 3.05 mmol) according to the procedure described above for **4h** and was obtained in an 83% yield (783 mg, 2.53 mmol) as a colorless oil. The spectral data of synthetic **4i** were in good agreement with those reported.[23] $[\alpha]^{22}_D$ −10 (c 1.0, $CHCl_3$) [lit. $[\alpha]^{20}_D$ −10.3 (c 1.0, $CHCl_3$)].

*tert-Butyl (R)-4-(2-Hydroxypropan-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (**4k**).* Compound **4k** was prepared using the reported procedure.[24] To a solution of 3-(*tert*-butyl) 4-methyl (*R*)-2,2-dimethyloxazolidine-3,4-dicarboxylate (2.54 g, 9.78 mmol) in dry THF (80 mL) was added MeMgBr (3.00 M in Et_2O, 13 mL, 39.1 mmol) dropwise at −78 °C under an argon atmosphere. After being stirred at 0 °C for 7 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 10:1) to afford the alcohol **4k** (2.26 g, 8.70 mmol, 89%) as a pale yellow oil. The spectral data of synthetic **4k** were in good agreement with those reported.[25] $[\alpha]^{21}_D$ +21 (c 0.95, MeOH) [lit. $[\alpha]^{23}_D$ +23 (c 1.0, MeOH)].

Boc-Val(3-OH)-OH. To a solution of the oxazolidine **4k** (1.56 g, 6.02 mmol) in dry MeOH (50 mL) was added $TsOH{\cdot}H_2O$ (114 mg, 602 μmol) at room temperature under an argon atmosphere. After being stirred at the same temperature for 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and concentrated in vacuo to remove MeOH. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the resulting crude amino alcohol was used for the next reaction without further purification.

To a solution of the crude alcohol in dry MeCN (13 mL) and pH 6.8 buffer (13 mL) were added $NaClO_2$ (1.96 g, 21.7 mmol), $PhI(OAc)_2$ (194 mg, 602 μmol), and TEMPO (188 mg, 1.20 mmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 13 h, the reaction mixture was quenched with 1 M aqueous Na_2CO_3. The aqueous layer was washed with EtOAc, acidified with 1 M aqueous HCl to pH 3, and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was recrystallized from Et_2O/hexane to afford the carboxylic acid (1.05 g, 4.50 mmol, 75% in two steps) as a white solid. The spectral data of the synthetic compound were in good agreement with those reported.[26] Mp 121−123 °C [lit. 125−126 °C]; $[\alpha]^{28}_D$ −3.0 (c 1.0, MeOH) [lit. (enantiomer) $[\alpha]^{20}_D$ +2.5 (c 1.0, MeOH)].

*Fmoc-Val(3-OH)-OtBu (**4j**).* To a solution of Boc-Val(3-OH)-OH (552 mg, 2.37 mmol) in dry CH_2Cl_2 (3.0 mL) was added TFA (911 μL, 11.8 mmol, 5.0 equiv) at 0 °C under an argon atmosphere. After being stirred at the same temperature for 6 h, the reaction mixture was concentrated in vacuo and azeotroped with toluene/MeOH (1:1) to remove excess TFA. The resulting crude amine was used for the next reaction without further purification.

To a solution of the crude amine in 1,4-dioxane (5.0 mL) and water (5.0 mL) were added Na_2CO_3 (401 mg, 3.78 mmol, 1.6 equiv) and FmocOSu (1.28 g, 3.78 mmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 12 h, the reaction mixture was diluted with EtOAc and quenched with 1 M aqueous HCl. The organic layer was separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with $CHCl_3$/MeOH = 60:1) to afford the *N*-Fmoc amine **S8** (729 mg, 2.05 mmol, 87% in two steps) as a white amorphous solid. The spectral data of the synthetic compound were in good agreement with those reported.[27] $[\alpha]^{22}_D$ −8.0 (c 1.0, $CHCl_3$) [lit. $[\alpha]^{19}_D$ −6.7 (c 1.03, $CHCl_3$)].

Compound **4j** was prepared from Fmoc-Val(3-OH)-OH (729 mg, 2.05 mmol) according to the procedure described above for **4h** and was obtained in a 90% yield (759 mg, 1.85 mmol) as a colorless oil. $[\alpha]^{22}_D$ −13 (c 1.1, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, 2H, J = 7.3 Hz), 7.60 (d, 2H, J = 7.6 Hz), 7.39−7.41 (m, 2H), 7.30−7.33 (m, 2H), 5.60 (brd, 1H, J = 8.7 Hz), 4.38−4.46 (m, 2H), 4.23 (t, 1H, J = 7.0 Hz), 4.16 (d, 1H, J = 8.7 Hz), 1.50 (s, 9H), 1.29 (s, 3H), 1.25 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 170.9, 156.4, 143.81, 143.75, 141.3, 127.7, 127.1, 125.1, 125.0, 119.99, 119.98, 81.1, 72.0, 67.1, 61.9, 47.2, 28.0, 26.8, 26.3; IR (neat) 3352, 2979, 1712, 1517, 1370, 1225, 1151, 741 cm^{-1}; HRMS[ESI] m/z calcd for $C_{24}H_{29}NO_5Na$ $[M + Na]^+$ 434.1938, found 434.1931.

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General Procedures for the *N,O*-Acetal Formation of 3 with Alcohols 4 (GP-2). To a solution of Ph_3PAuCl (0.1 equiv) in dry toluene (3.0 mL/mmol) was added AgOTf (0.1 equiv) at room temperature under an argon atmosphere. After being stirred at the same temperature for 1.5 h in the dark, the resulting solution of $Ph_3PAuOTf$ was used for the next reaction without further purification.

To a solution of the acyliminium cation precursors **3** (1.0 equiv) in dry toluene (17 mL/mmol) or dry toluene/dry CH_2Cl_2 (7:1, 17 mL/mmol) were added MS4A (100 wt %), the alcohols **4** (3.0 equiv), and the above solution of $Ph_3PAuOTf$ in toluene at room temperature under an argon atmosphere. After being stirred at the same temperature for 1.5 h, the reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography (eluted with hexane/EtOAc) on silica gel or preparative TLC (eluted with hexane/EtOAc) to afford the *N,O*-acetals **5** and the isocoumarin **6** (84−99% yields) as a colorless oil. The spectral data of synthetic **6** were in good agreement with those reported.[28]

The N,O-Acetal ***5aa***. Compound **5aa** was prepared from the acyliminium cation precursor **3a** (35.1 mg, 82.1 μmol) and 2-methyl-1-phenyl-propanol (**4a**) (38.0 μL, 246 μmol) according to GP-2 and was obtained in a 73% yield (22.5 mg, 59.9 μmol) as a colorless oil after purification by preparative TLC (eluted with hexane/EtOAc = 3:1). ^{1}H NMR (600 MHz, $CDCl_3$, rotamer mixture) δ 7.24−7.27 (m, 2H), 7.18−7.22 (m, 3H), 5.86−5.93 (m, 1H), 5.17−5.33 (m, 3H), 4.52−4.63 (m, 3H), 4.13 (brq, 2H, *J* = 6.8 Hz), 2.76−2.79 (m, 2H), 1.78 (brs, 1H), 1.65 (brs, 1H), 1.29 (brs, 1H), 1.17−1.22 (m, 10H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rotamer mixture) δ 172.6, 156.8, 138.1, 132.59, 132.58, 130.6, 3, 130.59, 127.8, 126.2, 126.1, 117.7, 117.0, 75.8, 75.4, 73.8, 73.6, 66.4, 66.2, 61.2, 48.1, 40.7, 25.4, 25.1, 14.24, 14.18; IR (neat) 2976, 2370, 1720, 1396, 1302, 1186, 1044, 702 cm^{-1}; HRMS[ESI] *m/z* calcd for $C_{21}H_{29}NO_5Na$ [M + Na]$^+$ 398.1938, found 398.1931.

Larger Scale Synthesis of ***5aa***. The *N,O*-acetal formation for the acyliminium cation precursor **3a** (248 mg, 581 μmol) with the alcohol **4a** (269 μL, 1.74 mmol) was carried out according to GP-2, and the *N,O*-acetal **5aa** was obtained in a 55% yield (121 mg, 322 μmol) after purification by column chromatography on silica gel (eluted with hexane/EtOAc = 5:1).

The N,O-Acetal ***5ba***. Compound **5ba** was prepared from the acyliminium cation precursor **3b** (24.9 mg, 56.1 μmol) and 2-methyl-1-phenyl-propanol (**4a**) (26.0 μL, 246 μmol) according to GP-2 and was obtained in a 79% yield (17.3 mg, 44.2 μmol) as a colorless oil after purification by preparative TLC (eluted with hexane/EtOAc = 3:1). ^{1}H NMR (600 MHz, $CDCl_3$, rotamer mixture) δ 7.24−7.26 (m, 2H), 7.18−7.21 (m, 3H), 5.28 (brd, 1H, *J* = 1.6 Hz), 4.47 (brd, 1H, *J* = 1.6 Hz), 4.13−4.12 (m, 2H), 2.76−2.79 (m, 2H), 1.78 (brs, 1H), 1.60 (brs, 1H), 1.44−1.47 (m, 9H), 1.10−1.25 (m, 11H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rotamer mixture) δ 173.3, 173.0, 155.8, 155.2, 138.3, 138.2, 130.63, 130.59, 127.7, 126.1, 126.0, 80.7, 80.3, 75.6, 75.0, 73.8, 73.1, 61.1, 48.2, 48.0, 40.9, 28.3, 25.5, 25.2, 24.9, 19.5, 16.3, 14.34, 14.32, 14.2; IR (neat) 2977, 2935, 1713, 1366, 1302, 1183, 1122 cm^{-1}; HRMS[ESI] *m/z* calcd for $C_{22}H_{33}NO_5Na$ [M + Na]$^+$ 414.2251, found 414.2248.

The N,O-Acetal ***5ca***. Compound **5ca** was prepared from the acyliminium cation precursor **3c** (18.1 mg, 37.9 μmol) and 2-methyl-1-phenyl-propanol (**4a**) (17.5 μL, 114 μmol) according to GP-2 and was obtained in a 62% yield (10.0 mg, 22.5 μmol) as a colorless oil after purification by preparative TLC (eluted with hexane/EtOAc = 3:1). ^{1}H NMR (600 MHz, $CDCl_3$, 2:1 rotamer mixture) δ 7.13−7.33 (m, 10H), 5.32 (brs, 1H), 5.13−5.21 (m, 2H), 4.53 (brs, 1H), 4.10−4.14 (m, 0.7H), 4.03 (brs, 1.3H), 2.77−2.80 (m, 1.3H), 2.71 (s, 1H), 1.78 (brs, 1H), 1.64 (brs, 1H), 1.10−1.28 (m, 11H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 2:1 rotamer mixture) δ 172.9, 172.7, 156.9, 156.1, 138.1, 136.5, 136.3, 130.61, 130.56, 128.4, 128.0, 127.9, 127.7, 127.5, 126.2, 126.1, 75.8, 75.3, 73.8, 73.5, 67.5, 67.3, 61.3, 48.1, 48.0, 41.5, 40.7, 25.4, 25.0, 19.5, 16.2, 14.1; IR (neat) 2975, 1720, 1301, 1186, 1122, 1044 cm^{-1}; HRMS[ESI] *m/z* calcd for $C_{25}H_{31}NO_5Na$ [M + Na]$^+$ 448.2094, found 448.2091.

The N,O-Acetal ***5da***. Compound **5da** was prepared from the acyliminium cation precursor **3d** (29.8 mg, 52.7 μmol) and 2-methyl-1-phenyl-propanol (**4a**) (24.4 μL, 158 μmol) according to GP-2 and was obtained in a 72% yield (19.6 mg, 38.2 μmol) as a colorless oil after purification by preparative TLC (eluted with hexane/EtOAc = 3:1). ^{1}H NMR (600 MHz, $CDCl_3$, 2:1 rotamer mixture) δ 7.75 (d, 2H, *J* = 7.6 Hz), 7.66 (d, 0.6H, *J* = 6.5 Hz), 7.54 (d, 1.4H, *J* = 6.2 Hz), 7.37−7.40 (m, 2H), 7.28−7.31 (m, 2H), 7.23−7.25 (m, 2H), 7.18−7.21 (m, 1H), 7.15−7.16 (m, 2H), 5.24 (d, 0.7H, *J* = 8.9 Hz), 5.09 (brs, 0.3H), 4.42−4.61 (m, 3H), 4.29 (t, 0.3H, *J* = 6.2 Hz), 4.18 (t, 0.7H, *J* = 5.1 Hz), 4.12 (q, 0.6H, *J* = 6.9 Hz), 3.89−3.93 (m, 1.4H), 2.73−2.77 (m, 2H), 1.63 (brs, 1H), 1.09−1.21 (m, 11H), 0.78 (brs, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 2:1 rotamer mixture) δ 172.7, 172.6, 156.9, 156.2, 144.0, 141.5, 141.3, 138.1, 137.9, 130.6, 127.7, 127.6, 127.0, 126.9, 126.2, 126.1, 125.0, 124.7, 124.5, 120.0, 119.9, 75.7, 75.2, 73.7, 73.3, 67.4, 67.2, 61.3, 61.2, 48.2, 48.0, 47.2, 47.1, 41.5, 40.5, 25.4, 24.8, 19.1, 16.2, 14.1; IR (neat) 2975, 1718, 1300, 1186, 1122, 1045 cm^{-1}; HRMS[ESI] *m/z* calcd for $C_{32}H_{35}NO_5Na$ [M + Na]$^+$ 536.2407, found 536.2405.

The N,O-Acetal ***5ab***. Compound **5ab** was prepared from the acyliminium cation precursor **3a** (25.0 mg, 58.5 μmol) and adamantan-1-ol (**4b**) (26.7 mg, 175 μmol) according to GP-2 and was obtained in a 67% yield (14.8 mg, 39.2 μmol) as a pale yellow solid after purification by column chromatography on silica gel (eluted with hexane/EtOAc = 7:1). Mp 58−59 °C; ^{1}H NMR (600 MHz, $CDCl_3$, rotamer mixture) δ 5.85−5.97 (m, 1H), 5.16−5.36 (m, 3H), 4.53−4.63 (m, 3H), 4.13 (brq, 2H, *J* = 6.6 Hz), 2.13 (brs, 3H), 1.91 (brs, 1H), 1.78 (brs, 5H), 1.71 (d, 1H, *J* = 2.4 Hz), 1.58−1.63 (m, 8H), 1.35 (brs, 1H), 1.22 (t, 3H, *J* = 7.1 Hz); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rotamer mixture) δ 173.0, 172.8, 156.7, 155.9, 132.6, 117.4, 116.9, 72.8, 72.6, 66.3, 66.2, 61.2, 45.4, 41.7, 40.7, 36.3, 36.1, 30.7, 30.5, 19.4, 1.3, 14.24, 14.18; IR (neat) 2909, 2852, 1721, 1200, 1183, 1079, 1041 cm^{-1}; HRMS[ESI] *m/z* calcd for $C_{21}H_{31}NO_5Na$ [M + Na]$^+$ 400.2094, found 400.2093

The N,O-Acetal ***5ac***. Compound **5ac** was prepared from the acyliminium cation precursor **3a** (30.8 mg, 72.0 μmol) and 1-methylcyclohexanol (**4c**) (24.7 mg, 216 μmol) according to GP-2 and was obtained in an 87% yield (21.2 mg, 62.5 μmol) as a colorless oil after purification by column chromatography on silica gel (eluted with hexane/EtOAc = 5:1). ^{1}H NMR (600 MHz, $CDCl_3$, rotamer mixture) δ 5.86−5.96 (m, 1H), 5.17−5.34 (m, 3H), 4.46−4.63 (m, 3H), 4.13 (brq, 2H, *J* = 6.9 Hz), 1.16−1.90 (m, 20H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rotamer mixture) δ 173.0, 172.8, 156.8, 156.0, 132.6, 117.6, 116.9, 74.1, 73.7, 73.1, 72.9, 66.3, 66.1, 61.2, 41.5, 40.8, 36.7, 36.5, 25.6, 24.9, 22.1, 19.6, 16.4, 14.23, 14.16; IR (neat) 2932, 2859, 1722, 1393, 1304, 1187, 1052 cm^{-1}; HRMS[ESI] *m/z* calcd for $C_{18}H_{29}NO_5Na$ [M + Na]$^+$ 362.1938, found 362.1935.

The N,O-Acetal ***5ad***. Compound **5ad** was prepared from the acyliminium cation precursor **3a** (28.8 mg, 67.4 μmol) and 2-(4-iodophenyl)propan-2-ol (**4d**) (53.0 mg, 202 μmol) according to GP-2 and was obtained in a 67% yield (22.0 mg, 45.1 μmol) as a colorless oil after purification by preparative TLC (eluted with hexane/EtOAc = 3:1). ^{1}H NMR (600 MHz, $CDCl_3$, rotamer mixture) δ 7.66−7.67 (m, 2H), 7.16−7.20 (m, 2H), 5.84−5.94 (m, 1H), 5.16−5.32 (m, 2H), 4.90 (brs, 1H), 4.59 (brd, 2H, *J* = 4.1 Hz), 4.35 (brs, 1H), 4.10 (brq, 2H, *J* = 6.9 Hz), 1.77 (brs, 1H), 1.66 (brs, 1H), 1.53−1.59 (m, 7H), 1.38 (brs, 1H), 1.19 (t, 3H, *J* = 6.9 Hz); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rotamer mixture) δ 172.7, 172.5, 156.6, 155.8, 145.5, 145.3, 147.3, 132.53, 132.46, 127.8, 117.9, 117.1, 92.7, 76.0, 75.7, 74.5, 74.3, 66.5, 66.3, 61.3, 41.6, 40.9, 28.5, 28.1, 19.8, 16.4, 14.2; IR (neat) 2979, 1720, 1391, 1304, 1187, 1041, 1004 cm^{-1}; HRMS[ESI] *m/z* calcd for $C_{20}H_{26}NO_5INa$ [M + Na]$^+$ 510.0748, found 510.0739.

The N,O-Acetal ***5ae***. Compound **5ae** was prepared from the acyliminium cation precursor **3a** (29.8 mg, 69.7 μmol) and N_3-PEG_3-OH (**4e**) (45.8 mg, 209 μmol) according to GP-2 and was obtained in a 75% yield (23.2 mg, 52.2 μmol) as a colorless oil after purification by column chromatography on silica gel (eluted with hexane/EtOAc = 1:1). ^{1}H NMR (600 MHz, $CDCl_3$, rotamer mixture) δ 5.86−5.94

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(m, 1H), 5.28−5.34 (m, 1H), 5.18−5.23 (m, 1H), 5.08 (brs, 1H), 4.76 (brs, 1H), 4.62 (brs, 2H), 4.12−4.13 (m, 2H), 3.60−3.68 (m, 14H), 3.39 (t, 2H, J = 5.2 Hz), 1.74 (brs, 1H), 1.68 (brs, 1H), 1.40 (brs, 1H), 1.20−1.23 (m, 4H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, rotamer mixture) δ 172.6, 172.4, 157.5, 156.0, 132.4, 117.8, 117.2, 79.6, 70.7, 70.6, 70.5, 70.4, 70.0, 67.6, 67.4, 66.43, 66.35, 61.3, 50.7, 41.0, 40.4, 29.7, 19.7, 16.3, 14.2; IR (neat) 2873, 2105, 1718, 1303, 1193, 1085, 1033, 938 cm^{-1}; HRMS[ESI] m/z calcd for $C_{19}H_{32}N_4O_8Na$ $[M + Na]^+$ 467.2112, found 467.2108.

The N,O-Acetal ***5af***. Compound **5af** was prepared from the acyliminium cation precursor **3a** (25.9 mg, 60.6 μmol) and phenol (**4f**) (17.1 mg, 182 μmol) according to GP-2 and was obtained in a 69% yield (19.3 mg, 41.6 μmol) as a colorless oil after purification by preparative TLC (eluted with hexane/EtOAc = 3:1). ^1H NMR (600 MHz, $CDCl_3$, rotamer mixture) δ 7.26−7.29 (m, 2H), 6.97 (d, 2H, J = 7.9 Hz), 6.89−6.91 (m, 1H), 5.88−5.93 (m, 1H), 5.70 (brs, 1H), 5.26−5.31 (m, 1H), 5.20 (d, 1H, J = 10.0 Hz), 5.12 (brs, 1H), 4.64 (brs, 2H), 4.07−4.14 (m, 2H), 1.70 (brs, 1H), 1.43 (brs, 1H), 1.26 (brs, 2H), 1.17 (t, 3H, J = 7.0 Hz); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, rotamer mixture) δ 172.5, 172.3, 156.8, 156.7, 155.5, 132.2, 129.5, 121.8, 121.6, 117.7, 117.4, 116.0, 115.7, 78.7, 77.9, 66.6, 61.5, 41.5, 40.6, 19.8, 16.6, 14.1; IR (neat) 2927, 1725, 1391, 1307, 1272, 1205, 1029 cm^{-1}; HRMS[ESI] m/z calcd for $C_{17}H_{21}NO_5Na$ $[M + Na]^+$ 342.1312, found 342.1309.

The N,O-Acetal ***5ag***. Compound **5ag** was prepared from the acyliminium cation precursor **3a** (29.9 mg, 69.9 μmol) and 2,6-dimethylphenol (**4g**) (25.6 mg, 210 μmol) according to GP-2 and was obtained in a 67% yield (16.2 mg, 46.6 μmol) as a colorless oil after purification by preparative TLC (eluted with hexane/EtOAc = 3:1). ^1H NMR (600 MHz, $CDCl_3$, 3:2 rotamer mixture) δ 7.00 (d, 2H, J = 7.3 Hz), δ 6.93 (t, 1H, J = 7.3 Hz), 5.88−5.94 (m, 0.6H), 5.79−5.85 (m, 0.4H), 5.17−5.34 (m, 3H), 4.84 (brs, 1H), 4.66 (brs, 1.2H), 4.61 (brs, 0.8H), 4.13 (brq, 2H, J = 6.8 Hz), 2.30 (s, 3.6H), 2.25 (s, 2.4H), 1.36−1.74 (m, 4H), 1.21 (t, 3H, J = 6.8 Hz); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, 3:2 rotamer mixture) δ 172.6, 172.5, 157.0, 156.0, 153.7, 153.2, 132.3, 132.1, 131.4, 131.1, 128.9, 124.34, 124.29, 118.2, 117.3, 81.4, 81.3, 66.7, 66.5, 61.5, 41.3, 20.0, 17.1, 16.7, 16.6, 14.19, 14.16; IR (neat) 2928, 1725, 1304, 1259, 1186, 1120, 982 cm^{-1}; HRMS[ESI] m/z calcd for $C_{19}H_{25}NO_5Na$ $[M + Na]^+$ 370.1625, found 370.1622.

The N,O-Acetal ***5ah***. Compound **5ah** was prepared from the acyliminium cation precursor **3a** (28.0 mg, 65.6 μmol) and Cbz-Ser-O*t*Bu (**4h**) (58.1 mg, 197 μmol) according to GP-2 and was obtained in an 89% yield (30.5 mg, 58.6 μmol) as a colorless oil after purification by preparative TLC (eluted with hexane/EtOAc = 3:1). $[\alpha]^{25}_D$ +1.8 (c 0.44, $CHCl_3$); ^1H NMR (600 MHz, CD_3CN, 50 °C, rotamer mixture) δ 7.31−7.38 (m, 5H), 5.90−5.96 (m, 1H), 5.83 (brs, 1H), 5.30 (d, 1H, J = 17.2 Hz), 5.19 (d, 1H, J = 10.3 Hz), 5.09 (s, 2H), 4.83 (brs, 2H), 4.59 (d, 2H, J = 5.2 Hz), 4.20−4.23 (m, 1H), 4.06−4.10 (m, 2H), 3.80 (dd, 1H, J = 10.0, 4.8 Hz), 3.74 (dd, 1H, J = 10.0, 3.5 Hz), 1.43 (brs, 13H), 1.17 (t, 3H, J = 7.1 Hz); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, rotamer mixture) δ 173.6, 170.4, 138.4, 134.1, 129.6, 129.3, 129.1, 128.9, 82.8, 80.8, 69.5, 67.4, 67.2, 62.3, 56.3, 28.4, 14.6; IR (neat) 3351, 2979, 1722, 1305, 1193, 1158, 1098, 1026 cm^{-1}; HRMS[ESI] m/z calcd for $C_{26}H_{36}N_2O_9Na$ $[M + Na]^+$ 543.2313, found 543.2307.

The N,O-Acetal ***5ai***. Compound **5ai** was prepared from the acyliminium cation precursor **3a** (38.3 mg, 89.6 μmol) and Cbz-Thr-O*t*Bu (**4i**) (83.1 mg, 269 μmol) according to GP-2 and was obtained in a 67% yield (32.2 mg, 60.2 μmol) as a colorless oil after purification by preparative TLC (eluted with hexane/EtOAc = 3:1). $[\alpha]^{25}_D$ −1.6 (c 0.29, $CHCl_3$); ^1H NMR (600 MHz, CD_3CN, 50 °C, rotamer mixture) δ 7.31−7.38 (m, 5H), 5.93 (brs, 1H), 5.72 (brs, 1H), 5.29 (d, 1H, J = 17.5 Hz), 5.19 (d, 1H, J = 10.0 Hz), 5.10 (d, 1H, J = 14.8 Hz), 5.08 (d, 1H, J = 14.8 Hz), 4.80 (brs, 2H), 4.58 (d, 2H, J = 3.8 Hz), 4.03−4.13 (m, 4H), 1.44 (brs, 13H), 1.16−1.18 (m, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, CD_3CN, 50 °C, rotamer mixture) δ 173.5, 170.9, 157.7, 138.4, 134.1, 129.6, 129.1, 128.9, 82.8, 67.5, 67.2, 62.3, 60.9, 28.4, 17.6, 14.6; IR (neat) 3353, 2979, 1723, 1370, 1306, 1188, 1157, 1025 cm^{-1}; HRMS[ESI] m/z calcd for $C_{27}H_{38}N_2O_9Na$ $[M + Na]^+$ 557.2470, found 557.2463.

The N,O-Acetal ***5aj***. Compound **5aj** was prepared from the acyliminium cation precursor **3a** (36.9 mg, 86.3 μmol) and Fmoc-Val(3-OH)-O*t*Bu (**4j**) (107 mg, 259 μmol) according to GP-2 and was obtained in a 74% yield (40.5 mg, 63.6 μmol) as a colorless oil after purification by preparative TLC (eluted with hexane/EtOAc = 3:1). $[\alpha]^{25}_D$ +1.5 (c 1.6, $CHCl_3$); ^1H NMR (600 MHz, CD_3CN, 50 °C, rotamer mixture) δ 7.84 (t, 2H, J = 7.0 Hz), 7.69 (brs, 2H), 7.41−7.44 (m, 2H), 7.33−7.36 (m, 2H), 5.93 (brs, 2H), 5.29 (d, 1H, J = 17.2 Hz), 5.17−5.20 (m, 1H), 4.81 (brs, 2H), 4.57 (brs, 2H), 4.38 (brs, 2H), 4.24−4.27 (m, 1H), 4.08−4.11 (m, 2H), 4.03 (brs, 1H), 1.43 (brs, 16H), 1,30 (brs, 3H), 1.18 (t, 3H, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (150 MHz, CD_3CN, 50 °C, rotamer mixture) δ 173.7, 170.5, 157.7, 157.4, 145.4, 142.4, 134.2, 128.9, 128.28, 128.27, 126.3, 121.1, 82.7, 77.1, 74.6, 67.6, 67.1, 64.0, 62.3, 43.4, 28.4, 23.9, 14.7; IR (neat) 3354, 2979, 1722, 1335, 1304, 1159, 1042, 741 cm^{-1}; HRMS[ESI] m/z calcd for $C_{35}H_{44}N_2O_9Na$ $[M + Na]^+$ 659.2939, found 659.2931.

The N,O-Acetal ***5ak***. Compound **5ak** was prepared from the acyliminium cation precursor **3a** (38.0 mg, 88.9 μmol) and the alcohol **4k** (37.6 mg, 293 μmol) according to GP-2 and was obtained in a 34% yield (14.7 mg, 30.3 μmol) as a colorless oil after purification by silica gel (eluted with hexane/EtOAc = 4:1). $[\alpha]^{25}_D$ +1.1 (c 0.79, $CHCl_3$); ^1H NMR (600 MHz, CD_3CN, 50 °C, rotamer mixture) δ 5.93 (brs, 1H), 5.29 (d, 1H, J = 15.8 Hz), 5.19 (d, 1H, J = 9.7 Hz), 4.81 (brs, 2H), 4.58 (d, 2H, J = 3.8 Hz), 4.04−4.11 (m, 3H), 3.95 (brs, 1H), 3.84 (dd, 1H, J = 9.3, 6.5 Hz), 1.54 (s, 3H), 1.44 (brs, 16H), 1.16−1.22 (m, 9H); $^{13}C\{^1H\}$ NMR (150 MHz, CD_3CN, 50 °C, rotamer mixture) δ 173.7, 157.6, 155.2, 134.3, 117.4, 95.9, 80.9, 74.4, 67.0, 65.2, 64.4, 62.2, 41.7, 30.5, 28.7, 27.5, 24.7, 22.3, 18.1, 14.7; IR (neat) 2979, 1721, 1699, 1367, 1171, 1062, 1035 cm^{-1}; HRMS[ESI] m/z calcd for $C_{24}H_{40}N_2O_8Na$ $[M + Na]^+$ 507.2677, found 507.2669.

Alloc-MeAsp(tBu)-OH. To a suspension of Fmoc-Asp(*t*Bu)-OH (3.03g, 7.36 mmol) in dry MeCN (15 mL) was added Et_2NH (3.7 mL) at 0 °C under an argon atmosphere. After being stirred at room temperature for 3 h, the reaction mixture was concentrated in vacuo. The resulting residue was azeotroped three times with toluene and dried under a vacuum. The crude amine was used for the next reaction without further purification.

To a solution of the crude amine in dry THF (1.8 mL) were added saturated aqueous $NaHCO_3$ (7.5 mL) and Alloc-Cl (1.2 mL, 11.0 mmol) at 0 °C. After being stirred at room temperature for 19 h, the reaction mixture was diluted with EtOAc and quenched with 1 M aqueous HCl. The organic layer was separated, washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 1:1) to afford the *N*-Alloc amine (1.45 g, 5.32 mmol, 72% in two steps) as a colorless oil. The spectral data of the synthetic compound were in good agreement with those reported.[29] $[\alpha]^{29}_D$ +18 (c 0.92, $CHCl_3$).

To a solution of the carbamate (457 mg, 1.67 mmol) in dry THF (15 mL) were added MeI (836 μL, 13.4 mmol) and NaH (60% in mineral, 268 mg, 6.69 mmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 9 h, the reaction mixture was diluted with Et_2O and quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 2:1) to afford the *N*-methylcarbamate (341 mg, 1.19 mmol, 71%) as a colorless oil. $[\alpha]^{28}_D$ −33 (c 1.37, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, rotamer mixture) δ 5.85−5.96 (m, 1H), 5.30 (d, 1H, J = 17.2 Hz), 5.19−5.23 (m, 1H), 4.87−4.90 (m, 1H), 4.61−4.63 (m, 2H), 2.98−3.11 (m, 4H), 2.66−2.78 (m, 1H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamer mixture) δ 175.1, 175.0, 169.8, 169.6, 156.3, 155.8, 132.5, 132.3, 117.7, 117.5, 81.6, 81.4, 66.6, 66.5, 57.2, 56.8, 36.2, 35.6, 33.4, 33.1, 27.89, 27.86; IR (neat) 2980, 2939, 2370,

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2320, 1714, 1370, 1317, 1257, 1153, 992 cm^{-1}; HRMS[ESI] m/z calcd for $C_{13}H_{21}NO_6Na$ $[M + Na]^+$ 310.1261, found 310.1257.

The Dipeptide ***7***. To a solution of Alloc-MeAsp(*t*Bu)-OH (201 mg, 700 μmol) and ethyl 1-aminocyclopropane-1-carboxylate hydrochloride (116 mg, 700 μmol,) in dry CH_2Cl_2 (7.0 mL) were added DIEA (488 μL, 2.80 mmol), HOBt (129 mg, 840 μmol), and EDCI·HCl (161 mg, 840 μmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 17 h, the reaction mixture was diluted with EtOAc and quenched with 1 M aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 2:1) to afford the dipeptide **7** (196 mg, 492 μmol, 70%) as a colorless oil. $[\alpha]^{29}_D$ −58 (*c* 0.65, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 2:1 rotamer mixture) δ 6.69 (brs, 0.7H), 6.45 (brs, 0.3H), 5.91−5.98 (m, 1H), 5.33 (d, 1H, *J* = 17.4 Hz), 5.24 (d, 1H, *J* = 10.8 Hz), 5.08 (t, 0.7H, *J* = 7.5 Hz), 5.00 (brs, 0.3H), 4.63−4.65 (m, 2H), 4.10−4.16 (m, 2H), 2.91−3.02 (m, 4H), 2.55 (dd, 1H, *J* = 15.9, 8.1 Hz), 1.63 (brs, 2.5H), 1.42−1.47 (m, 8.5H), 1.18−1.26 (m, 4H), 1.08−1.12 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 2:1 rotamer mixture) δ 172.01, 171.97, 170.7, 169.7, 157.1, 132.5, 118.2, 117.8, 84.1, 66.7, 61.4, 55.4, 34.2, 33.4, 30.1, 28.0, 27.9, 17.7, 17.4, 17.3, 14.1; IR (neat) 3324, 2979, 1729, 1687, 1509, 1370, 1298, 1156, 845 cm^{-1}; HRMS[ESI] m/z calcd for $C_{19}H_{30}N_2O_7Na$ $[M + Na]^+$ 421.1945, found 421.1938.

*Chloromethyl 2-(Hex-1-yn-1-yl)benzoate (****8****).* To a solution of the carboxylic acid **2** (204 mg, 1.01 mmol) in dry CH_2Cl_2 (2.0 mL) and water (2.0 mL) were added $NaHCO_3$ (254 mg, 3.03 mmol), Bu_4NHSO_4 (34.3 mg, 101 μmol), and chloromethyl chlorosulfate (200 mg, 1.21 mmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 15 h, the reaction mixture was diluted with CH_2Cl_2 and quenched with water. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 7:1) to afford the *O*-chloromethyl adduct **8** (207 mg, 824 μmol, 82%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (dd, 1H, *J* = 7.7, 1.2 Hz), 7.54 (dd, 1H, *J* = 7.7, 1.2 Hz), 7.47 (td, 1H, *J* = 7.7, 1.2 Hz), 7.34 (td, 1H, *J* = 7.7, 1.2 Hz), 5.95 (s, 2H), 2.49 (t, 2H, *J* = 7.2 Hz), 1.61−1.66 (m, 2H), 1.48−1.54 (m, 2H), 0.96 (t, 3H, *J* = 7.5 Hz); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 164.1, 134.4, 132.4, 130.6, 130.0, 127.2, 125.4, 97.2, 78.8, 69.1, 30.6, 22.0, 19.5, 13.6; IR (neat) 2958, 2932, 1752, 1279, 1234, 1112, 1064, 756, 718 cm^{-1}; HRMS[ESI] m/z calcd for $C_{14}H_{15}O_2ClNa$ $[M + Na]^+$ 273.0653, found 273.0657.

The Precursor ***9***. To a solution of the amide **7** (52.7 mg, 132 μmol) in dry THF (1.0 mL) was added KHMDS (0.50 M in THF, 317 μL, 159 μmmol) at −78 °C under an argon atmosphere, and the mixture was stirred at the same temperature for 1.5 h. A solution of the chloride **8** (82.9 mg, 331 μmol) in dry THF (0.3 mL) was then added to the above mixture at −78 °C. After being stirred at room temperature for 1.5 h, the reaction mixture was quenched with water and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 7:1) to afford the acyliminium cation precursor **9** (38.3 mg, 62.5 μmol, 47%) as a colorless oil. $[\alpha]^{23}_D$ −79 (*c* 0.93, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 3:2 rotamer mixture) δ 7.93 (d, 0.6H, *J* = 7.3 Hz), 7.80 (d, 0.4H, *J* = 7.5, 3.9 Hz), 7.49−7.52 (m, 1H), 7.39−7.45 (m, 1H), 7.23−7.33 (m, 1H), 5.13−6.05 (m, 6H), 4.42−4.67 (2H, m), 4.00−4.13 (m, 2H), 2.88−3.14 (m, 2.8H), 2.77 (s, 1.2H), 2.45−2.49 (m, 2.6H), 2.34−2.41 (m, 0.4H), 1.60−1.68 (m, 3H), 1.08−1.53 (m, 17H), 0.96 (t, 3H, *J* = 7.5 Hz); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 3:2 rotamer mixture) δ 171.9, 171.3, 170.1, 169.8, 165.3, 164.8, 155.7, 134.5, 134.4, 132.6, 132.4, 131.8, 131.6, 130.3, 127.00, 126.95, 125.3, 124.9, 118.5, 118.3, 117.7, 96.8, 96.4, 81.1, 80.0, 79.1, 74.1, 66.7, 66.6, 62.5, 61.5, 52.6, 52.1, 41.6, 41.5, 35.3, 35.1, 30.73, 30.69, 29.7, 29.5, 27.9, 22.07, 22.05, 20.9, 20.8, 19.54, 19.53, 19.2, 18.8, 14.0, 13.9, 13.8, 13.7; IR (neat) 2933, 1730, 1690, 1394, 1369, 1300, 1237, 1146, 1037 cm^{-1}; HRMS[ESI] m/z calcd for $C_{33}H_{44}N_2O_9Na$ $[M + Na]^+$ 635.2939, found 635.2933.

The N,O-Acetal ***10***. Compound **10** was prepared from the acyliminium cation precursor **9** (22.1 mg, 36.1 μmol) and 2-methyl-1-phenylpropanol (**4a**) (16.7 μL, 108 μmol) according to GP-2 and was obtained in a 72% yield (14.5 mg, 25.9 μmol) as a colorless oil after purification by preparative TLC (eluted with hexane/EtOAc = 3:1). $[\alpha]^{29}_D$ −44 (*c* 0.57, $CHCl_3$); ^{1}H NMR (600 MHz, CD_3CN, 50 °C, 2:1 rotamer mixture) δ 7.11−7.27 (m, 5H), 5.92−5.99 (m, 1H), 5.07−5.73 (m, 4H), 4.46−4.68 (m, 3H), 3.95−4.07 (m, 2H), 2.67−2.80 (m, 6H), 2.49 (dd, 0.7H, *J* = 15.9, 7.5 Hz), 2.37 (brd, 0.3H, *J* = 15.6 Hz), 1.09−1.60 (m, 22H); ^{13}C{^{1}H} NMR (150 MHz, CD_3CN, 50 °C, 2:1 rotamer mixture) δ 173.1, 173.0, 171.1, 170.6, 139.7, 139.4, 134.44, 134.38, 131.91, 131.85, 128.9, 127.3, 127.2, 81.9, 81.7, 76.8, 76.5, 74.2, 73.8, 67.3, 67.2, 62.1, 54.4, 54.0, 49.3, 48.6, 42.2, 36.5, 30.5, 28.5, 26.1, 25.5, 25.3, 25.2, 20.4, 18.3, 17.1, 14.6, 14.4; IR (neat) 2977, 2374, 2311, 1729, 1679, 1144, 1045, 702 cm^{-1}; HRMS[ESI] m/z calcd for $C_{30}H_{44}N_2O_8Na$ $[M + Na]^+$ 583.2990, found 583.2980.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02640.

Copies of ^{1}H and ^{13}C NMR spectra for all new and known compounds (PDF)

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Notes

The authors declare no competing financial interest.

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