HETEROCYCLES, Vol. 106, No. 5, 2023, pp. 841 - 846. © 2023The Japan Institute of Heterocyclic Chemistry
Received, 8th February, 2023, Accepted, 15th March, 2023, Published online, 20th March, 2023
DOI: 10.3987/COM-23-14820

SYNTHESES OF TWO NEW FLUOROUS CROWN ETHERS CARRYING SUGAR MOLECULES WITH A MULTIVALENT BFP MODIFICATION: INVESTIGATIONS OF THEIR PARTITION RATIOS IN FLUOROUS BIPHASIC SYSTEMS AND RECYCLABILITY DURING ACETOXYLATION REACTION

Takashi Yamanoi,[1]* Kenji Koike,[2] Taro Koda,[1] and Yoshiki Oda[3]

[1]Faculty of Pharmacy and Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-0295, Japan; [2]Department of Chemistry, School of Science, Tokai University, 4-1-1 Kitakaname, Hiratsuka, Kanagawa 259-1292, Japan; [3]Technology Joint Management Office, Tokai University, 4-1-1 Kitakaname, Hiratsuka, Kanagawa 259-1292, Japan

Abstract – This paper describes the design and synthesis of two new fluorous crown ethers (named **1** and **2**) carrying sugar molecules modified with multivalent Bfp. Subsequently, we investigated their partition ratios in biphasic systems using FC 72 and several organic solvents. Then, we assessed the activities of **1** or **2** in an FC 72/acetonitrile biphasic system *via* the acetoxylation reaction using 2-(bromomethyl)naphthalene and potassium acetate, followed by examinations of their recyclability in a two-layer system based on their immobilization in an FC 72 solvent during the acetoxylation reactions.

Since crown ether molecules are important phase transfer catalysts, increasing their availability is a significant subject in organic chemistry. Therefore, as proposed candidates for this purpose, highly fluorinated substances, so-called fluorous compounds, have been identified for their unique physical properties and high solubility in perfluorinated (fluorous) solvents.[1] Besides that, while fluorous chemistry provides a powerful separation technology to facilitate the recovery of a catalyst or reaction product, the fluorous tag, which enables binding to the appropriate functional groups, is beneficial for converting nonfluorous compounds into fluorous ones.[2] Hence, based on this background, the preparation of several crown ethers conjugated with the fluorous tags of commercially available simple fluorinated carbon chain(s) have been reported, including studies on the products *via* some relevant organic reactions in biphasic systems containing fluorous solvents.[3] However, these crown ethers comprise such low fluorine contents that they are rarely recyclable by immobilizing in fluorous solvents. Previously, Miura et al. reported that Bfp-OH (bisfluorous chain type propionic acid), as shown in Figure 1, could be a useful fluorous tagging reagent in oligosaccharide syntheses.[4] Their study also suggested that the multivalent Bfp-conjugated sugar molecules function as heavy fluorine content units to design fluorous compounds. Similarly, another study proposed sugar-based crown ether molecules, such as the crown ethers modified with sugar moieties or cyclofructans containing a crown ether framework.[5] Our former research also prepared glucopyranose-based crown ethers with a spiroketal structure.[6] We supposed that the novel fluorous crown ethers could be designed by introducing Bfp into the sugar moieties of these sugar-based crown ethers.

Therefore, we describe the syntheses of two new fluorous crown ethers (**1** and **2**) carrying sugar molecules modified with multiple Bfp groups, as shown in Figure 1, followed by assessments of their fluorous specificity using fluorous and organic solvents based on the partition ratios in a two-layer system. Afterward, we investigated the recyclability of **1** and **2** during catalytic acetoxylation reactions on the basis of their immobilization in fluorous solvents of a two-layer system.

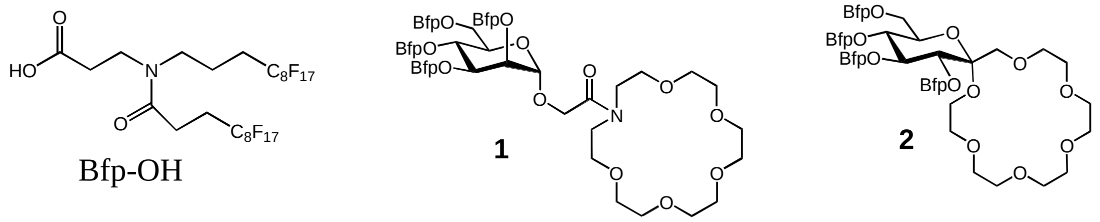
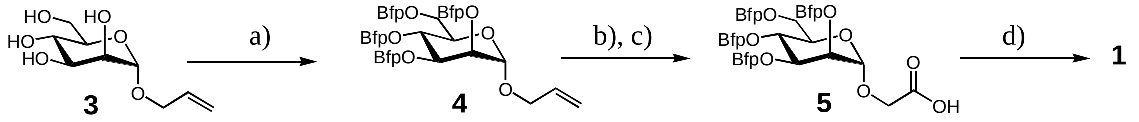


Figure 1. Bfp-OH and two new fluorous crown ethers

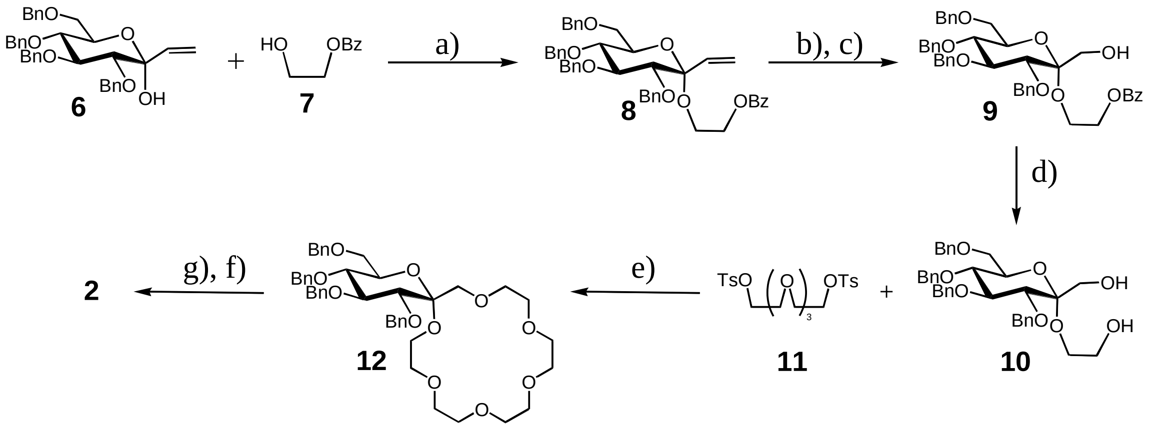
Synthesis of the crown ethers (1 and 2)

Scheme 1 shows the synthetic route for **1**. The condensation reaction of allyl mannopyanoside (**3**) with Bfp-OH (4.8 eq) using *N*,*N'*-dicyclohexylcarbodiimide (DCC, 4.8 eq) in the presence of 4-dimethylaminopyridine (DMAP, 4.8 eq) in dichloromethane–Novec 7100 (1–1) for one week produced the desired Bfp conjugated compound (**4**) in an 80% yield. Subsequently, **4** was oxidized by bubbling in O_3 with dichloromethane–Novec 7100 (1–1) containing triphenylphosphine (3 eq) for two hours, followed by the addition of $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-butanol, and water for three hours, which yielded 99% of **5**. Finally, we obtained 62% of the desired crown ether (**1**)[8] by the condensation between 1-aza-18-crown-6 (1.2 eq) and **5** using DCC (2 eq) in the presence of dichloromethane–Novec 7100 (1–1) containing DMAP (2 eq) for 12 hours under ultrasonic irradiation.

Scheme 2 shows the synthetic route for **2**. First, we reacted **6**[7] with 2-hydroxyethyl benzoate (**7**) (1.2 eq) using TfOH (0.05 eq) in the presence of $CaSO_4$ for four hours, giving **8** in an 86% yield. Next, **8** was oxidized by bubbling in O_3 with dichloromethane containing triphenylphosphine (3 eq) for two hours, followed by subsequent reactions using sodium borohydride (3 eq) in methanol overnight, yielding 80% of **9**. We then treated **9** with 28% MeONa in methanol to produce **10** in a 99% yield, after which **10** was reacted with tetraethylene glycol ditosylate (**11**) in sodium hydride for three hours at 60 °C to yield 83% of **12**. Finally, the desired crown ether (**2**)[8] was obtained in a good yield of 92% after bubbling **12** in H_2 gas with $Pd(OH)_2$ (4.6 eq) for 72 hours and further reactions using Bfp-OH (4.6 eq), DCC (5.8 eq), and DMAP (5.8 eq) in dichloromethane–Novec 7100 (1–1) for 17 hours under ultrasonic irradiation.



Scheme 1. Reagents and conditions: a) Bfp-OH (4.8 eq), DCC (4.8 eq), DMAP (4.8 eq)/ CH_2Cl_2–Novec 7100 (1–1), 1 week, 80%; b) O_3, PPh_3 (3 eq)/ CH_2Cl_2–Novec 7100 (1–1), 2 h; c) $NaClO_2$ (10 eq), $Me_2C=CHMe$, NaH_2PO_4 (3 eq), ^{t}BuOH/ CH_2Cl_2–Novec 7100 (1–1), 3 h, 99%; d) 1-aza-18-crown-6 (1.2 eq), DCC (2 eq), DMAP (2 eq)/ CH_2Cl_2–Novec 7100 (1–1), SW, 12 h, 62%



Scheme 2. Reagents and conditions: a) TfOH (0.05 eq)/ MeCN, $CaSO_4$, 4 h, 86%; b) O_3, PPh_3 (3 eq)/ CH_2Cl_2, 2 h, c) $NaBH_4$ (3 eq)/ MeOH, 60 °C, overnight, 80%; d) 28% MeONa/ MeOH, 1 h, 99%; e) **11** (1.2 eq), NaH/ THF, 3 h, 83%; f) $Pd(OH)_2$ (4.6 eq), H_2/ H_2O, MeOH, THF, 72 h; g) Bfp-OH (4.6 eq), DCC (5.8 eq), DMAP (5.8 eq)/ CH_2Cl_2–Novec 7100 (1–1), 17 h, SW, 92% (total yield of f and g)

Partition ratios of 1 and 2 between the fluorous and organic solvents in a biphasic system

Next, we investigated the partition ratios of the two fluorous crown ethers (**1** and **2**) in a two-layer system using fluorous and organic solvents to elucidate their affinities to fluorous solvents. For this investigation, while we utilized the commercially available FC 72, comprising perfluorohexane (C_6F_{14}) isomers, as the fluorous solvent, methanol, dichloromethane, benzene, acetonitrile, chloroform, ethyl acetate, tetrahydrofuran (THF), dichloroethane, and toluene were used as the organic solvents. Table 1 shows the partition ratios for **1** and **2** in the biphasic systems combining FC 72 with these organic solvents. Although the partition ratios of **1** to the FC 72/organic solvent in the biphasic systems using chloroform and ethyl acetate were 80/20 and 90/10, respectively, **1** was almost partitioned to the FC 72 solvent in the biphasic systems using other organic solvents. However, the crown ether **2** was favorably partitioned to the FC 72 solvent in the biphasic systems using these organic solvents, with its partition ratios ranging from >99/1 to 85/15. We also observed that the fluorine contents of **1** and **2** were 57% and 58%, respectively. Although these values were almost similar, the results of their partition ratios somewhat differed, proposed to be because of the structural differences between **1** and **2**.

Table 1. Partition ration of **1** or **2** to FC 72/organic solvent[a)]

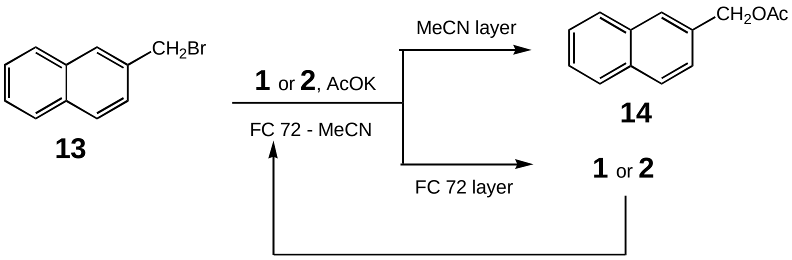
Entry	Crown ether	Partition ration of FC 72/organic solvent							
		MeOH	CH_2Cl_2	C_6H_6	MeCN	$CHCl_3$	AcOEt	C_6H_5Me	THF
1	**1**	>99/1	>99/1	>99/1	>99/1	80/ 20	90/10	>99/1	>99/1
2	**2**	95/5	85/15	92/8	>99/1	89/11	89/11	94/6	85/15

a) The partition ratio was determined by the ^{19}F-NMR analysis of each FC 72 and organic solvent separated from the biphasic system, using benzotrifluoride as the standard.

Recyclable abilities of 1 and 2 during the catalytic acetoxylation reactions in a fluorous biphasic system

Finally, we investigated the activities of the crown ethers (**1** and **2**) *via* the acetoxylation reaction, using potassium acetate (based on the partition ratio experimental results of **1** and **2** in a two-layer system) and FC 72/acetonitrile solvents since they possessed 18-crown-6-like ligands with the coordinative ability of a potassium cation. As shown in Scheme 3, we first reacted 2-(bromomethyl)naphthalene (**13**) with potassium acetate (1.5 eq) using **1** (0.2 eq) in FC 72–acetonitrile (1–1) under reflux conditions for 1.5 hours. After the reaction, each solvent in the two-layer system was separated into their acetonitrile and FC 72 layers to recover the reaction product and **1**, including a desired naphthalen-2-ylmethyl acetate (**14**)[8] from the separated acetonitrile layer at a high yield of 98%. Since similar reaction conditions that did not use **1** still gave **14** at only a 20% yield, we established **1** as an excellent phase transfer catalyst in a two-layer system using FC 72 and the acetonitrile solvents. Next, we investigated the recyclability of **1** *via* the acetoxylation reaction similarly repeated two more times using the separated FC 72 layer containing **1**. The second acetoxylation reaction conducted by adopting a similar procedure under an FC 72/acetonitrile biphasic system using the separated FC 72 layer containing **1** showed the isolation of the desired **14** at a high yield of 97%. Therefore, we conducted a third acetoxylation reaction using the FC 72 layer recovered from the second time reaction. Accordingly, the third reaction afforded **14** at a high yield of 96% from the recovered acetonitrile layer. Examinations after the third reaction following the isolation of **1** also revealed that **1** was recovered at a high efficiency of 92% from the FC 72 layer of the reaction system.

Subsequently, we investigated the acetoxylation reaction using **2** and the same experimental procedure in **1**. After the acetoxylation reaction had been repeated thrice under the above reaction conditions, the yields of the desired **14** at the first, second and third reactions were 98%, 98%, and 97%, respectively. However, we recovered **2** from the FC 72 layer after the third reaction at a high efficiency of 95%. Thus, since the crown ethers (**1** and **2**) were repeatedly used in the acetoxylation reaction using an FC 72/acetonitrile biphasic system, **1** and **2** were proven to be possible recyclable phase transfer catalysts based on their immobilization in an FC 72 solvent.



Scheme 3

Table 2. Acetoxylation reaction using **13** and AcOK in the presence of **1** or **2**.[a)]

Entry[a)]	Crown ether	Reaction yield (%)			Recovery yield (%) of **1** or **2** after 3rd reaction
		1st	2nd	3rd	
1	None	20	-	-	-
2	**1**	98	97	96	92
3	**2**	98	98	97	95

a) Reaction conditions; Molar ratio: **13**: AcOK: **1** (or **2**) = 1: 1.5: 0.2; Solvent: FC 72–MeCN= (1–1); Temp.: 85 °C (Reflux); Time: 1.5 h.

In conclusion, this study successfully synthesized two new fluorous crown ethers (**1** and **2**) carrying sugar molecules modified with multivalent Bfp. Then, we elucidated their partition ratios in a two-layer system using fluorous and organic solvents, followed by investigations in an FC 72/acetonitrile biphasic system. Notably, we observed that both fluorous crown ethers worked as phase transfer catalysts in the presence of 2-(bromomethyl)naphthalene and potassium acetate during the acetoxylation reaction. Therefore, we subsequently confirmed their potential as recyclable phase transfer catalysts by immobilizing them in an appropriate fluorous biphasic system containing a fluorous solvent.

SUPPORTING INFORMATION

Supplementary (1. General procedure to determine the partition ratios of **1** and **2** between the fluorous and organic solvents in a biphasic system, 2. General procedure of acetoxylation reactions in a fluorous biphasic system, 3. ^{1}H-NMR, ^{13}C-NMR, and MS spectra of **1** and **2**.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27884/106/5

REFERENCES AND NOTES

1. (a) I. T. Horváth, 'Fluorous Chemistry,' Springer Berlin, Heidelberg, 2012; (b) I. T. Horváth and J. Rábai, *Science*, 1994, **266**, 72; (c) J.-M. Vincent, *Chem. Commun.*, 2012, **48**, 11382.
2. (a) A. Studer, S. Hadida, R. Ferritto, S.-Y. Kim, P. Jeger, P. Wipf, and D. P. Curran, *Science*, 1997, **275**, 823; (b) W. Zhang, *Curr. Opin. Drug Discov. Devel.*, 2004, **7**, 784.
3. (a) B. Gourdet, K. Singh, A. M. Stuart, and J. A. Vidal, *J. Fluorine. Chem.*, 2010, **131**, 1133; (b) S. Elshani, E. Kobzar, and R. A. Bartsch, *Tetrahedron*, 2000, **56**, 3291; (c) A. M. Stuart and J. A. Vidal, *J. Org. Chem.*, 2007, **72**, 3735.
4. T. Miura, Y. Hirose, M. Ohmae, and T. Inazu, *Org. Lett.*, 2001, **3**, 3947.
5. (a) N. S. Mani and P. P. Kanakamma, *Tetrahedron Lett.*, 1994, **35**, 3629; (b) F. Faltin, V. Fehring, and R. Miethchen, *Synthesis*, 2002, 1851; (c) B. Dumont-Hornebeck, J. P. Joly, J. Coulon, and Y. Chapleur, *Carbohydr. Res.*, 1999, **321**, 214; (d) F. Louis, M. I. Garcia-Moreno, P. Balbuena, C. O. Mellet, and J. M. Garcia-Fernandez, *Tetrahedron*, 2008, **64**, 2792.
6. T. Yamanoi, Y. Oda, H. Muraishi, and S. Matsuda, *Molecules*, 2008, **13**, 1840.
7. T. Yamanoi, Y. Nara, S. Matsuda, Y. Oda, A. Yoshida, K. Katsuraya, and M. Watanabe, *Synlett*, 2007, 785.
8. Compound **1**; ^{1}H-NMR ($CDCl_3$, 600 Mz) δ: 1.82 - 1.89 (8H, m), 2.097 - 2.10 (8H, m), 2.46 - 2.71 (24H, m), 3.40 - 3.75 (40H, m), 3.99 - 4.07 (1H, m), 4.27 - 4.32 (1H, m), 4.39 - 4.58 (3H, m), 5.01 - 5.02 (1H, m), 5.23 - 5.30 (1H, m), 5.38 - 5.45 (2H, m); MALDI-TOF MASS: Found: *m/z* $[M + Na]^+$ 4523.04: calcd for $C_{120}H_{89}F_{136}N_{45}O_{20}$ $[M + Na]^+$ 4526.38. Compound **2**; ^{1}H-NMR ($CDCl_3$, 600 Mz) δ: 1.85 - 2.17 (16H, m), 2.43 - 2.71 (24H, m), 3.43 - 4.53 (38H, m), 5.05 - 5.09 (1H, m), 5.27 - 5.29 (1H, m), 5.41 - 5.44 (1H, m); MALDI-TOF MASS: Found: *m/z* $[M + Na]^+$ 4454.39: calcd for $C_{117}H_{84}F_{136}N_4O_{19}$ $[M + Na]^+$ 4455.35. Compound **14**; ^{1}H-NMR ($CDCl_3$, 600 Mz) δ: 2.10 (3H, s, CH_3), 5.30 (2H, s, CH_2), 7.40-7.50 (3H, m, Nap), 7.78-7.85 (4H, m, Nap).