Synthesis and Shuttling Behavior of Rotaxanes Consisting of Crown Ether Wheel and Disulfide Dumbbell with Two Ammonium Centers†

Yoshio Furusho,‡ Ryoko Sanno,‡ Tomoya Oku, and Toshikazu Takata*

Department of Organic and Polymeric Materials, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152-8552, Japan
‡Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan
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Several [2]- and [3]rotaxanes bearing some functional groups on their wheel components and spacers with different lengths between two ammonium centers on their dumbbell components were prepared in good yields from dibenzo-24-crown-8-ether derivatives and dumbbell-shaped bis(sec-ammonium salt)s having a centrally located disulfide linkage, by utilizing the reversible thiol-disulfide interchange reaction. The shuttling behaviors of the [2]rotaxanes were investigated by ^{1}H NMR by use of the spin polarization transfer-selective inversion recovery technique. It was found that the change in spacer length in the axle resulted in a drastic change in shuttling rate of the [2]rotaxanes, although the introduction of the functional groups to the wheels did not affect the shuttling behavior at all.

Key Words : [2]Rotaxane, Crown ether, Ammonium salt, Disulfide, Shuttling

Introduction

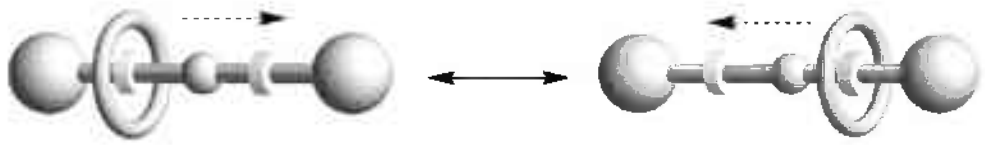
One of the most striking features of interlocked molecules such as catenanes and rotaxanes is that their components can undergo relative movement without breaking covalent bonds.[1] This kind of dynamic processes such as shuttling have attracted much attention, because it is possible to control the relative positioning of their components through some external stimuli and they are hence expected to be molecular modules for future nano-scaled devices such as nano-computers (Scheme 1).[2]

Recently, Stoddart *et al.* reported a catenane-based nano-calculator.[3] In order to understand the relative movement such as shuttling processes and to explore catenane- and rotaxane-based nano-devices, it is necessary to investigate the effects of wheel and axle structures *etc*. Meanwhile, we have recently developed a new synthetic method "entering" for [2]- and [3]rotaxanes by utilizing the thiol-disulfide interchange reaction (Scheme 2).[4]

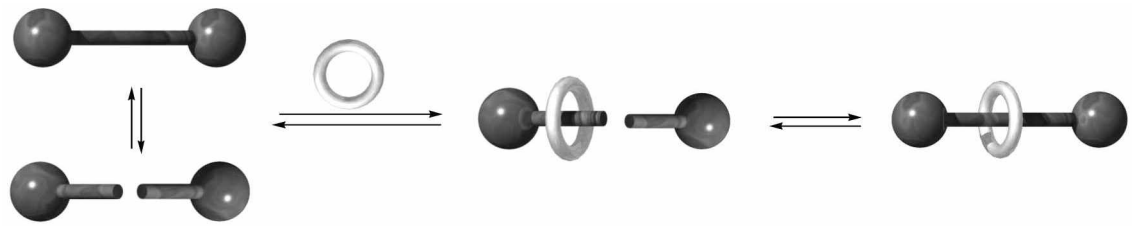
The yields of the rotaxanes can be well-controlled by the solvent, concentration, and temperature, since the whole process is reversible. Important features of this method involve the efficient thioldisulfide interchange reaction under mild conditions and the tolerance of disulfide for many functional groups so that it is possible to introduce some functionalities to rotaxanes to control their shuttling behaviors. In this paper, we describe synthesis and shuttling behavior of rotaxanes having different functional group on the wheel and different spacer length in the axle.

Results and Discussion

Synthesis of Rotaxane. A catalytic amount (0.010 mol·L^{-1}) of benzenethiol was added to a degassed $CDCl_3/CD_3CN$

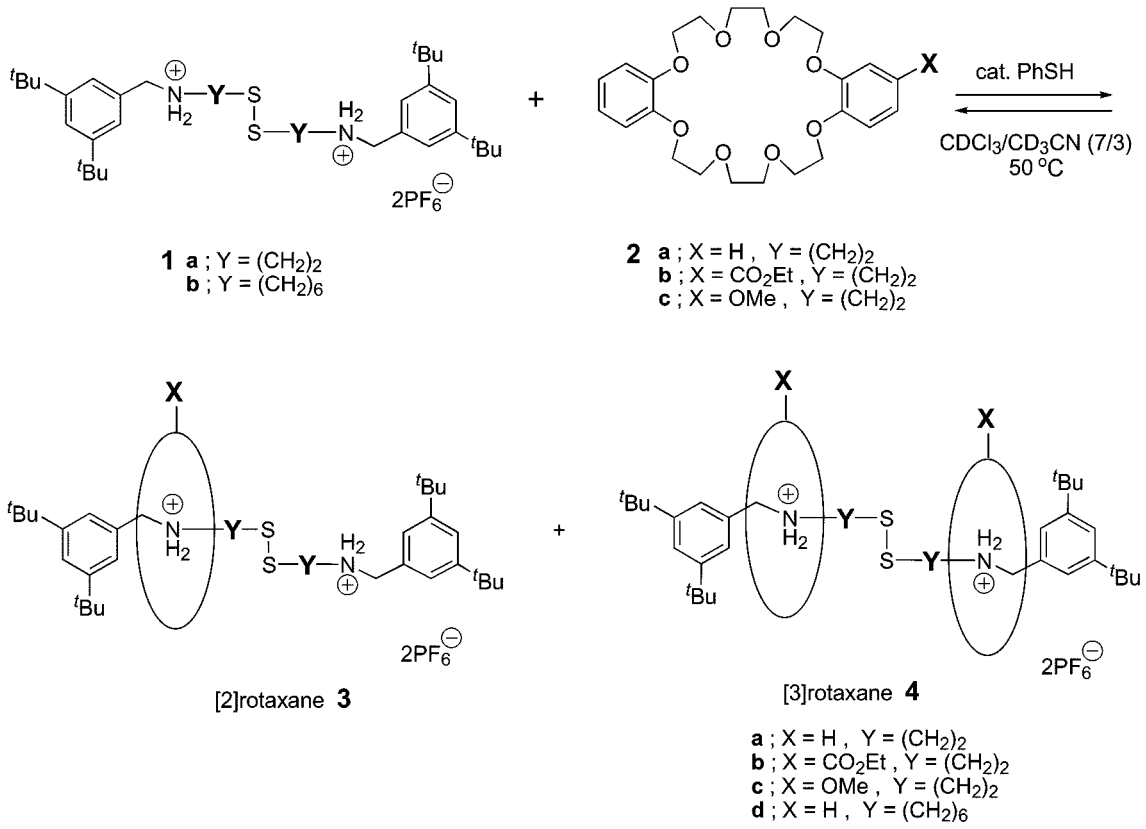


Scheme 1. Shuttling of [2]rotaxane.



Scheme 2. Entering method for preparation of rotaxane.

†Dedicated to Professor Yong Hae Kim for his distinguished achievements in organic chemistry.
*Corresponding Author. e-mail: ttakata@polymer.titech.ac.jp



Scheme 3. Synthesis of [2]- and [3]rotaxanes by utilization of reversible cleavage of disulfide linkage.

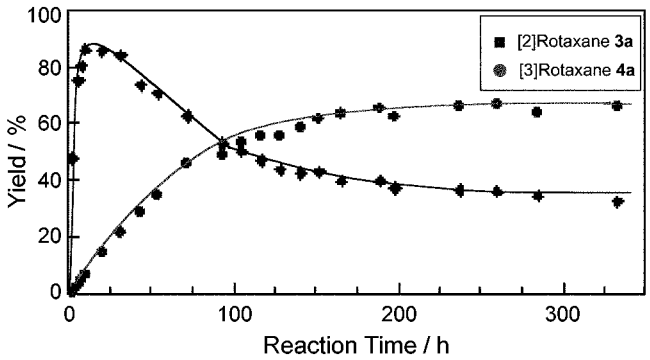


Figure 1. The Time Course of the Yields of [2]Rotaxane (**3a**) and [3]Rotaxane (**4a**). [**1a**] = 0.10 mol·L^{-1}, [**2a**] = 0.20 mol·L^{-1}, [PhSH] = 0.010 mol·L^{-1} in $CDCl_3/CD_3CN$ (7/3) at 50 °C.

(7/3) solution of a mixture of a dumbbell shaped ammonium salt with a centrally located disulfide linkage[4a-b] (**1a**) (0.10 mol·L^{-1}) and dibenzo-24-crown-8-ether (**2a**) (0.20 mol·L^{-1}). The mixture was allowed to stand at 50 °C (Scheme 3). The reaction progress was monitored by ^{1}H NMR and the yields of [2]rotaxane[4a-b] (**3a**) and [3]rotaxane[4a-b] (**4a**) were determined by ^{1}H NMR. The time courses of the yields of **3a** and **4a** are shown in Figure 1.

The rotaxane **3a** was formed soon after the initiation, while **4a** gradually appeared. The yield of **3a** reached its maximum value (89%) after 10 h, and rapidly decreased to that at a certain equilibrium state. The signals of **4a** appeared after ca. 4 h and the yield of **4a** increased with a decrease of that of **3a**. The system reached the equilibrium state after ca. 240 h (*i.e.* 10 days), where the yields of **3a** and **4a** were 35% and 65%, respectively (Table 1). Although the yield of **4a** can be easily enhanced up to *ca.* 90% by using excess amount of **2a**,[4b] 1 : 2 mixture of **1a** and **2a** was used in this case for comparison with other systems. Both **3a** and **4a** were isolated with preparative HPLC in similar yields to those of ^{1}H NMR. The structures of them were characterized by ^{1}H NMR, FAB-MS, and elemental analysis.

By the same procedures, rotaxanes bearing ethoxycarbonyl groups ([2]rotaxane (**3b**) and [3]rotaxane (**4b**)) and methoxy groups ([2]rotaxane (**3c**) and [3]rotaxane (**4c**)) were synthesized starting from 1 : 2 mixture of **1a** and **2b**,[5] and from **1a** and **2c**, respectively (Scheme 3). The rotaxanes **3b**, **4b**, **3c**, and **4c** were purified with preparative HPLC. The structures of them were characterized by the ^{1}H NMR, FAB-MS, and elemental analysis. The yields of these rotaxanes at

Table 1. Yields of [2]rotaxane **3** and [3]rotaxane **4** at equilibrium in $CDCl_3/CD_3CN$ (7/3) at 50 °C after 14 days

Entry	X	Y	[2]Rotaxane/Yield[a]	[3]Rotaxane/Yield[a]
1	H	$(CH_2)_2$	**3a**/35%	**4a**/65%
2	$CO_2C_2H_5$	$(CH_2)_2$	**3b**/34%	**4b**/64%
3	OCH_3	$(CH_2)_2$	**3c**/37%	**4c**/61%
4	H	$(CH_2)_6$	**3d**/54%	**4d**/46%

[a]Determined by 1H NMR.

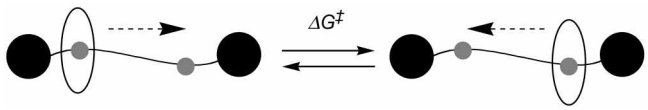
the equilibrium states determined by ^{1}H NMR were nearly equal to those of **3a** and **4a**. Thus, neither electron-withdrawing nature of the ethoxycarbonyl group **2b** nor the electron-donating nature of the methoxy group of **2c** affected the equilibria, i.e. the yields of the rotaxanes. These results suggest that a wide range of molecular designs can be performed in this synthetic protocol for rotaxane,[4a-b] undoubtedly being advantageous from viewpoint of the applications of rotaxanes.

Rotaxanes bearing a longer spacer (hexamethylene spacer) between the two ammonium centers ([2]rotaxane (**3d**) and [3]rotaxane (**4d**)) were similarly synthesized by employing 1 : 2 mixture of a dumbbell-shaped bisammonium salt having a centrally-located disulfide linkage[6] (**1b**) and dibenzo-24-crown-8 ether (**2a**). The reaction forming the rotaxanes was slightly slower than those of the rotaxanes having ethylene spacers (**3a-c** and **4a-c**), and the system reached the equilibrium within 14 days. The yields of **3d** and **4d** were 54% and 46%, respectively, by ^{1}H NMR at the equilibrium state. The total ratio of the complexation between the wheel and the dumbbell ammonium sites (146/200) in this case was lower than those of other cases (*e.g.* **3a** & **4a** : 165/200).

Shuttling Behavior. The energy barriers of shuttling and spinning processes in interlocked systems have been determined by the standard coalescence method in many cases.[7] However, this method has disadvantages that the determination of coalescence temperature is inherently subjective and often becomes difficult because of poor shimming *etc*. On the other hand, the dynamic spin polarization transfer by selective inverse recovery (SPT-SIR) technique[8] has none of these disadvantages mentioned above and has emerged as a new tool for determination of the energy barriers of shuttling processes. The shuttling behavior of the [2]rotaxanes (**3a-d**) was investigated by the SPT-SIR technique. The results are summarized in Table 2.

As indicated in Table 2, the activation free energy $\Delta G^{\ddagger}_{295}$ for the shuttling of **3a** showed 15.9 ± 0.1 kcal·mol^{-1} that corresponded to the shuttling rate of 8.88 s^{-1} (entry 1). **3b** and **3c** had the same $\Delta G^{\ddagger}_{295}$ of 15.9 ± 0.1 kcal·mol^{-1} as that of **3a** (entries 2 and 3). On the other hand, $\Delta G^{\ddagger}_{295}$ of **3d** was estimated to be 17.9 ± 0.5 kcal·mol^{-1} that corresponded to the shuttling rate of 0.323 s^{-1}, which was much slower than those of **3a-c** (entry 4). Thus, it is concluded that the shuttling is hardly affected by the substitutent on the wheel crown ether. However, the elongation of the spacer between the two ammonium centers (*i.e.* the two stations) resulted in considerable lowering in rate of the shuttling. These results clearly reveal that the distance between the two stations of the ammonium centers is an important factor for the control over the shuttling behavior. The fact that there is no effect by introduction of polar group on the wheel seems to coincide the assumption that the shuttling can be affected by the structural rigidity at the transition state much more than electronic effect, judging from the higher activation free energy in the case with a longer spacer presumably attributable to the higher structural flexibility of the dumbbell.

Table 2. Shuttling behavior of [2]rotaxane **3** in CD_3CN



Entry	X	Y	[2]rotaxane/$\Delta G^{\ddagger}_{295}$[a]
1	H	$(CH_2)_2$	**3a**/15.9 ± 0.1 kcal·mol^{-1}
2	$CO_2C_2H_5$	$(CH_2)_2$	**3b**/15.9 ± 0.1 kcal·mol^{-1}
3	OCH_3	$(CH_2)_2$	**3c**/15.9 ± 0.1 kcal·mol^{-1}
4	H	$(CH_2)_6$	**3d**/15.9 ± 0.1 kcal·mol^{-1}

[a]Determined by ^{1}H NMR using SPT-SIR technique.

Summary

Regardless of the substituent on the crown ether wheel, [2]- and [3]rotaxanes could be synthesized in good yields. Although the introduction of a longer spacer between the two ammonium stations to the axle component causes a decrease in ratio of the complexation to the rotaxane formation, the synthetic method utilized in the construction of interlocked systems via the thiol-disulfide interchange reaction is emphasized again as an excellent protocol.[4a-b] As for the control over shuttling behavior, distance between the two stations on the axle component was proved to exert the rate of the shuttling much more effectively than electronic effect of the substituent on the wheel in this system. This may be attributed to the flexibility change in the axle component.

Experimental Section

General. The melting points were measured on a Yanagimoto micro melting-point apparatus and were uncorrected. IR spectra were recorded on a JASCO FT-IR model 230 spectrometer. ^{1}H NMR measurements were performed on a JEOL JNM-GX-270 spectrometer in $CDCl_3$ with tetramethylsilane as an internal reference. FAB-MS measurements were performed on a Finnigan TSQ-70 instrument. For preparative HPLC, a JAICO LC-908 system with columns JAIGEL 1 (ϕ 20 mm × 600 mm) and JAIGEL 2 (ϕ 20 mm × 600 mm) was used.

4-Methoxy-dibenzo-24-crown-8 Ether (2b). To a solution of 4-formyl-dibenzo-24-crown-8-ether (447 mg, 0.938 mmol)[9] in CH_2Cl_2 (6.0 mL) was added *m*-chloroperbenzoic acid (mCPBA, 69 mg, 0.40 mmol) and the mixture was stirred at ambient temperature for 43 h. The mixture was subjected to suction filtration and the filtrate was evaporated to dryness. The residue was dissolved in ethyl acetate, and the solution was washed successively with 3%Na_2SO_3, water, and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was chromatographed over SiO_2 ($CHCl_3$/ethy acetate (1/1)) to afford 4-formyloxy-dibenzo-24-crown-8-ether (DB24C8-OCHO) in 74% yield as a white solid. ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.26 (s, 1H, CHO), 6.91-6.66 (m, 7H, ArH), 4.16-4.12 (m,

8H, CH_2), 3.93-3.80 (m, 16H, CH_2).

A mixture of DB24C8-OCHO thus prepared (330 mg, 0.670 mmol), K_2CO_3 (2.23 g, 16.1 mmol) in MeOH (16 mL) was stirred under Ar atmosphere at ambient temperature for 9 h. The mixture was subjected to the ordinary suction filtration. To the mixture was added 2 M HCl aq. and the resulting mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness to afford 4-hydroxy-dibenzo-24-crown-8 ether (DB24C8-OH) in 98% yield as a white solid. ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.89 (s, 5H, ArH), 6.73 (d, J = 8.6 Hz, 1H, ArH), 6.46 (s, 1H, OH), 6.33 (d, J = 8.7 Hz, 1H, ArH), 4.15-4.06 (m, 8H, CH_2), 3.92-3.76 (m, 16H, CH_2).

To a suspension of NaH (60% oil dispersion, 32.6 mg, 0.814 mmol) in THF (3.0 mL) was added a solution of DB24C8-OH prepared above (291 mg, 0.626 mmol) in THF (9.0 mL) under Ar atmosphere, and the mixture was stirred at ambient temperature for 1 h. After addition of MeI (267 mg, 1.88 mmol), the mixture was refluxed for 3 h and then allowed to cool to 0 °C. To the mixture was added 2 M HCl aq. and the resulting mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was chromatographed over SiO_2 to afford 4-methoxy-dibenzo-24-crown-8 ether (**2c**) in 86% yield as a white solid. Mp. 68-71 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.88-6.79 (m, 5H, ArH), 6.48 (d, J = 3.0 Hz, 1H, ArH), 6.38 (dd, J_1 = 8.9 Hz, J_2 = 3.0 Hz, 1H, ArH), 4.17-4.08 (m, 8H, CH_2), 3.93-3.83 (m, 16H, CH_2), 3.75 (s, 3H, OMe). FAB-MS (matrix: mNBA) m/z 478 [M^+].

General Procedure for the Synthesis of [2]Rotaxane (3) and [3]Rotaxane (4). To a $CD_3CN/CDCl_3$ solution (0.3 mL/0.7 mL) of **1** (0.10 mmol) and **2** (0.20 mmol) was added a catalytic amount of benzenethiol (1.0 μL, 0.010 mmol). The solution was sealed in an NMR tube (ϕ 5 mm), which was heated at 50 °C. The reaction progress was monitored by ^{1}H NMR. The mixture was evaporated to dryness. The residue was subjected to preparative HPLC to afford [2]rotaxane (**3**) and [3]rotaxane (**4**).

The spectral data of [2]rotaxane (**3a**) and [3]rotaxane (**4a**) were reported previously.[4a-b]

[2]Rotaxane (3b): ^{1}H NMR (270 MHz, CD_3CN) δ 7.6-7.2 (m, 13H, ArH), 4.65 (m, 2H, $ArCH_2N$), 4.3-3.0 (m, 32H, CH_2), 2.8-2.5 (m, 4H, CH_2), 1.32 (s, 18H, *t*-Bu), 1.31 (m, 3H, CH_3), 1.17 (s, 18H, *t*-Bu). FAB-MS (matrix: mNBA) m/z 1079 [M-2PF_6]$^+$. Elemental analysis calcd (%) for $C_{61}H_{94}F_{12}N_2O_{10}P_2S_2\cdot(H_2O)_{0.5}$: C53.15, H6.95, N2.03; found: C53.11, H7.15, N2.06.

[3]Rotaxane (4b): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 8.5 Hz, 2H, ArH), 7.46 (s, 2H, ArH), 7.25-7.17 (m, 10H, ArH, NH), 4.52-4.45 (m, 4H, CH_2), 4.26 (q, J = 7.0 Hz, 4H, CH_2), 4.20-3.32 (m, 52H, CH_2), 2.20-2.17 (m, 4H, CH_2), 1.30 (t, J = 7.0 Hz, 6H, CH_3), 1.29 (s, 36H, *t*-Bu). FAB-MS (matrix: mNBA) m/z 1600 [M-2PF_6]$^-$. Elemental analysis calcd (%) for $C_{88}H_{130}F_{12}N_2O_{20}P_2S_2\cdot(H_2O)_1$: C55.39, H6.97, N1.47; found: C55.44, H7.11, N1.48.

[2]Rotaxane (3c): ^{1}H NMR (270 MHz, CD_3CN) δ 7.6-6.4 (m, 13H, ArH), 4.65 (m, 2H, $ArCH_2N$), 4.3-3.4 (m, 31H, CH_2 and OCH_3), 3.14 (m, 2H, CH_2), 2.8-2.5 (m, 4H, CH_2), 1.32 (s, 18H, *t*-Bu), 1.19 (s, 18H, *t*-Bu). FAB-MS (matrix: mNBA) m/z 1036 [M-2PF_6]$^+$. Elemental analysis calcd (%) for $C_{59}H_{92}F_{12}N_2O_9P_2S_2\cdot(H_2O)_1$: C52.67, H7.04, N2.08; found: C52.91, H7.13, N2.12.

[3]Rotaxane (4c): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.19 (m, 10H, ArH, NH), 6.81-6.75 (m, 10H, ArH), 6.36 (s, 2H, ArH), 6.35 (d, J = 8.5 Hz, 2H, ArH), 4.53-4.46 (m, 2H, CH_2), 4.15-3.99 (m, 8H, CH_2), 3.89-3.73 (m, 8H, CH_2), 3.6-3.48 (m, 34H, CH_2, CH_3), 2.18-2.14 (m, 4H, CH_2), 1.11 (s, 36H, *t*-Bu). FAB-MS (matrix: mNBA) m/z 1514 [M-2PF_6]$^-$. Elemental analysis calcd (%) for $C_{84}H_{126}F_{12}N_2O_{18}P_2S_2\cdot(H_2O)_1$: C55.31, H7.07, N1.54; found: C55.16, H7.17, N1.57.

[2]Rotaxane (3d): ^{1}H NMR (270 MHz, CD_3CN) δ 7.6-6.8 (m, 14H, ArH), 4.62 (m, 2H, $ArCH_2N$), 4.2-2.4 (m, 34H, CH_2), 1.7-1.0 (m, 16H, CH_2), 1.31 (s, 18H, *t*-Bu), 1.19 (s, 18H, *t*-Bu).

[3]Rotaxane (4d): ^{1}H NMR (270 MHz, CD_3CN) δ 7.6-6.8 (m, 24H, ArH), 4.62 (m, 4H, $ArCH_2N$), 4.3-3.2 (m, 56H, CH_2), 2.47 (t, J = 7.2 Hz, 4H, CH_2), 1.5-1.0 (m, 16H, CH_2), 1.19 (s, 36H, *t*-Bu). FAB-MS (matrix: mNBA) m/z 1569 [M+2H-2PF_6]$^+$.

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