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Tetrahedron Letters 46 (2005) 8293–8297
Tetrahedron Letters

Synthesis of peptides and oligosaccharides by using a recyclable fluorous tag

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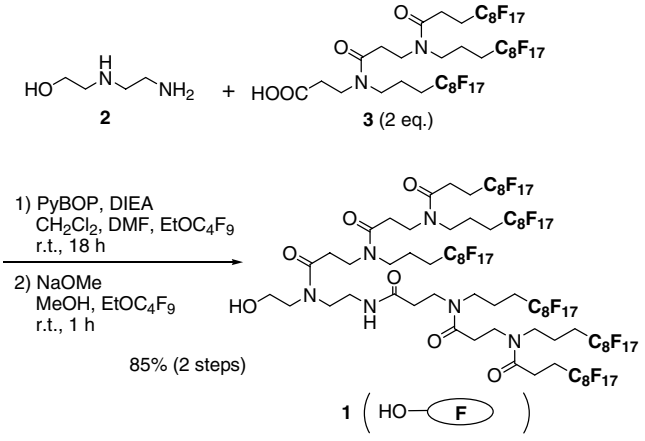
Received 24 August 2005; revised 26 September 2005; accepted 28 September 2005
Available online 13 October 2005

Abstract—A hexakis(fluorous chain)-type alcohol was used in the synthesis of oligosaccharides and peptides through connection with a linker suitable for the particular type of target compound. After the preparation of the desired compound, the fluorous alcohol was easily recovered in good yields under basic conditions. It appears that the fluorous alcohol can be recovered, recycled, and reused.

Since fluorous chemistry was first reported by Horváth and Rábai,[1] who used a fluorous biphasic system, it has been applied in various fields.[2] For example, Curran and co-workers[3] described a fluorous synthesis (the fluorous tag method) that is suitable as a strategic alternative to solid-phase synthesis. This strategy is very efficient because, alike the case for the solid-phase method, it does not inevitably resort to chromatography. Recently, we have also achieved the syntheses of oligosaccharides and peptides by using various fluorous tags.[4,5] In peptide syntheses, however, it is impossible or very difficult to recycle the fluorous tags because they are partially decomposed under the acidic condition present in the final deprotection step.[5a,b,d] Furthermore, in oligosaccharide synthesis, a hydrogenolysis step changed a benzylic-type fluorous tag to a toluene-type fluorous tag that was not recyclable.[5c] To realize a practical fluorous synthesis, the recycling of the fluorous tags is essential for both environmental and economic reasons. We describe the concept of a novel recyclable system using the fluorous tag **1** (Scheme 1) and its applications in peptide and oligosaccharide syntheses. Our concept of a fluorous synthesis using a recyclable tag with a sacrificial linker is shown in Figure 1.

A linker that is suitable for the particular group of target compounds, such as peptides or oligosaccharides, must be introduced into the fluorous tag. The synthesis of the target compound is then carried out by using a method based on the fluorous tag with a sacrificial linker. Each intermediate containing the fluorous tag is obtained in a straightforward manner simply by simple partitioning between FC72[6] and an organic solvent, such as MeCN or MeOH, without the need for column chromatography. The desired compound is obtained after selective cleavage at *Point 1* (Fig. 1) followed by a single column-chromatographic run. On the other hand, selective cleavage at *Point 2* permits the recovery of the fluorous tag. This concept enables various types of fluorous tags, which are otherwise very difficult to recycle, to be readily recycled. We synthesized the



Scheme 1. Preparation of recyclable fluorous tag **1**.

Keywords: Fluorous; Recylce; Peptide; Oligosaccharide.
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doi:10.1016/j.tetlet.2005.09.160

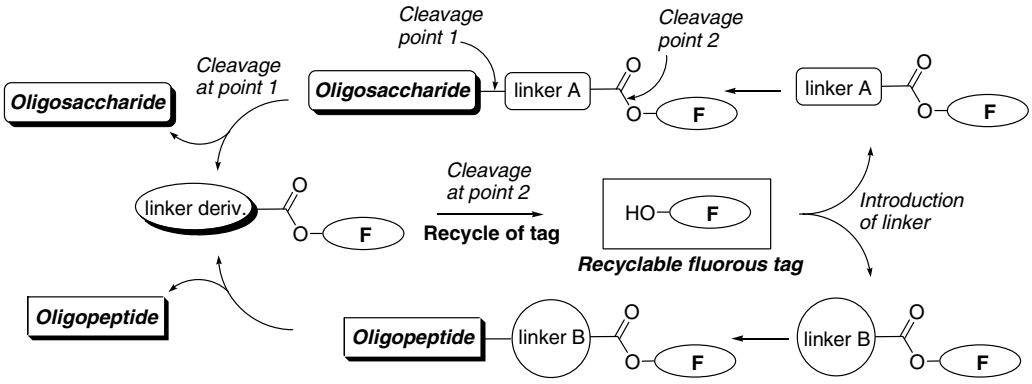
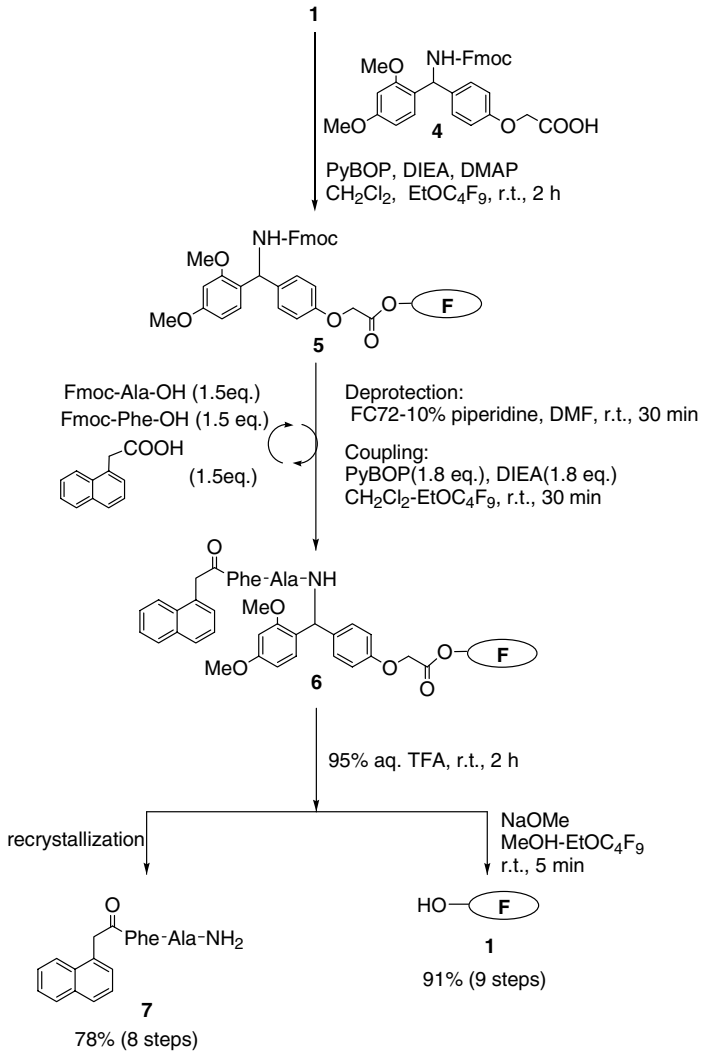


Figure 1. Fluorous synthesis strategy based on a recoverable tag with a sacrificial linker.



Scheme 2. Synthesis of a C-terminal amide-type peptide.

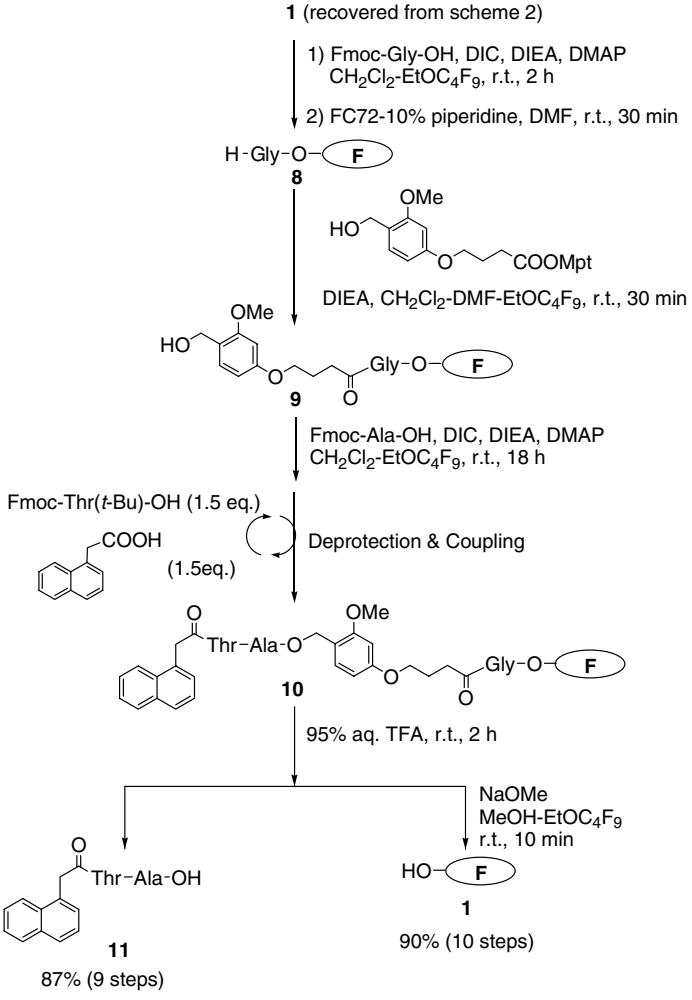
hexakis(fluorous chain)-type alcohol **1** as a recyclable fluorous tag (Scheme 1).

The coupling reaction of 2-[(2-aminoethyl)amino]ethanol **2** with the fluorous carboxylic acid **3**[4] followed by treatment with NaOMe gave the alcohol **1**[7] in an 89% yield. First, the synthesis of the C-terminal amide-type peptide on the fluorous tag **1** was attempted (Scheme 2).

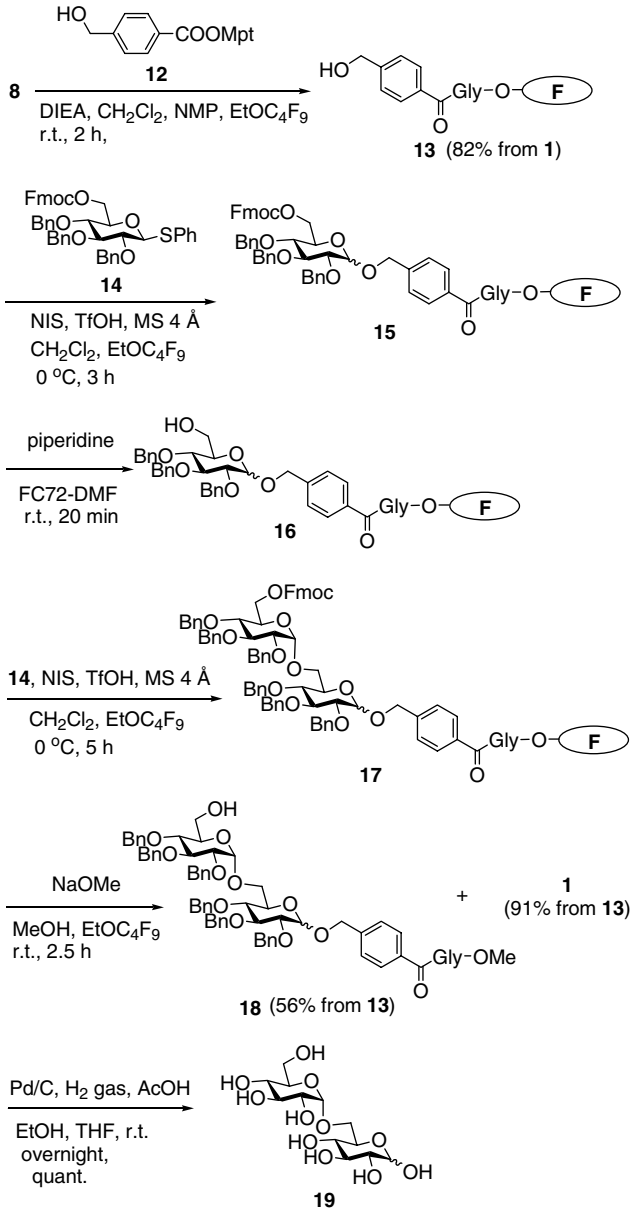
Compound **1** was coupled with linker **4** to afford compound **5**.[8] The fluorous peptide derivative **6** was prepared by using the Fmoc strategy.[9] The deprotection of the Fmoc group was carried out by using the

FC72–10% piperidine/DMF (1:1) immiscible system, and the coupling was performed with a 1.5-fold excess of Fmoc-Ala-OH, Fmoc-Phe-OH, and naphthylacetic acid with PyBOP as the coupling reagent in the mixed homogeneous solvents CH_2Cl_2 and $EtOC_4F_9$.[10] Each of the fluorous intermediates from **5** to **6**[8] could be obtained in a straightforward manner simply by partitioning between FC72 and MeCN. These compounds, including the fluorous tag, were extracted into the FC72 layer, whereas the other reagents remained in the MeCN layer. No further purification, such as silica-gel column chromatography, was necessary. Finally, the fluorous peptide **6** was treated with TFA containing 5% H_2O to cleave the peptide derivative **7** from the fluorous linker. A partitioning step with FC72 and MeCN was then performed as above, and crude **7** was obtained from the MeCN layer. After recrystallization, compound **7**[11] was obtained in a 78% overall yield from **1**. TLC of the FC72 layer showed the presence of a complex mixture, because the linker moiety bound to **1** was partially decomposed under the acidic conditions.[12] This mixture was treated with NaOMe and, after a fluorous partitioning step, alcohol **1** was extracted into the FC72 layer. After silica gel column chromatography, the fluorous tag **1** was recovered in a 91% yield and reused for other peptide syntheses, as shown in Scheme 3.

The synthesis of the HMPB-type[13] fluorous support **9** was achieved by using the dimethylphosphinothioic mixed anhydride (Mpt-MA) method.[14] The fluorous peptide derivative **10**[8] was prepared through the Fmoc strategy by using the fluorous synthesis strategy. Finally, the crude peptide on the fluorous support **10** was treated with TFA containing 5% H_2O, and then partitioned between FC72 and MeCN. The crude dipeptide derivative **11**[15] extracted into the MeCN layer, was purified by silica-gel column chromatography to give an 87% overall yield. The fluorous compounds extracted into the FC72 layer were treated with NaOMe and then partitioned between FC72 and MeOH. After concentration of the FC72 layer and purification by silica-gel column chromatography, the fluorous tag **1** was recovered in a 90% yield (Scheme 3). Furthermore, the synthesis of an oligosaccharide by using the fluorous alcohol **1** recovered from the peptide synthesis was demonstrated. A benzylic-type fluorous tag has been already reported.[5c] In this study, this benzylic-type fluorous tag was changed into a toluene-type tag that displays a hydrogenolytic cleavage reaction. Although we tried to



Scheme 3. Synthesis of a C-terminal carboxyl-type peptide.



Scheme 4. Disaccharide synthesis on the fluorous tag.

regenerate the toluene-type tag to the benzylic type, it was impossible to recycle it.[16] Therefore, our novel 'tag and linker' concept was applied to the synthesis of an oligosaccharide using the benzylic-type fluorous linker **13**[17] (Scheme 4).

The synthesis of **13** was achieved by using the Mpt-MA method in an 82% yield from **1**. The glycosylation[18] of **13** with a 2.0-fold excess of the glycosyl donor **14**[19] gave compound **15**.[8] After the deprotection of the Fmoc group, the reaction of **16** with a 2.0-fold excess of **14** under similar glycosylation conditions as described above gave the fluorous disaccharide **17**.[8] Each of the fluorous intermediates **15**, **16**, and **17** could be obtained in a straightforward manner by a simple partitioning between FC72 and an organic solvent such as MeOH or MeCN. No further purifications, such as silica-gel column chromatography, were necessary. Finally, the removal of the fluorous tag and Fmoc group was carried out by treatment with NaOMe, and the crude **18** was extracted into a MeOH layer by partitioning the mixture between FC72 and MeOH. After silica-gel column chromatographic separation, the disaccharide **18**[20] was obtained in a 56% overall yield from **13**. On the other hand, alcohol **1** was recovered from the FC72 layer in a 91% yield and could be recycled. All the benzyl groups of compound **18** were easily removed by hydrogenation in the presence of Pd/C to afford the deprotected disaccharide **19**.[21,22]

In conclusion, we achieved the syntheses of peptides and an oligosaccharide in high yields by using a recyclable fluorous tag. This fluorous tag **1** was readily introduced onto various linkers, and could be removed from the target compounds by the usual procedure in each case. Moreover, it was easily recyclable in excellent yields after treatment with NaOMe. Each fluorous synthetic intermediate could be obtained in a straightforward manner simply by simple partitioning between FC72 and an organic solvent. As a result, the desired compounds were obtained after only a single silica-gel column chromatographic purification step.

Acknowledgments

This work was performed through the Noguchi Fluorous Project by our institute.

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6. FC72 is a commercially available fluorocarbon solvent that consists mainly of perfluorohexane (C_6F_{14}) isomers and is called Fluorinert™ FC-72.
7. Compound **1**: white powder, ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 1.77$–1.97 (m, 8H), 1.98–2.19 (m, 8H), 2.34–2.86 (m, 16H), 3.30–3.86 (m, 25H), 6.80–7.24 (m, 1H). MALDI-TOF MS: Calcd for $C_{82}H_{58}F_{102}N_6O_7Na$ m/z $[M+Na]^+$: 3199.26. Found: 3199.28.
8. The product mixtures containing the fluorous compounds **5**–**6**, **8**–**10**, **13**, and **16** were partitioned between FC-72 and MeCN. Compounds **15** and **17** were partitioned between FC-72 and MeOH. None of the fluorous compounds was detected by TLC of the organic layer after three extractions with FC-72, showing that they were quantitatively extracted into the FC-72 layer.
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10. $EtOC_4F_9$ is a commercially available fluorocarbon solvent called Novec™ HFE-7200 (3M, Tokyo) that is miscible in common organic solvents and fluorous solvents.
11. Compound **7**: ^{1}H NMR (600 MHz, DMSO-d_6) $\delta = 1.19$ (d, $J = 7.1$ Hz, 3H), 2.27 (dd, $J = 10.0$, 13.9 Hz, 1H), 3.04 (dd, $J = 3.9$, 13.9 Hz, 1H), 3.85 (s, 2H), 4.19 (quint, $J = 7.1$ Hz, 1H), 4.53 (dt, $J = 3.9$, 10.3 Hz, 1H), 7.01 (s, 1H), 7.14–7.28 (m, 7H), 7.31–7.50 (m, 3H), 7.76 (d, $J = 8.1$ Hz, 1H), 7.84 (d, $J = 9.3$ Hz, 1H), 7.86 (d, $J = 8.7$ Hz, 1H), 8.09 (d, $J = 7.1$ Hz, 1H), 8.43 (d, $J = 8.5$ Hz, 1H). HRMS (ESI-TOF MS.): Calcd for $C_{24}H_{25}N_3O_3$ m/z $[M+H]^+$: 404.1969. Found: 404.1990.
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13. HMPB; 4-(4-Hydroxymethyl-3-methoxyphenyloxy)-butanoyl.
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15. Compound **11**: white powder, ^{1}H NMR (600 MHz, DMSO-d_6) $\delta = 1.02$ (d, $J = 6.2$ Hz, 3H), 1.25 (d, $J = 7.6$ Hz, 3H), 3.92–3.97 (m, 1H), 3.99, (d, $J = 15.1$ Hz, 1H), 4.06, (d, $J = 15.8$ Hz, 1H), 4.17–4.25 (m, 2H), 7.40–7.53 (m, 4H), 7.80 (dd, $J = 2.7$, 6.9 Hz, 1H), 7.90 (t, $J = 4.1$ Hz, 1H), 8.00 (d, $J = 6.9$ Hz, 1H), 8.06–8.12 (m, 2H). HRMS (ESI-TOF): Calcd for $C_{19}H_{23}N_2O_5$ m/z $[M+H]^+$: 359.1602. Found: 359.1600.
16. Unpublished work.
17. Compound **13**: ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 1.74$–1.97 (m, 8H), 1.97–2.23 (m, 8H), 2.36–2.86 (m, 16H), 3.24–3.79 (m, 24H), 4.06–4.38 (m, 4H), 4.74 (s, 2H), 6.73–7.17 (m, 1H), 7.41–7.49 (m, 2H), 7.74–7.86 (m, 2H). MALDI-TOF MS: $C_{93}H_{69}F_{102}N_7O_{10}Na$ m/z $[M+Na]^+$: 3390.32. Found: 3392.72.
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20. Compound **18** (MALDI-TOF): Calcd for $C_{65}H_{69}NO_{14}Na$ m/z $[M+H]^+$: 1110.5. Found: 1110.9.
21. The β-isomer of **19** (i.e., gentiobiose) was not detected by NMR spectroscopic analysis.
22. Compound **19** was purified by chromatography on Sephadex LH-20 (eluted by 50% aq. MeOH) and identified by comparison with spectroscopic data for an authentic sample (isomaltose). ^{1}H NMR (600 MHz, D_2O) $\delta = 4.51$ (d, $J = 8.2$ Hz, H-1 of β-anomer), 4.79 (d, $J = 3.4$ Hz, H-1′), 4.80 (d, $J = 4.1$ Hz, H-1′), 5.08 (d, $J = 4.1$ Hz, H-1 of α-anomer). ^{13}C NMR (150 MHz, D_2O) $\delta = 60.40$, 65.62, 65.70, 69.34, 69.44, 69.48, 69.96, 71.35, 71.41, 71.45, 71.71, 71.74, 72.96, 73.01, 73.98, 74.23, 75.90, 92.13, 96.02, 97.87, 97.91. HRMS (ESI-TOF MS.): Calcd for $C_{12}H_{22}O_{11}Na$ m/z $[M+Na]^+$: 365.1054. Found: 365.1068.