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Tetrahedron
Tetrahedron 60 (2004) 8967–8973

# Simple and efficient per-*O*-acetylation of carbohydrates by lithium perchlorate catalyst

Kuo-Cheng Lu,[a] Shu-Yi Hsieh,[a,b] Laxmikant N. Patkar,[a] Chien-Tien Chen[b] and Chun-Cheng Lin[a,c,*]

[a]*Institute of Chemistry, Academia Sinica, 128, Sec. 2, Yen-Chiu-Yuan Rd, Nankang, Taipei 115, Taiwan*
[b]*Department of Chemistry, National Taiwan Normal University, Taipei 106, Taiwan*
[c]*Department of Applied Chemistry, National Chiao Tung University, Hsinchu 300, Taiwan*

Received 23 March 2004; revised 24 June 2004; accepted 29 June 2004

Available online 21 August 2004

**Abstract**—Lithium perchlorate is demonstrated to be a highly efficient and convenient catalyst for the per-*O*-acetylation of various saccharides with excellent yields.


## 1. Introduction

Acetylation of alcohols is a basic and widely used transformation in organic chemistry,[1] primarily to synthetically protect hydroxyl groups, and as an aid to structurally elucidate polyhydroxyl containing natural products such as oligosaccharides. In the context of carbohydrate chemistry, fully acetylated monosaccharides are widely used as starting materials to synthesize oligosaccharides and glycoconjugates. Among the reagents available for alcohol acetylation, acetic anhydride or acetyl chloride is frequently used as an acetyl source under basic media[1c,2] or with Lewis base[1,3] or acid catalysts.[1,4] In preparing per-*O*-acetylated saccharides, the most widespread reaction condition is pyridine as solvent with a catalytic amount of 4-dimethylaminopyridine (DMAP).[5] Recently, various reagents have been designed for catalyzing saccharide per-*O*-acetylation, including: sodium acetate,[6] Lewis acids ($ZnCl_2$,[6] $FeCl_3$,[7] $V(O)(OTf)_2$,[8] Cu $(OTf)_2$ and $Sc(OTf)_3$[9]), Bronsted acids ($HClO_4$,[6] $H_2SO_4$[10]), heterogeneous catalysts (montmorillonite K-10,[11] H-beta zeolite,[12] zirconium sulfophenyl phosphonate[13]), iodine,[14] and ionic liquid.[15] Although the previously mentioned catalysts perform acetylation efficiently, some are incompatible with the sensitive functional groups contained in alcohols. Additionally, most reaction conditions using a significant excess of acetic anhydride result in difficulties in large-scale handling and the disposal of spent catalyst and reagent. Furthermore, acetylation of carbohydrates or its intermediates is challenging despite the impressive array of acetylation catalyst owing to its easy isomerization from pyranose to furanose form, as well as the presence of other sensitive functional groups which may be transformed with the catalyst. Therefore, the search in carbohydrate chemistry for a new mild, efficient and selective peracetylation catalyst that minimizes isomerization and loss of sensitive functional groups is continuing.

## 2. Results and discussion

Lithium perchlorate ($LiClO_4$) is well known as a mild and efficient Lewis acid catalyst for various organic reactions.[16,17] Prompted by a recent report of alcohol acetylation using litium perchlorate[4b] as a mild catalyst, we explored $LiClO_4$ for carbohydrate acetylation. The findings of this work are outlined below. Initially, to optimize reaction conditions using lithium perchlorate catalyst, various proportions of catalyst and acetic anhydride and commonly used solvents were tried (Table 1) with **1** as a substrate.

The amount of catalyst used and reaction temperature influence reaction rate. When a large excess of acetic anhydride (20 equiv, 5 equiv of $Ac_2O$ per OH) and 0.4 equiv of lithium perchlorate were used at ambient temperature, acetylation was very slow, whereas when the temperature was raised to 40 °C, peracetylation was completed within 1 h (Table 1, entries 1 and 2). When the amount of catalyst was reduced to 0.1 equiv, the reaction took four days under the same reaction conditions (entry 3).

*Keywords*: Acetylation; Sialic acid; Lithium perchlorate.
* Corresponding author.; e-mail: cclin@chem.sinica.edu.tw

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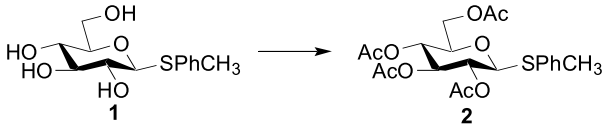
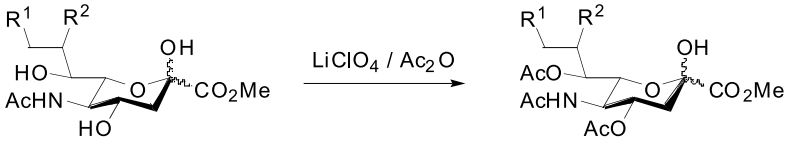
doi:10.1016/j.tet.2004.06.138

**Table 1.** Acetylation of **1** by using $LiClO_4$ as catalyst




| Entry | $Ac_2O$ | $LiClO_4$ | Temperature (°C) | Solvent | Time (h) |
|---|---|---|---|---|---|
| 1 | 20 | 0.4 | rt | — | Slow |
| 2 | 20 | 0.4 | 40 | — | 1 |
| 3 | 20 | 0.1 | 40 | — | 4 days |
| 4 | 4.4 | 0.4 | 40 | — | 1 |
| 5 | 4.4 | 0.4 | 40 | $CH_2Cl_2$ | 1 |
| 6 | 4.4 | 0.4 | 40 | $CH_3CN$ | 1 |
| 7 | — | 0.4 | 40 | AcOH | — |

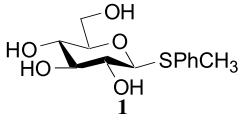
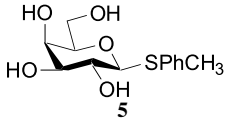
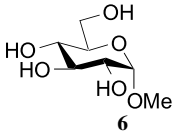
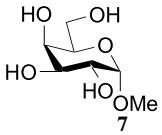
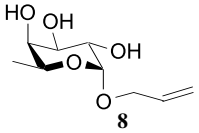
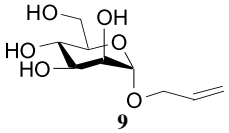
**Table 2.** Acetylation of sialic acid derivatives catalyzed by $LiClO_4$




| Entry | Substrate | $R^1$ | $R^2$ | Time h | Product | β:α | Yield % |
|---|---|---|---|---|---|---|---|
| 1[a] | **3a** | OH | OH | 12 | **4a**[19b] | 1:0 | 98 |
| 2 | **3b**[20] | OTBDPS | OH | 18 | **4b** | 10:1 | 85 |
| 3 | **3c** | OBz | OH | 28 | **4c** | 5:1 | 85 |
| 4 | **3d**[21] | *O*-4-Pentenoyl | OH | 22 | **4d** | 4:1 | 81 |
| 5 | **3e**[22] | SAc | OAc | 16 | **4e** | 7:1 | 90 |

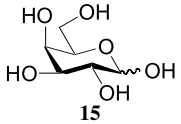
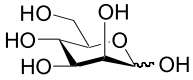
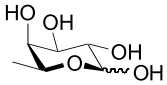
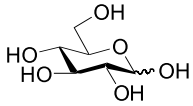
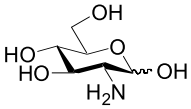
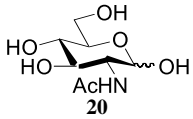
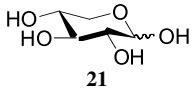
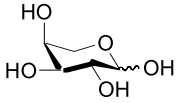
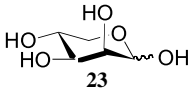
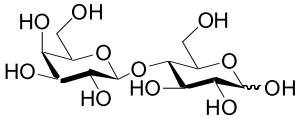
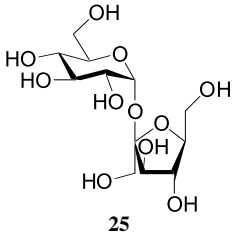
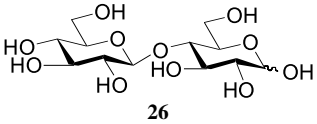
[a] In the presence of $CH_2Cl_2$ as cosolvent, two days were needed to complete the reaction.
[b] For this compound $R^1=R^2=OAc$.

**Table 3.** Peracetylation of anomeric protected sugars by using $LiClO_4$

| Entry | Substrate | Time (h) | Product | Yield (%)[a] |
|---|---|---|---|---|
| 1 |  **1** | 1 | **2** | 99 |
| 2 |  **5** | 20 | **10**[18] | 99 |
| 3 |  **6** | 18 | **11**[23] | 99 |
| 4 |  **7** | 30 | **12**[24] | 99 |
| 5 |  **8** | 15 | **13**[25] | 99 |
| 6 |  **9** | 12 | **14**[26] | 99 |

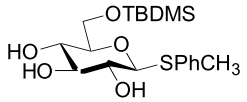
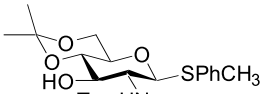
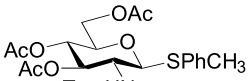
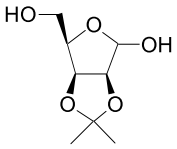
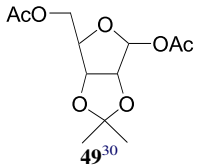
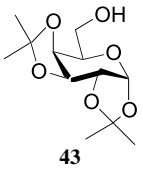
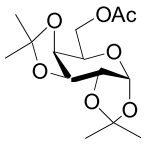
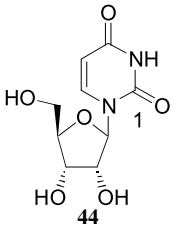
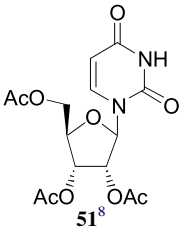
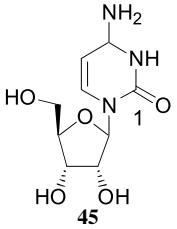
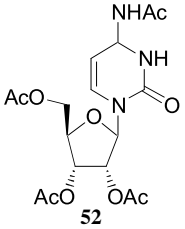
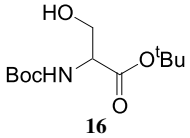
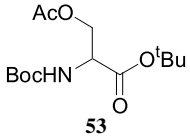
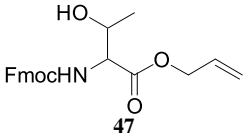
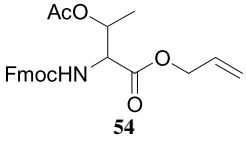
[a] Yield of crude product with purity higher then 97% according to $^1H$ NMR spectroscopy.

**Table 4.** Acetylation of sugars by using $LiClO_4$ as catalyst

| Entry | Substrate | Time (h) | Product | Total[a] (%) | Pyranose (α/β)/Furanose |
|---|---|---|---|---|---|
| 1 |  **15** | 10 | **28**[14] | 98 | 45/55 |
| 2 |  **16** | 5 | **29**[14] | 99 | (1.1/1)[b] |
| 3 |  **17** | 2 | **30**[11] | 99 | 50(1/5)[b]/50 |
| 4 |  **18** | 5.5 | **31**[14] | 99 | (1.1/1[b]) |
| 5 |  **19** | 13[c] | **32**[14] | 98 | — |
| 6 |  **20** | 13[c] | **32** | 98 | — |
| 7 |  **21** | 10 | **33**[27] | 99 | 80(1/1.1)[b]/20 |
| 8 |  **22** | 15 | **34**[27] | 98 | 63(1/1.4)[b]/37 |
| 9 |  **23** | 9 | **35**[27] | 99 | 79(1/4.2)[b]/21 |
| 10 |  **24** | 12 | **36**[8] | 99 | (1/1)[b] |
| 11 |  **25** | 5 | **37**[15] | 98 | — |
| 12 |  **26** | 72 | **38**[11] | 96 | — |
| 13 | β-Cyclodextrin **27** | 50 | **39**[28] | 93 | — |

[a] Yield of crude product with purity higher than 97% according to $^1H$ NMR spectrosopy.
[b] Ratio of α/β.
[c] Reaction temperature is 60 °C.

**Table 5.** Acetylation of substrates with acid-labile-protecting groups by using $LiClO_4$

| Entry | Substrate | Time (h) | Product | Yield (%)[a] |
|---|---|---|---|---|
| 1[b] |  **40** | 30 | 2 | 91[c] |
| 2[b] |  **41** | 30 |  **48**[29] | 99[c] |
| 3[b] |  **42** | 24 |  **49**[30] | 90 |
| 4 |  **43** | 48 |  **50** | 96 |
| 5 |  **44** | 10 |  **51**[8] | 94 |
| 6 |  **45** | 10 |  **52** | 99 |
| 7[b] |  **16** | 8 |  **53** | 90[c] |
| 8 |  **47** | 2 |  **54** | 95 |

[a] Yield of crude product with purity higher than 97% according to $^1H$ NMR spectroscopy.
[b] $CH_2Cl_2$ was used as co-solvent.
[c] Yield after silica gel column chromatography.

Using 4.4 equiv of acetic anhydride (1.1 equiv of $Ac_2O$ per OH) as solvent and reagent at 40 °C with 0.4 equiv of catalyst (0.1 equiv of $LiClO_4$ per OH) obtained product **2**[18] in 1 h (entry 4). To increase the solubility of starting material and partial acetylated product and enhance the reaction rate, dichloromethane and acetonitrile were used, but the reaction rate was unchanged (entries 5 and 6). Using acetic acid as both an acetylation reagent and solvent, did not produce any peracetylated product **2** (entry 7). Notably, the use of catalytic amount of LiOAc and $HClO_4$ (0.1 equiv per OH) with 4.4 equiv of acetic acid as solvent, resulted in

a very slow reaction. Catalytic amount of $HClO_4$ combined with acetic anhydride gave good yield of peracetylated product. Although these results indicate the possible role of $HClO_4$ as an active catalyst, it should be noted that the acetylation of compound **3a** (Table 2) catalyzed by $HClO_4$ (0.1 equiv per OH)[19] gave full peracetylated product while with use of $LiClO_4$ only **4a** was obtained. Thus, the peracetylation mechanism by $LiClO_4$ needs to be further investigated. In this report, the optimum reaction conditions for the acetylation were determined to be 1.1 equiv of acetic anhydride with 0.1 equiv of lithium perchlorate for each OH at 40 °C.

The above reaction conditions were then applied to numerous other peracetylations of anomeric center protected monosaccharides, obtaining very high yields, as listed in Tables 2 and 3. Particularly interesting is the acetylation of **3a** (Table 3) to the corresponding product **4a** in which the hydroxyl at C-2 position is not acetylated. Compound **4a** is an important precursor for the synthesis of sialic acid phosphite donor. The preparation of **4a** is usually preformed by acetic anhydride with $HClO_4$. However, high yield is not always reproducible because full acetylation is a serious competing side reaction, especially in large-scale synthesis. Many sialic acid derivatives were peracetylated by the present conditions and gave desired products as shown in Table 2. Thus, our method provides an easy access to prepare sialic acid derivatives with 2-hydroxyl group unprotected.

More examples of the per-*O*-acetylations of free saccharides are listed in Table 4. The anomeric configurations and the ratio between pyranose and furanose were determined based on 400 MHz $^1$H NMR spectral analyses. Generally, the peracetylation of hexoses with 'galactosyl type' configuration (entries 1 and 3) and pentoses (entries 7–9) produced a mixture of pyranose and furanose. Notably, the long reaction time in entries 12 and 13 may be caused by the low substrate solubility under the reaction conditions. Also, β-cyclodextrin, which contains 21 hydroxyl groups, was peracetylated efficiently under the same conditions. The peracetylation conditions employed here were also applied to the saccharides with acid-labile-protecting groups, as listed in Table 5. Although the TBDMS and terminal acetonide protecting groups were cleaved (Table 5, entries 1 and 2) under $LiClO_4/Ac_2O$ reaction conditions, internal acetonide, Boc, and *t*-butyl protecting groups survived.

## 3. Conclusion

In summary, this study has demonstrated the utility of lithium perchlorate as a peracetylation catalyst in carbohydrate chemistry. The conditions used are very mild, yields are high, and only simple workup procedures are required. Thus, the method presented here displays potential for large-scale preparation of per-*O*-acetylated intermediates of carbohydrates.

## 4. Experimental

### 4.1. General per-*O*-acetylation procedure

A mixture of sugar (1 mmol), $Ac_2O$ (1.1 equiv per OH), and $LiClO_4$ (0.1 equiv per OH) was stirred at 40 °C (oil bath temperature). The reaction progress was followed with TLC. Once the reaction was completed, it was quenched with water and extracted with ethyl acetate. The resulting organic layer was successively washed with saturated $NaHCO_3$, brine, and dried over $Na_2SO_4$. Solvent evaporation yielded almost pure per-*O*-acetylated saccharide.

Compounds **2**,[18] **4a**,[19] **10-14**,[18,23–26] **28-39**,[8,11,14,15,27,28] **48**,[29] **49**[30] and **51**[8] have previously been reported and the NMR spectral data are in good agreement with the literature data.

**4.1.1. Methyl (5-acetamido-9-*O*-*tert*-butyldiphenylsilyl-4,7,8-tri-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranoside)onate (4b).** $^1$H NMR ($CDCl_3$, 400 MHz): δ 1.03 (s, 9H), 1.90 (s, 3H), 2.00 (s, 3H), 2.03 (s, 3H), 2.10–2.12 (m, 1H), 2.12 (s, 3H), 2.58 (dd, 1H, *J*=13.6, 4.8 Hz), 3.70 (s, 3H), 3.70–3.82 (m, 1H), 3.93 (q, 1H, *J*=10.4 Hz), 4.01 (dd, 1H, *J*=2.8, 11.2 Hz), 4.24 (dd, 1H, *J*=2.0, 10.4 Hz), 5.05–5.09 (m, 1H), 5.30–5.37 (m, 1H), 5.48 (dd, 1H, *J*=2.0, 6.0 Hz), 5.61 (d, 1H, *J*=10.4 Hz), 7.36–7.45 (m, 6H), 7.61–7.66 (m, 4H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 19.18, 20.66, 20.79, 23.11, 26.63, 26.79, 35.69, 49.74, 52.95, 61.74, 67.72, 69.09, 69.45, 72.26, 73, 97.60, 127.55, 127.67, 129.59, 133.31, 135.50, 135.52, 166.30, 168.17, 170.06, 170.12, 170.74. HRMS (EI) Calcd for $C_{34}H_{45}O_{12}NSiNa$ $[M+Na]^+$: 710.2609. Found: 710.2621.

**4.1.2. Methyl (5-acetamido-9-*O*-benzoyl-4,7,8-tri-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranoside)onate (4c).** $^1$H NMR ($CDCl_3$, 400 MHz): δ 1.90 (s, 3H), 1.99 (s, 3H), 2.01–2.06 (m, 1H), 2.08 (s, 3H), 2.15–2.20 (m, 1H), 2.17 (s, 3H), 3.84 (s, 3H), 4.15 (q, 1H, *J*=10.0 Hz), 4.22–4.29 (m, 1H), 4.30 (dd, 1H, *J*=2.4, 10.8 Hz), 4.85 (dd, 1H, *J*=2.4, 12.8 Hz), 5.19–5.25 (m, 1H), 5.38–5.49 (m, 2H), 6.00 (d, 1H, *J*=10.0 Hz) 7.39–7.49 (m, 2H), 7.52–7.57 (m, 1H), 7.98–8.04 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 20.75, 20.80, 23.08, 29.23, 29.66, 36.03, 36.13, 49.48, 53.51, 63.16, 68.30, 69.19, 71.20, 71.68, 94.93, 128.27, 128.44, 132.97, 166.35, 166.09, 170.31, 170.40, 170.88, 171.20. HRMS (EI) Calcd for $C_{25}H_{32}O_{13}N$ $[M+H]^+$: 554.1874. Found: 554.1867.

**4.1.3. Methyl (5-acetamido-9-*O*-(4-pentenoyl)-4,7,8-tri-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranoside)onate (4d).** $^1$H NMR ($CDCl_3$, 400 MHz): δ 1.91 (s, 3H), 2.03 (s, 3H), 2.04–2.15 (m, 2H), 2.10 (s, 3H), 2.15 (s, 3H), 2.34–2.49 (m, 4H), 3.74–3.89 (m, 1H), 3.87 (s, 3H), 4.03 (dd, 1H, *J*=7.2, 12.4 Hz), 4.12–4.18 (m, 2H), 4.49 (dd, 1H, *J*=2.4, 12.4 Hz), 4.98–5.13 (m, 2H), 5.21–5.38 (m, 3H), 5.77–5.85 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 20.99, 23.08, 28.47, 33.17, 36.09, 49.33, 53.38, 62.51, 67.99, 68.26, 70.96, 71.34, 71.44, 94.84, 115.38, 136.61, 166.31, 169.01, 170.23, 170.27, 171.02, 172.88. HRMS (EI) Calcd for $C_{21}H_{27}O_{11}S$ $[M+H]^+$: 487.1196. Found: 487.1194.

**4.1.4. Methyl (5-acetamido-9-thioacetyl-4,7,8-tri-*O*-acetyl-3,5,9-trideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranoside)onate (4e).** $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.89 (s, 3H), 2.02 (s, 3H), 2.04 (s, 3H), 2.16 (s, 3H), 2.20–2.25 (m, 2H), 2.31 (s, 3H), 2.72 (dd, 1H, $J$=10.0, 14.4 Hz), 3.73 (dd, 1H, $J$=2.8, 14.4 Hz), 3.84 (s, 3H), 4.13–4.20 (m, 1H), 4.22 (dd, 1H, $J$=2.0, 10.0 Hz), 5.01 (ddd, 1H, $J$=2.8, 4.4, 10.0 Hz), 5.19–5.26 (m, 1H)), 5.34 (dd, 1H, $J$=2.0, 4.4 Hz), 5.82 (d, 1H, $J$=10.0 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 20.89, 23.13, 29.47, 30.47, 49.73, 53.35, 68.78, 69.40, 71.09, 73.11, 94.94, 169.02, 170.33, 170.44, 170.76, 171.09, 195.94. HRMS (EI) Calcd for $C_{20}H_{30}O_{12}NS$ $[M+H]^+$: 508.2489. Found: 508.1479.

**4.1.5. 1,2,3,4-Diisopropylidene-6-acetyl-D-galactopyranose (50).** $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.33 (s, 3H), 1.34 (s, 3H), 1.45 (s, 3H), 1.52 (s, 3H), 2.09 (s, 3H), 4.01–4.04 (m, 1H), 4.19 (dd, 1H, $J$=7.6, 11.6 Hz), 4.24 (dd, 1H, $J$=8.0, 2.0 Hz), 4.29 (dd, 1H, $J$=4.8, 11.6 Hz), 4.25 (dd, 1H, $J$=5.2, 2.4 Hz), 4.62 (dd, 1H, $J$=2.4, 8.0 Hz), 5.54 (d, 1H, $J$=5.2 Hz). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ 20.71, 24.36, 24.82, 24.83, 25.83, 25.85, 63.36, 63.84, 70.32, 70.58, 70.95, 96.17, 108.61, 109.46, 170.79. HRMS (FAB) Calcd for $C_{14}H_{23}O_7$ $[M+H]^+$: 303.1439. Found: 303.1444.

**4.1.6. 2,3,5-*O*-Acetyl-*N*-acetyl-cytidine (52).** $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 2.05 (s, 3H), 2.05–2.07 (m, 1H), 2.07 (s, 3H), 2.11 (s, 3H), 2.24 (s, 3H), 4.36–4.39 (m, 3H), 5.30 (t, 1H, $J$=5.6 Hz), 5.44 (dd, 1H, $J$=3.6, 5.6 Hz), 6.01 (d, 1H, $J$=3.6 Hz), 7.47 (d, 1H, $J$=7.6 Hz), 7.91 (d, 1H, $J$=7.6 Hz). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ 20.54, 20.89, 24.95, 40.85, 62.72, 69.65, 73.84, 79.87, 89.64, 97.37, 144.24, 155.02, 163.33, 169.56, 169.64, 170.33, 131.37. HRMS (FAB) Calcd for $C_{17}H_{22}O_9N_3$ $[M+H]^+$: 412.1350. Found: 412.1356.

**4.1.7. *O*-Acetyl-*N*-carbo-*tert*-butyloxy-serine-*tert*-butyl-ester (53).** $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.46 (s, 9H), 1.46 (s, 9H), 2.05 (s, 3H), 4.28 (dd, 1H, $J$=4.4, 12.0 Hz), 4.44–4.46 (m, 2H), 5.29 (d, 1H, $J$=7.2 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 20.62, 27.90, 28.28, 53.42, 64.73, 80.07, 82.70, 155.19, 168.70, 170.45. HRMS (FAB) Calcd for $C_{14}H_{26}O_6N$ $[M+H]^+$: 304.1760. Found: 304.1755.

**4.1.8. 2-(9*H*-Fluoren-9-ylmeyhoxycarbonylamino)-3-acetyl-butyric acid allyl ester (54).** $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.31 (d, 3H, $J$=6.4 Hz), 2.04 (s, 3H), 4.27 (t, 1H, $J$=6.8 Hz), 4.47 (d, 2H, $J$=6.8 Hz), 4.54 (dd, 1H, $J$=2.6, 9.8 Hz), 4.60–4.70 (m, 2H), 5.28 (dd, 1H, $J$=1.2, 10.4 Hz), 5.35 (dd, 1H, $J$=1.2, 16.6 Hz), 5.45–5.52 (m, 2H), 5.86–5.95 (m, 1H), 7.30–7.35 (m, 2H), 7.40–7.44 (m, 2H), 7.62–7.65 (m, 2H), 7.79 (d, 2H, $J$=7.6 Hz). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ 17.06, 21.03, 40.97, 42.74, 47.28, 57.78, 66.51, 67.40, 70.48, 119.36, 120.13, 120.14, 125.19, 127.23, 127.89, 129.62, 131.44, 141.44, 143.76, 143.95, 156.66, 169.73, 169.84. HRMS (FAB) Calcd for $C_{24}H_{26}O_6N$ $[M+H]^+$: 424.1766. Found: 424.1760.

## Acknowledgements

The authors would like to thank Academia Sinica (AS92IC6), National Taiwan Normal University, and National Science Council of Taiwan (NSC91-3112-P-001-041-Y and 91-2113-M-001-013) for financial support.

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