# Studies on the Alkylation and Chlorination of Fluorenes: Preparation of 9-(2-Hydroxyethyl)fluorene and 2,7-Dichloro-9-(2-hydroxyethyl)fluorene

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Efficient large-scale syntheses of 9-(2-hydroxyethyl)fluorene (1) and its 2,7-dichloro derivative 2 are described. Major differences exist in the reactivity of fluorene and its 2,7-dichloro derivative toward 9-alkylation. These differences are attributed to the difference in acidity of the protons in the 9-position of these compounds. Also 2,7-dichlorination of fluorene and its derivatives was satisfactorily achieved by treatment with NCS and conc. HCl in acetonitrile under carefully controlled conditions. Specifically, a highly concentrated solution of substrates and elevated temperatures were required for facile 2,7-dichlorination.

Fluorene and its derivatives are versatile reagents which are used for various synthetic purposes.[1] The presence of two acidic protons at the 9-position makes these compounds excellent candidates for alkylation reactions. Fluorene-9-methanol is the key component for the preparation of 9-fluorenylmethoxycarbonyl (Fmoc) protected amino acids.[2–4] Recently we found that the carbamate derivatives of 9-(2-hydroxyethyl)fluorene and 2,7-dichloro-9-(2-hydroxyethyl)fluorene with p-aminobenzoic acid, i.e. N-{[2-(9H-fluoren-9-yl)ethoxy]carbonyl}-4-amino-benzoic acid (NPC 16570) and N-{[2-(2,7-dichloro-9H-fluoren-9-yl)ethoxy]carbonyl}-4-aminobenzoic acid (NPC 17923), produce antiinflammatory actions following oral administration in various animal models of inflammation.[5] These compounds are of particular interest because of their unique mechanism of action; prevention of infiltration of leukocytes into inflamed tissue.[6] To support development of these compounds, efficient large-scale syntheses of 9-(2-hydroxyethyl)fluorene (1) and its 2,7-dichloro derivative 2 were required. This prompted us to study the alkylation and chlorination reactions of fluorene more closely.
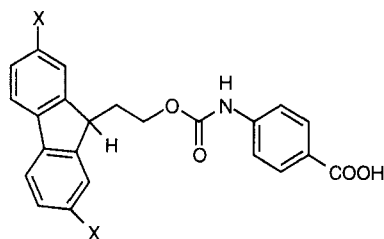


X = H: NPC 16570
X = Cl: NPC 17923

## Alkylation of Fluorene:

Although the synthesis of 1 has been reported[7] via reduction of fluorene-9-acetic acid, a more convenient and less expensive method was developed. Thus, as illustrated in Scheme 1, a slight excess of fluorene was treated with butyllithium and the resulting 9-lithio derivative was alkylated with less than one equivalent of ethylene oxide. Use of excess ethylene oxide resulted in a substantial amount of 9,9-bis(2-hydroxyethyl)fluorene; however, its use as the limiting reagent provided the monohydroxyethylated product 1 in 93% yield.
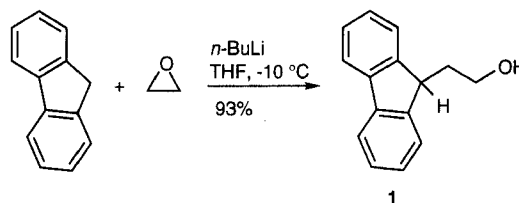


Scheme 1

Attempts to extend this method to the synthesis of 2,7-dichloro derivative 2 were unsuccessful as bisalkylated product 3 was obtained as the major product (Scheme 2).
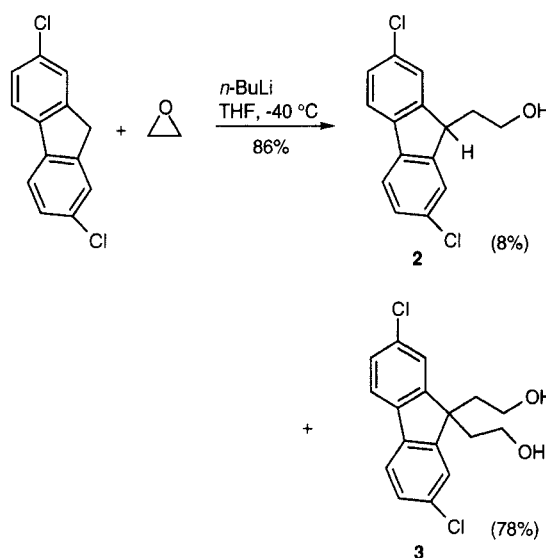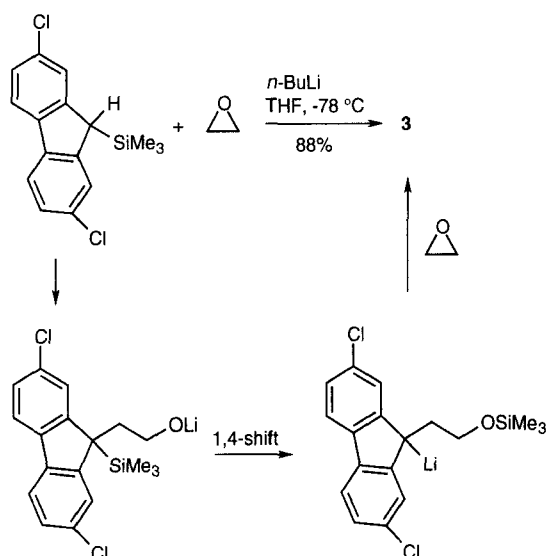


Scheme 2

Bisalkylation of 2,7-dichlorofluorene under conditions that enable monohydroxyethylation of fluorene can be attributed to the increased acidity of the C-9 protons.[8] Consequently, the alkoxide anion intermediate from the reaction of ethylene oxide with 2,7-dichlorofluorene may abstract the second proton from position 9. Subsequent reaction of the resulting anion with another equivalent of epoxide may account for the bisalkylated product. Modification of reaction conditions, e.g., inverse addition of the anion or limiting reagents, did not significantly alter the product ratio.

In an alternative attempt to achieve monohydroxyethylation of 2,7-dichlorofluorene, reaction of a trimethylsilyl protected derivative[9] with ethylene oxide was studied. As illustrated in Scheme 3, apparently a 1,4-shift of the silyl group from carbon to oxygen occurs after the initial alkylation thus producing an anion at the 9 position of the tricyclic system. The anion thus formed may undergo

a second alkylation with the epoxide to produce the bis-alkylated material **3**.
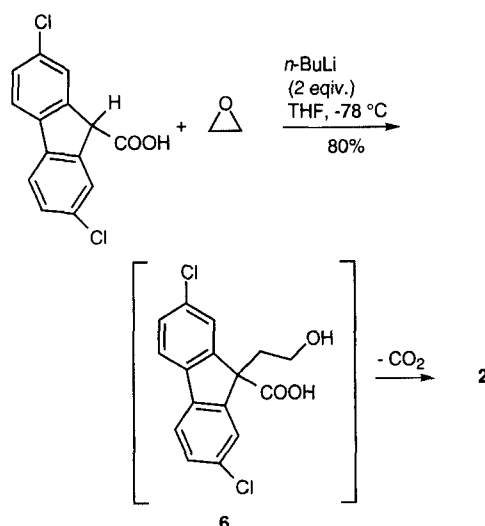


**Scheme 3**

In another attempt to obtain 9-monohydroxyethylated products of fluorene and 2,7-dichlorofluorene, reaction of the corresponding 9-carboxylic acid derivatives was examined. The monohydroxyethylated derivative of fluorene was readily achieved via fluorene-9-carboxylic acid, i.e. via protective 9-carboxylation of fluorene, in good overall yield as illustrated in Scheme 4. Accordingly, the dianion generated by treatment of fluorene-9-carboxylic acid with two equivalents of butyllithium provided 9-hydroxyethylated product **4** which was lactonized to **5** with hydrochloric acid. Saponification of **5** was accompanied by decarboxylation to afford **1**.
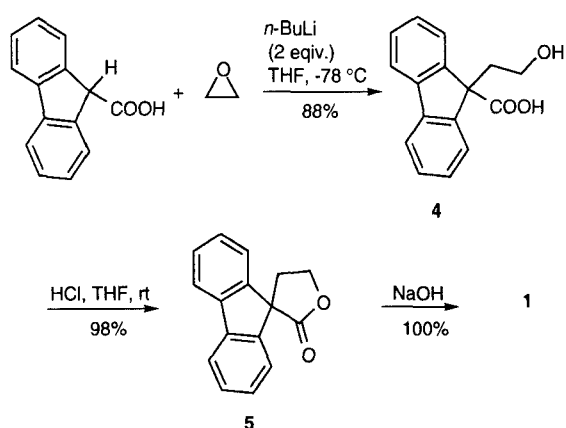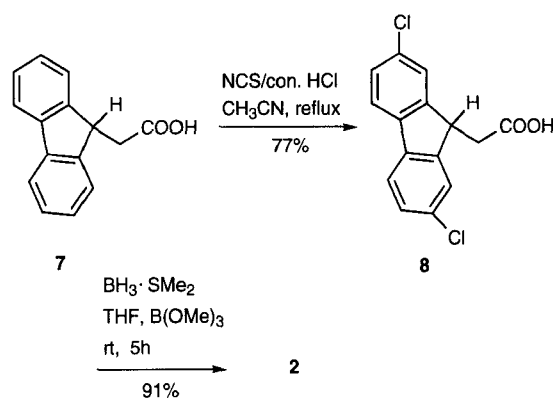


**Scheme 4**

Similar reaction of 2,7-dichlorofluorene-9-carboxylic acid, as shown in Scheme 5, provided an unstable hydroxyethyl intermediate **6**, that underwent facile decarboxylation to provide the 9-hydroxyethylated product **2**. However, the unavailability of the starting material and its two-step synthesis made this route unattractive for synthesis on a large scale.



**Scheme 5**

2,7-Dichloro-9-(2-hydroxyethyl)fluorene (**2**) was finally prepared in multigram quantities using a procedure similar to that originally reported for the synthesis of **1**. Accordingly, as shown in Scheme 6, fluorene-9-acetic acid[10] (**7**) was chlorinated with NCS under carefully controlled conditions. Specifically, a highly concentrated solution of the fluorene-9-acetic acid, and elevated temperatures were required for facile 2,7-dichlorination (see experimental). The 2,7-dichlorofluorene-9-acetic acid (**8**), thus obtained, was conveniently reduced by $BH_3 \cdot Me_2S$ complex[11] to provide **2** in quantities required for large-scale conversion to NPC 17923.



**Scheme 6**

The reactions described above demonstrate major differences in the reactivity of fluorene and its 2,7-dichloro derivative toward 9-alkylation. These differences are attributed to the difference in acidity of the protons in the 9-position of these compounds.

**Chlorination of Fluorenes:**

The need for a large amount of 2,7-dichlorofluorene-9-acetic acid (**8**) prompted us to investigate an efficient method for the preparation of 2,7-dichlorofluorenes. Fluorene undergoes chlorination at its most electron-rich centers providing 2,7-dichloro derivatives. The literature

reports the chlorination of fluorene using NCS in acetic acid with concentrated hydrochloric acid;[12] however, this method gives low yields (25 %) and there is no report of a method for chlorination of fluorene derivatives. We report here an efficient methodology for 2,7-dichlorination of the fluorene ring that is successful not only for the parent compound, but also for several of its derivatives (Scheme 7).



**9a-h** **10a-h**
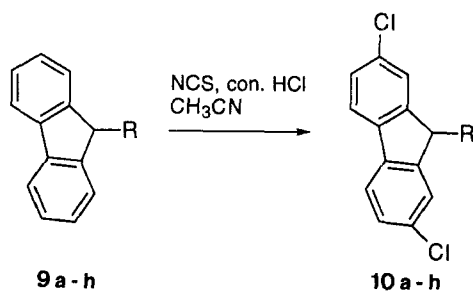
**Scheme 7**

The chlorination reactions were done in acetonitrile solvent at high concentration (50 wt % of substrate) using NCS and concentrated HCl. The high concentration and slightly elevated temperatures are the key to the success of the reaction. Under these conditions, the product (Table 1) typically precipitates out of the reaction mixture. If this precipitation does not occur, isolation of the product in most instances is unsuccessful or tedious chromatography is required. In the case of compound **10h**, the precipitation did not occur and the product was isolated by column chromatography. However, this alcohol can easily be prepared by a $BH_3 \cdot THF$ reduction of the corresponding acid **10f**.

**Table 1.** Chlorination of Fluorene and Its Derivatives

| 10 | R | Yield[a] (%) | mp/(°C) | Solvent for Crystallization |
|---|---|---|---|---|
| 10a | H | 90 | 125–126[b] | MeOH |
| 10b | Me | 55 | 108–109 | MeOH |
| 10c | Et | 73 | 72–73 | MeOH |
| 10d | Br | 58 | 168–170 | EtOH |
| 10e | SiMe₃ | 65 | 127–128 | EtOH |
| 10f | CH₂CO₂H | 77 | 180–181 | AcOH |
| 10g | (CH₂)₂CO₂H | 52 | 184–185 | AcOH |
| 10h | CH₂CH₂OH | 65 | 76–78 | hexane |

[a] Yields of isolated products. Compounds **10a–g** gave C, H, Cl analysis ± 0.15% (no Cl analysis for **10d**). Compounds **2–5** gave C, H analysis ± 0.14%.
[b] Lit.[12] mp 125.5–126.5°C.

Compounds **9a,c,d** were purchased from Aldrich Chemical Co. Compounds **9b**,[13] **9e**,[14] and **9f**[15] were prepared according to literature procedure. Compounds **9g** and **9h** were prepared by direct alkylation of fluorene anion (generated by BuLi) with 3-bromopropionic acid (Li-salt) and ethylene oxide, respectively.

In conclusion, 2,7-dichloro derivatives of fluorenes (**10a–h**) can be conveniently prepared in satisfactory yields using NCS and concentrated HCl in acetonitrile under special reaction conditions.

**9-(2-Hydroxyethyl)fluorene (1) from Fluorene-9-acetic Acid:**

To a solution of $BH_3 \cdot THF$ (60 mL, 60.0 mmol) was added dropwise over 1 h with stirring a solution of fluorene-9-acetic acid (10.0 g, 45.0 mmol) in THF (70 mL). The hydrogen gas formed was properly vented into the hood. After 2 h, conc. HCl (200 mL) in crushed ice (300 g) was added and stirred for 20 min. The product was then extracted with CHCl₃ (× 3). The combined organic layer was washed with aq NaHCO₃, dried (MgSO₄), and concentrated to yield 9.0 g (95 %) of 1 as a white solid, mp 98–99°C (hexane) (Lit.,[7] 100–101°C).

FTIR (KBr): v = 3273, 3044, 2926, 1475, 1445, 1344, 1087, 1046 cm⁻¹.

$^1$H NMR (300 MHz, CDCl₃): δ = 2.43 (q, 2H, J = 7.5 Hz), 3.67 (t, 2H, J = 7.5 Hz), 4.21 (t, 1H, J = 7.5 Hz), 7.43 (m, 4H), 7.59 (d, 2H, J = 7.2 Hz), 7.79 (d, 2H, J = 7.2 Hz).

**9-(2-Hydroxyethyl)fluorene (1) from Fluorene and Ethylene Oxide:**

To a solution of fluorene (116 g, 700 mmol) in dry THF (800 mL) under argon at −5°C was added slowly 2.5 M BuLi (280 mL, 700 mmol) in hexane, keeping the temperature below −5°C. Stirring was continued for 10 min, then 1.5 M ethylene oxide (357 mL, 536 mmol) in Et₂O was added rapidly, keeping the temperature below −5°C. Stirring was continued at r.t. for 5 h, then sat. aq NH₄Cl (50 mL) was added, and concentrated under reduced pressure. The residue was diluted with EtOAc. The organic layer was separated, dried (MgSO₄), and concentrated under reduced pressure until precipitation began. The crystals were filtered, washed with hexane, and dried in vacuo to provide 104 g (93 %) of 9-(2-hydroxyethyl)fluorene (1) as a white solid which was identical to the compound prepared previously.

**9,9-Bis(2-hydroxyethyl)-2,7-dichlorofluorene (3):**

To a solution containing 2,7-dichlorofluorene (46.0 g, 196 mmol) in dry THF (250 mL) was added dropwise 2.5 M BuLi (78.4 mL, 196 mmol) in hexane at −78°C. The temperature was raised to −40°C, then 1.5 M ethylene oxide (134 mL, 201 mmol) in Et₂O was added all at once. Stirring was continued for 10 h at r.t. and the mixture was treated with sat. aq NH₄Cl (50 mL), concentrated in vacuo, and extracted with EtOAc. The organic layer was dried (MgSO₄) and concentrated under reduced pressure to obtain a white solid which was filtered off and dried in vacuo. Recrystallization from 20 % EtOAc/hexane provided 38 g (78 %) of 9,9-bis(2-hydroxyethyl)-2,7-dichlorofluorene (3) as white needles, mp 159–160°C.

FTIR (KBr): v = 3365, 2933, 2884, 1460, 1424, 1267, 1164, 1077, 1023, 877 cm⁻¹.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 2.23 (t, 4H, J = 4.5 Hz), 2.60 (m, 4H), 4.17 (t, 2H, J = 4.5 Hz), 7.38 (d, 2H, J = 8.1 Hz), 7.64 (s, 2H), 7.82 (d, 2H, J = 8.1 Hz).

**Compound 3 from 2,7-Dichloro-9-(trimethylsilyl)fluorene:**

To a solution of 2,7-dichloro-9-(trimethylsilyl)fluorene (3.0 g, 10.0 mmol) in dry THF (30 mL) at −78°C was added 2.5 M BuLi (4.0 mL, 10.0 mmol) in hexane. Stirring was continued for 2 h at −78°C, then 1.58 M ethylene oxide (12.5 mL, 20.0 mmol) in Et₂O was added. Stirring was continued for 1 h at −78°C and then 2 h at r.t. The reaction mixture was treated with 10% aq HCl, concentrated at reduced pressure, extracted with EtOAc, dried (MgSO₄), and evaporated to obtain a residue which on trituration with 20% EtOAc/hexane provided 2.2 g (64%) of 9,9-bis(2-hydroxyethyl)-2,7-dichlorofluorene (3) as a white solid which was identical to the compound previously prepared.

**9-(2-Hydroxyethyl)fluorene-9-carboxylic Acid (4):**

To a solution of fluorene-9-carboxylic acid (5.0 g, 24 mmol) in THF (100 mL) was added 2.4 M BuLi (20 mL, 48 mmol) at −78°C under argon. A 1.58 M solution of ethylene oxide (16.5 mL, 26 mmol) in

Et$_2$O was added slowly and the mixture was stirred overnight at r.t. The reaction was then quenched with 10% aq HCl and the product was extracted with EtOAc. The organic layer was dried (MgSO$_4$) and evaporated to give a residue which on crystallization from 10% EtOAc/hexane provided 4.8 g (78%) of **4** as a white solid, mp 133–134°C.

FTIR (KBr): $\nu$ = 3560, 1694, 1522, 1452, 1080, 837 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): Compound **4** undergoes partial decarboxylation and lactonization in DMSO-$d_6$ solvent.

### Fluorene Lactone (5):

The above 9-(2-hydroxyethyl)fluorene-9-carboxylic acid (**4**) (1.0 g, 3.9 mmol) was dissolved in THF (10 mL) and treated with 10% aq HCl (2 mL) for 45 min at 50°C. The lactone **5** was isolated by extraction with EtOAc. The organic layer was dried (MgSO$_4$) and concentrated under reduced pressure to provide 0.9 g (98%) of **5** as a white solid, mp 183–184°C (MeOH).

FTIR (KBr): $\nu$ = 1766, 1479, 1437, 1370, 1159, 1049, 1023, 948, 762, 745 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.81 (t, 2 H, $J$ = 7.0 Hz), 4.80 (t, 2 H, $J$ = 7.0 Hz), 7.32–7.75 (m, 8 H).

### Saponification of Lactone 5 and Formation of 1:

To a solution of the above fluorene lactone **5** (500 mg, 2.1 mmol) in THF (5 mL) was added NaOH (120 mg, 3.0 mmol) in water (5 mL). The mixture was heated at 65°C for 5 h, cooled and extracted with EtOAc. The organic layer was then dried (MgSO$_4$) and evaporated to give an oil which on crystallization from 5% EtOAc/hexane provided 440 mg (100%) of 9-(2-hydroxyethyl)fluorene (**1**) as a white solid, which was identical to the compound prepared previously.

### 2,7-Dichlorofluorene-9-acetic Acid (8):

See Chlorination of Fluorenes, General Procedure.

### 9-(2-Hydroxyethyl)-2,7-dichlorofluorene (2):

To a solution of **8** (240 g, 0.8 mol) and trimethylborate (290 mL) in THF (500 mL) under argon was added 2 M BH$_3$ · Me$_2$S (400 mL, 0.8 mol) in THF over 1.5 h. The evolved hydrogen gas was properly vented into the hood. An exothermic reaction occured which was controlled by ice-water cooling. After stirring at r.t. for 2 h, MeOH (200 mL) was added dropwise over 1 h. Stirring was continued for an additional 1 h. The reaction mixture was concentrated, the residue was then taken up in Et$_2$O, washed with 10% aq NaHCO$_3$, dried (MgSO$_4$), and finally passed through a column containing basic alumina to remove traces of unreacted 2,7-dichlorofluorene-9-acetic acid. The Et$_2$O solution was concentrated to an oil which was recrystallized from 5% EtOAc/hexane to provide 208 g (91%) of alcohol **2** as a white solid, mp 76–78°C.

FTIR (KBr): $\nu$ = 3278, 2928, 1455, 1414, 1164, 1079, 1033, 894, 815 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.25 (q, 2 H, $J$ = 6.6 Hz), 3.64 (t, 2 H, $J$ = 6.6 Hz), 4.13 (t, 1 H, $J$ = 6.6 Hz), 7.35 (d, 2 H, $J$ = 8.1 Hz), 7.52 (s, 2 H), 7.62 (d, 2 H, $J$ = 8.1 Hz).

### Chlorination of Fluorenes; General Procedure:

To a mechanically stirred slurry of fluorene-9-acetic acid (2.34 g, 10.4 mmol) and NCS (3.34 g, 25.0 mmol) in MeCN (5 mL) was added conc. HCl (1.1 mL) dropwise. An exothermic reaction occurred during the addition of the HCl and cooling with a water bath was required to keep the temperature below the boiling point of MeCN. After the completion of the addition (5 min), a clear solution resulted, the temperature started to fall and the product slowly precipitated out. The suspension was stirred overnight, filtered and the solid recrystallized from AcOH to provide 2.3 g (77%) of 2,7-dichlorofluorene-9-acetic acid (**10f**) as white needles.

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 2.85 (d, 2 H, $J$ = 7.1 Hz), 4.31 (t, 1 H, $J$ = 7.1 Hz), 7.42 (dd, 2 H, $J$ = 1.1, 8.1 Hz), 7.65 (s, 2 H), 7.91 (d, 2 H, $J$ = 8.1 Hz), 12.52 (s, 1 H).

### 10a:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 4.50 (s, 2 H), 7.42 (dd, 2 H, $J$ = 1.1, 8.1 Hz), 7.65 (s, 2 H), 7.91 (d, 2 H, $J$ = 8.1 Hz).

### 10b:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.24 (d, 3 H, $J$ = 7.1 Hz), 3.93 (q, 1 H, $J$ = 7.1 Hz), 7.34 (d, 2 H, $J$ = 7.8 Hz), 7.47 (s, 2 H), 7.63 (d, 2 H, $J$ = 7.8 Hz).

### 10c:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.67 (t, 3 H, $J$ = 7.1 Hz), 2.09 (m, 2 H), 3.97 (t, 1 H, $J$ = 7.1 Hz), 7.34 (dd, 2 H, $J$ = 7.5, 1.5 Hz), 7.41 (s, 2 H), 7.60 (d, 2 H, $J$ = 7.5 Hz).

### 10d:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 5.85 (s, 1 H), 7.26 (d, 2 H, $J$ = 8.1 Hz), 7.45 (d, 2 H, $J$ = 8.1 Hz), 7.61 (s, 1 H).

### 10e:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.09 (s, 9 H), 3.85 (s, 1 H), 7.37 (dd, 2 H, $J$ = 1.1, 7.1 Hz), 7.45 (s, 2 H), 7.75 (d, 2 H, $J$ = 7.1 Hz).

### 10g:

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 1.80 (m, 2 H), 2.35 (m, 2 H), 4.18 (t, 1 H, $J$ = 7.5 Hz), 7.47 (d, 2 H, $J$ = 7.1 Hz), 7.72 (s, 2 H), 7.93 (d, 2 H, $J$ = 7.1 Hz), 12.05 (s, 1 H).

### 10h:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.25 (q, 2 H, $J$ = 6.6 Hz), 3.64 (t, 2 H, $J$ = 6.6 Hz), 4.13 (t, 1 H, $J$ = 6.6 Hz), 7.35 (d, 2 H, $J$ = 8.1 Hz), 7.52 (s, 2 H), 7.62 (d, 2 H, $J$ = 8.1 Hz).

(1) Gualtieri, F.; Teodori, E.; Bellucci, C.; Pesce, E.; Piacenza, G.
    J. Med. Chem. **1985**, 28, 1621.
    Fritz, H.E.; Peck, D.W.; Atkins, K.E. J. Org. Chem. **1968**, 33, 2575.
(2) Chong, J.M.; Lajoie, G.; Tjepkema, M. W. Synthesis **1992**, 819.
(3) Fields, G.B.; Noble, R.L. Int. J. Pept. Protein Res. **1990**, 35, 161.
(4) Carpino, L.A. Acc. Chem. Res. **1987**, 20, 401.
    Carpino, L.A.; Sadat-Aalaee, D.; Beyermann, M. J. Org. Chem. **1990**, 55, 1673.
    Beyermann, M.; Bienert, M.; Niedrich, H.; Carpino, L.A.; Sadat-Aalaee, D. J. Org. Chem. **1990**, 55, 721.
(5) Burch, R.M.; Weitzberg, M.; Blok, N.; Muhlhauser, R.; Martin, D.; Farmer, S.G.; Bator, J.M.; Connor, J.R.; Ko, C.; Kuhn, W.; McMillan, B.A.; Raynor, M.; Shearer, B.G.; Tiffany, C.; Wilkins, D.E. Proc. Natl. Acad. Sci. USA **1991**, 88, 355.
(6) Burch, R.M.; Weitzberg, M.; Noronha-Blob, L.; Lowe, V.C.; Bator, J.M.; Perumattam, J.; Sullivan, J.P. Drug News and Perspectives **1992**, 5, 331.
    Noronha-Blob, L.; Laemont, K.; Lowe, V.C.; Perumattam, J.; Burch, R.M. Gastroenterology **1992**, 102(4), A672.
(7) Maercker, A.; Passlack, M. Chem. Ber. **1983**, 116, 710.
(8) Carpino, L.A.; Chao, H.G.; Tien, J-H. J. Org. Chem. **1989**, 54, 4302.
(9) Smith, W.K.; Hardin, J.N.; Rabideau, P.W. J. Org. Chem. **1990**, 55, 5301.
(10) Bachmann, W.E.; Sheehan, J.C. J. Am. Chem. Soc. **1940**, 62, 2687.
(11) Lane, C.F.; Myatt, H.L.; Daniels, J.; Hopps, H.B. J. Org. Chem. **1974**, 39, 3052.
(12) Carpino, L.A. J. Org. Chem. **1980**, 45, 4250.
(13) Browne, S.E.; Asher, S.E.; Cornwall, E.H.; Frisoli, J.K.; Harris, L.J.; Salot, E.A.; Sauter, E.A.; Trecoske, M.A.; Veale, Jr., P.S. J. Am. Chem. Soc. **1984**, 106, 1432.
(14) Smith, W.K.; Hardin, J.N.; Rabideau, P.W. J. Org. Chem. **1990**, 55, 5301.
(15) Bachmann, W.E.; Sheehan, J.C. J. Am. Chem. Soc. **1940**, 62, 2687.