

Supplementary Materials for

A polyaromatic receptor with high androgen affinity

Masahiro Yamashina, Takahiro Tsutsui, Yoshihisa Sei, Munetaka Akita, Michito Yoshizawa*

*Corresponding author. Email: yoshizawa.m.ac@m.titech.ac.jp

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Other Supplementary Material for this manuscript includes the following:

(available at advances.sciencemag.org/cgi/content/full/5/4/eaav3179/DC1)

Crystal data of **1•2a** (.cif format)

Crystal data of **1•5c** (.cif format)

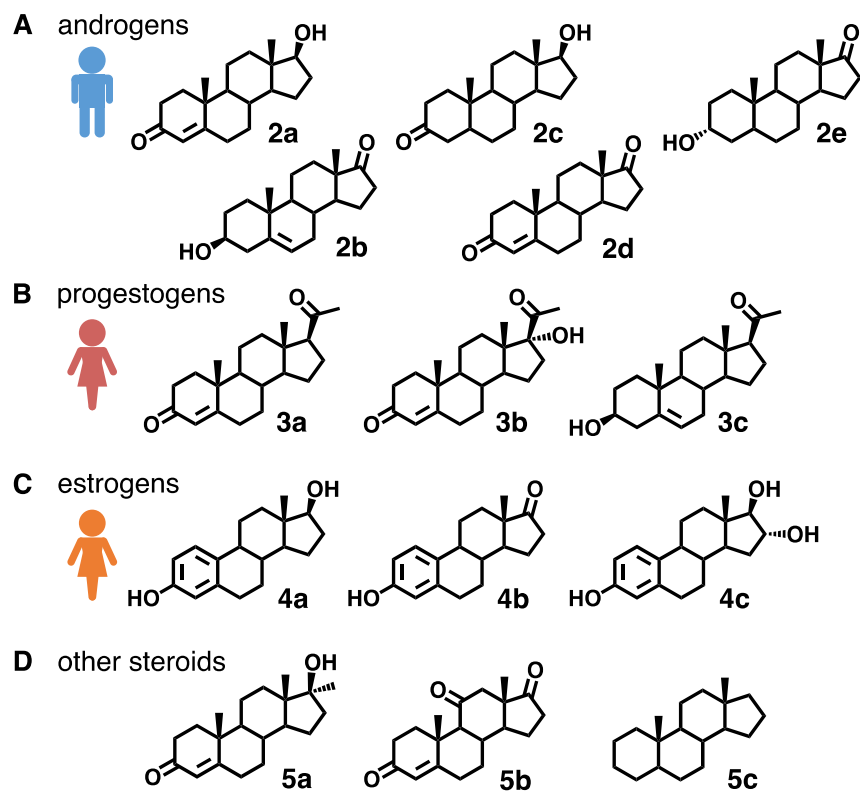


Fig. S1. Chemical structures of steroid hormones. (A) Male hormones 2a-e, (B and C) female hormones 3a-c and 4a-c, and (D) other steroids 5a-c.

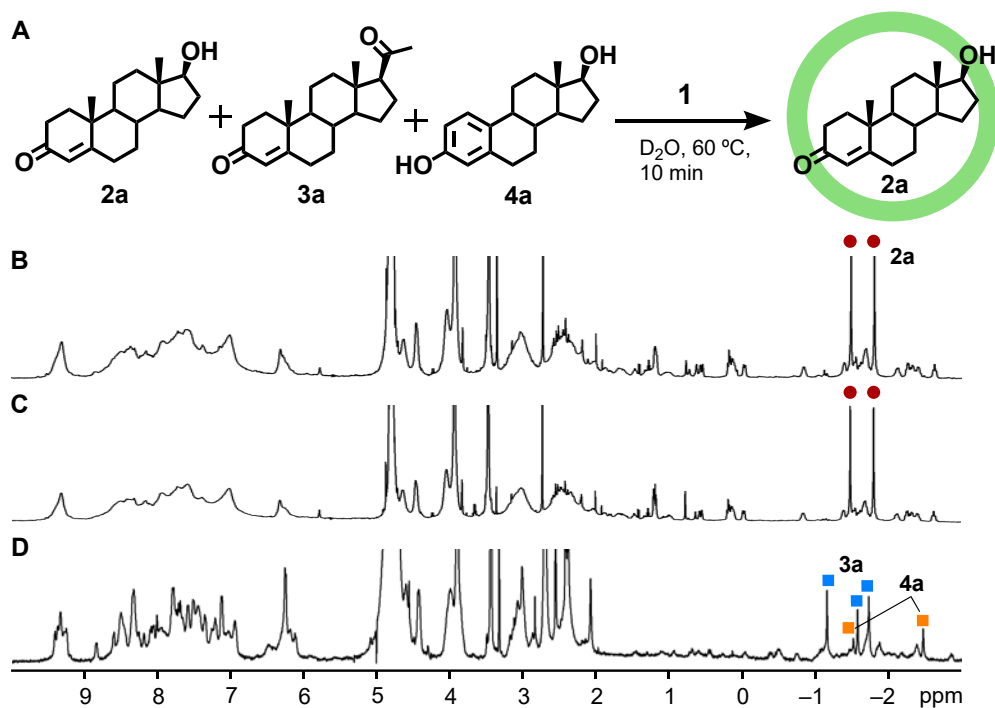


Fig. S2. Competitive binding experiment of 2a, 3a, and 4a with 1. (A) Schematic representation of the selective binding of testosterone (2a) by receptor 1 from a mixture of 2a, progesterone (3a) and β -estradiol (4a) in water. (B) 1H NMR spectrum (500 MHz, D_2O , room temperature) of products after mixing 1 with 2a, 3a, and 4a in a 1 : 1 : 1 ratio at 60 °C for 10 min. 1H NMR spectra (500 MHz, D_2O , room temperature) of products after mixing 1 with 2a, 3a, and 4a in a 1 : 100 : 100 ratio (C) at 60 °C for 10 min and (D) at room temperature for 1 min (red circle: 1•2a, blue square: 1•3a, orange square: 1•4a).

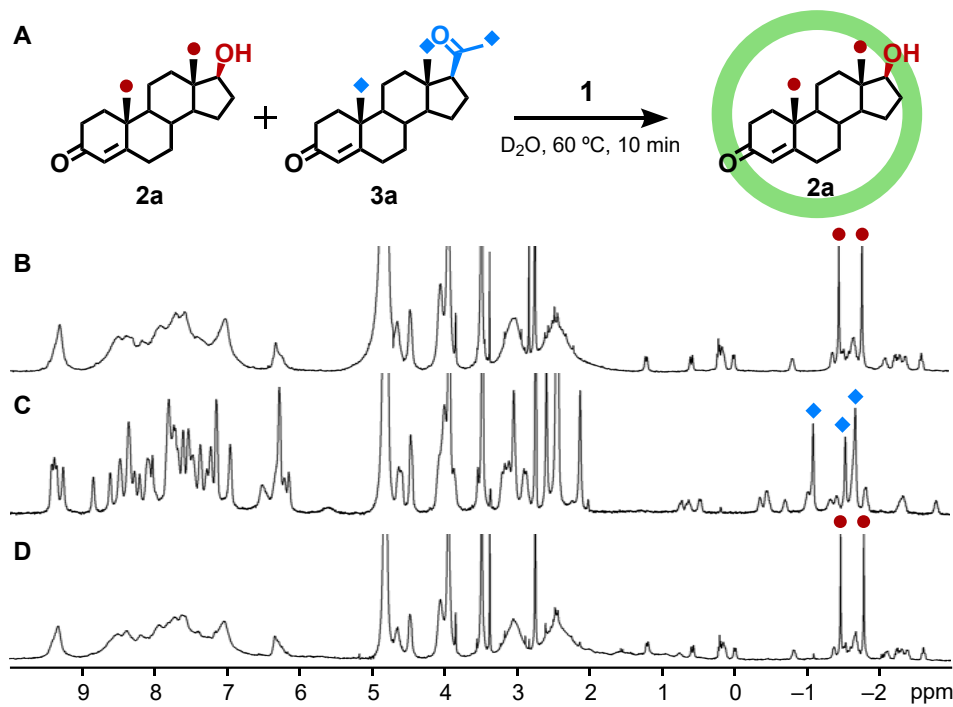


Fig. S3. Competitive binding experiment of 2a and 3a with 1. (A) Schematic representation of the competitive binding experiment of 2a and 3a with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) 1•2a, (C) 1•3a, and (D) products after mixing 2a and 3a with 1.

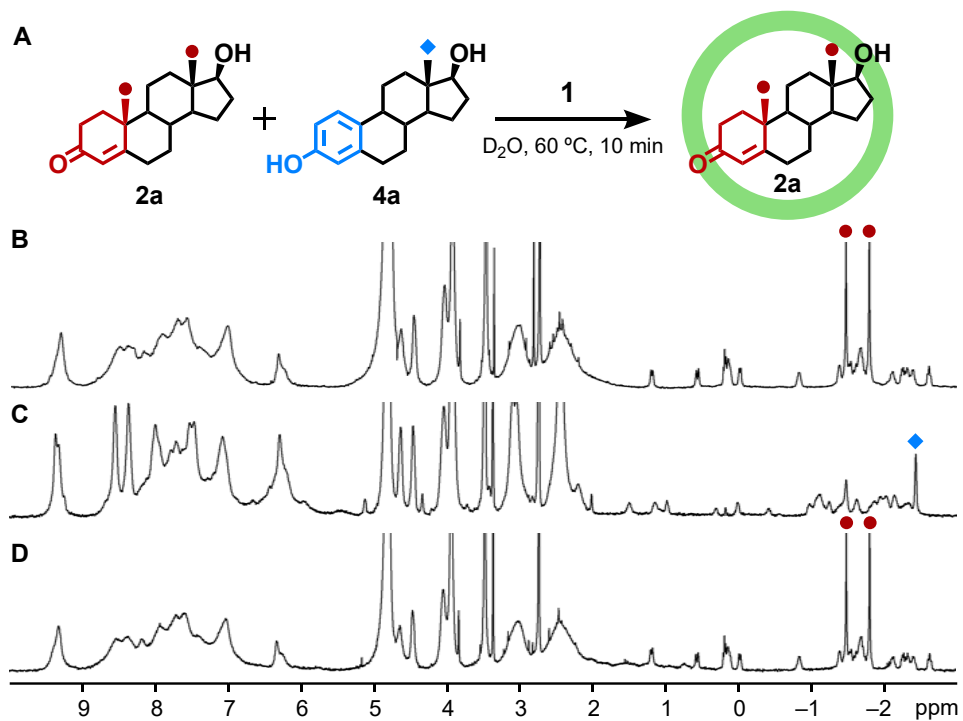
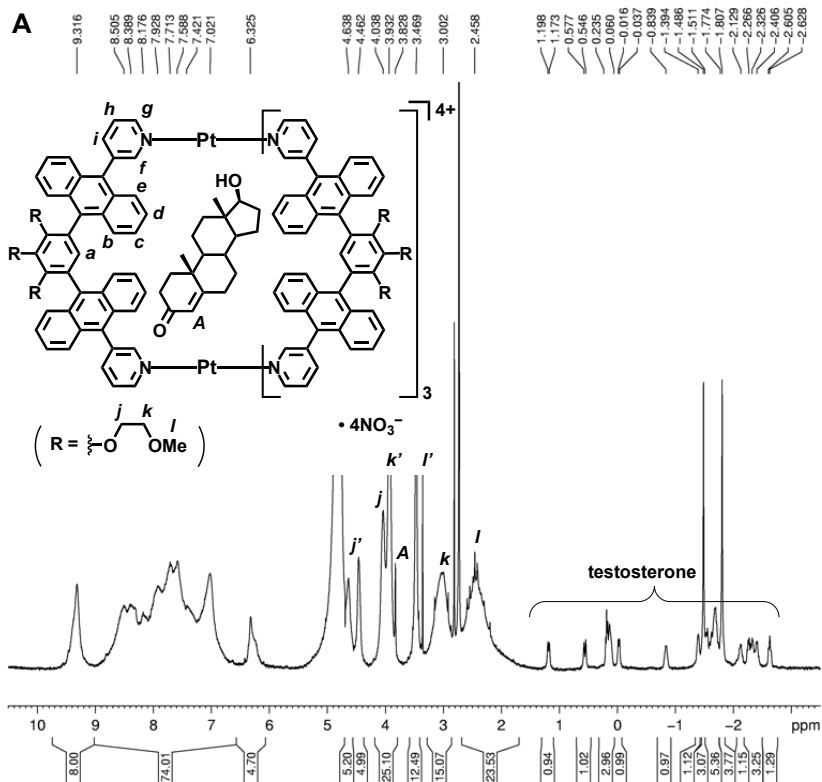
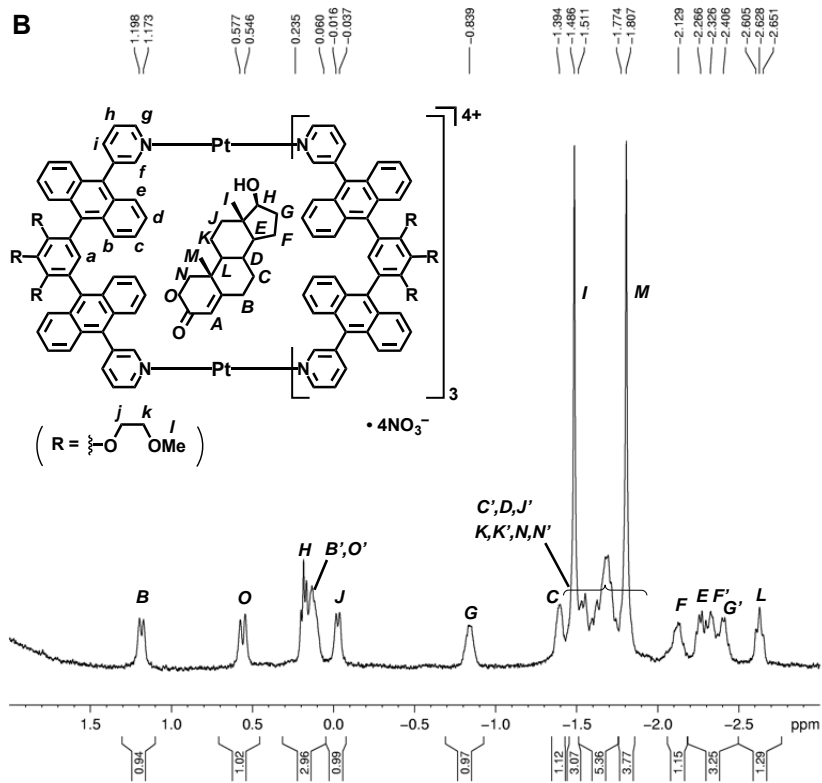


Fig. S4. Competitive binding experiment of 2a and 4a with 1. (A) Schematic representation of the competitive binding experiment of 2a and 4a with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) $1\cdot 2a$, (C) $1\cdot 4a$, and (D) products after mixing 2a and 4a with 1.



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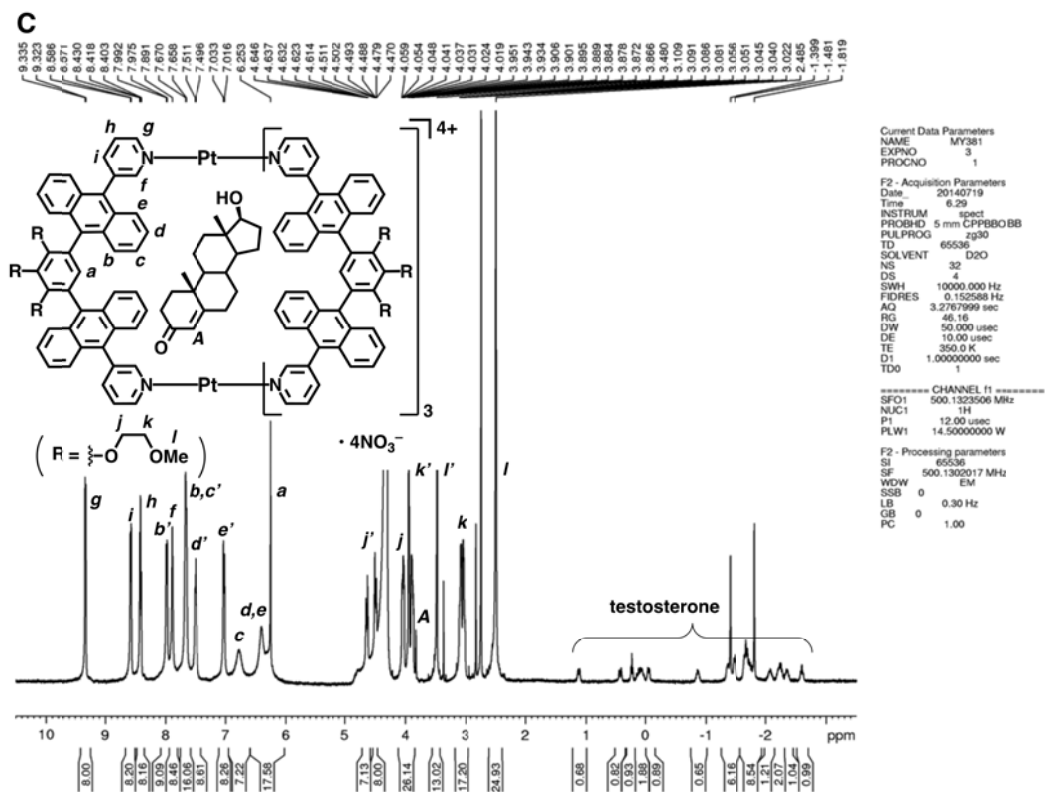
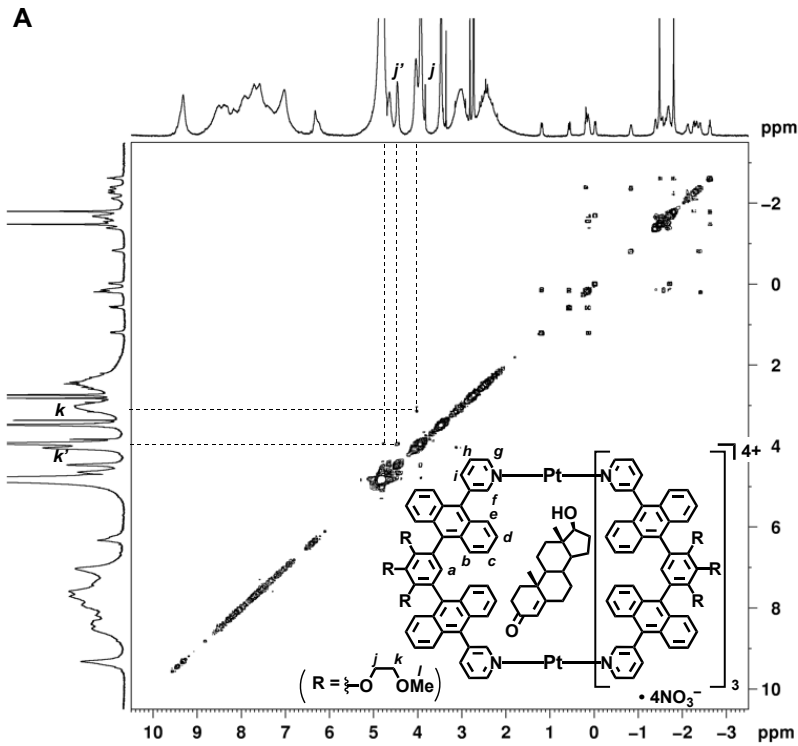


Fig. S5. NMR spectra of **1•2a**. (A) 1H NMR spectra (500 MHz, D_2O) of **1•2a** and (B) its aliphatic region at room temperature, and (C) 1H NMR spectrum (500 MHz, D_2O) of **1•2a** at 80 °C.

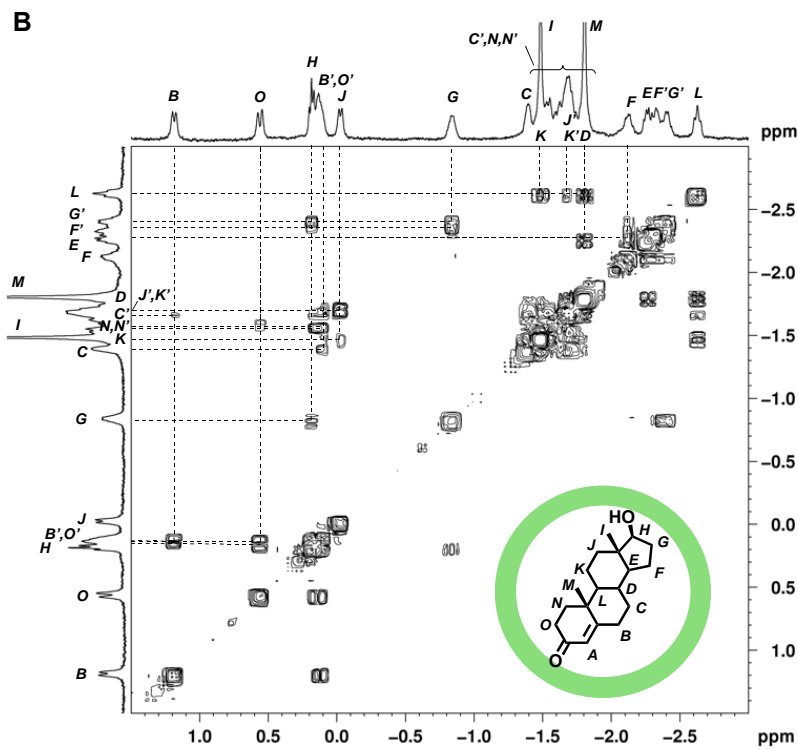


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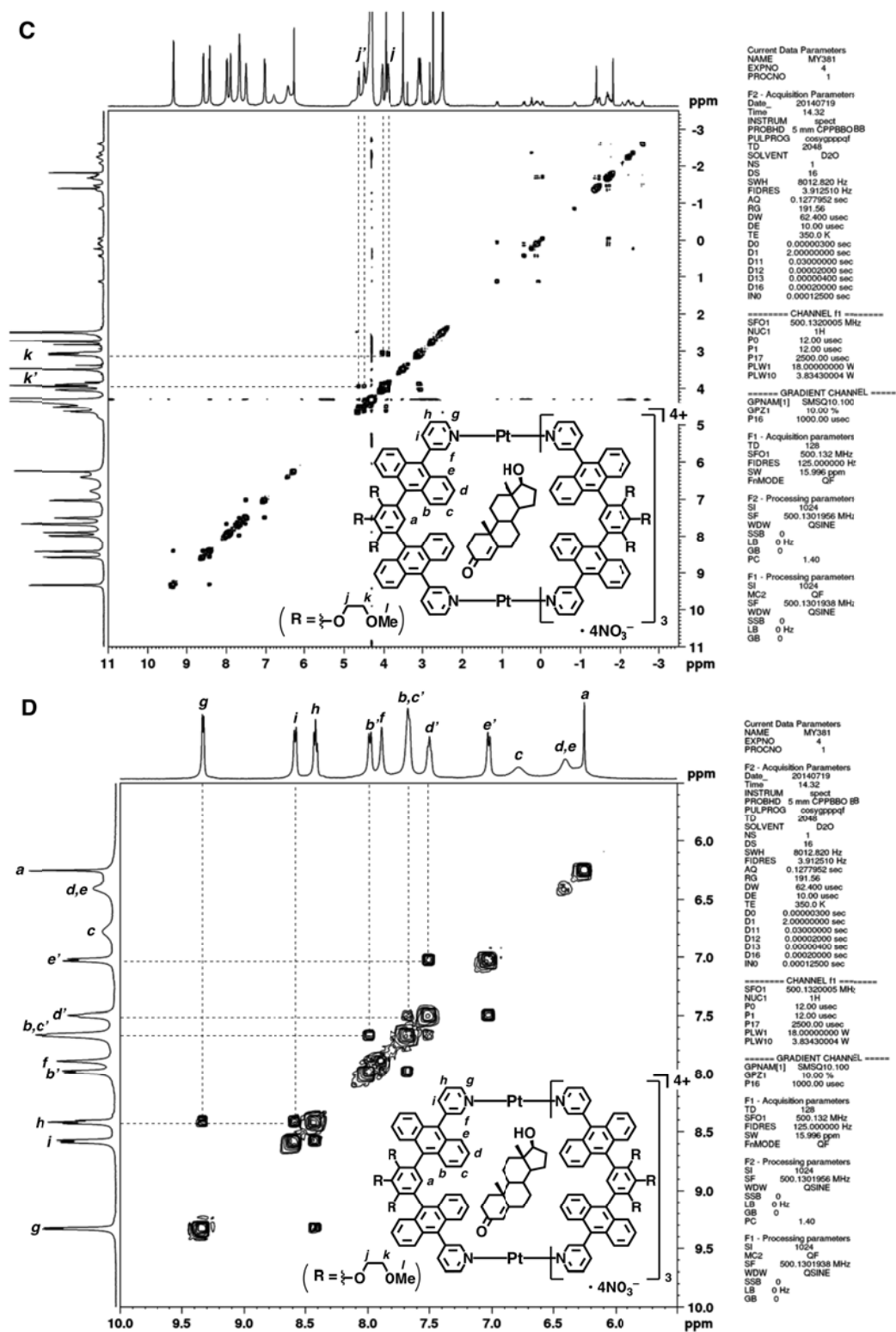


Fig. S6. Correlation spectroscopy spectra of **1•2a**. (A) ^1H - ^1H COSY spectra (500 MHz, D_2O) of **1•2a** and (B) its aliphatic region at room temperature, and (C) ^1H - ^1H COSY spectra (500 MHz, D_2O) of **1•2a** and (D) its aromatic region at 80 °C.

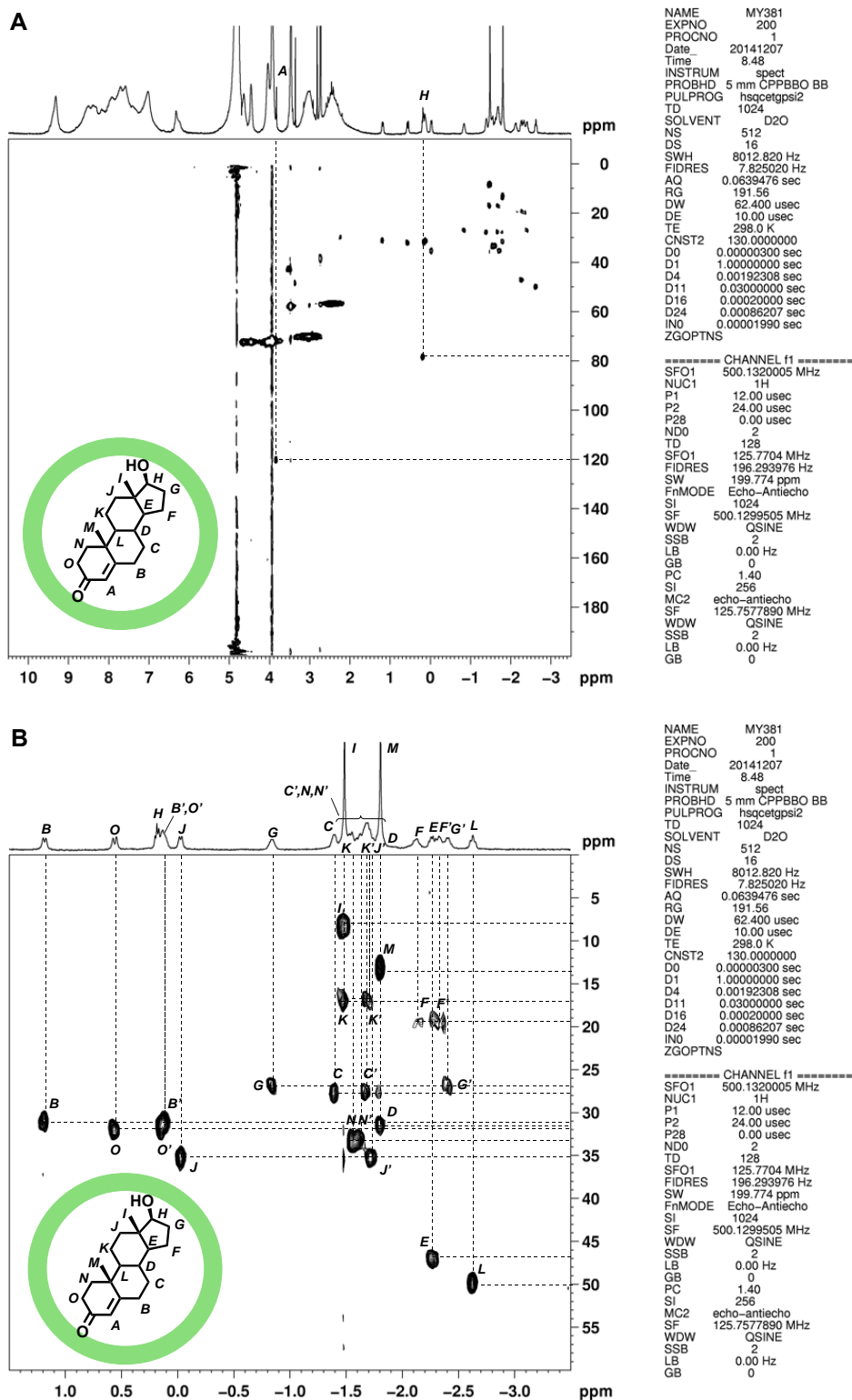


Fig. S7. Heteronuclear single quantum coherence spectra of 1•2a. (A) HSQC spectra (500 MHz, D₂O, room temperature) of 1•2a and (B) its aliphatic region.

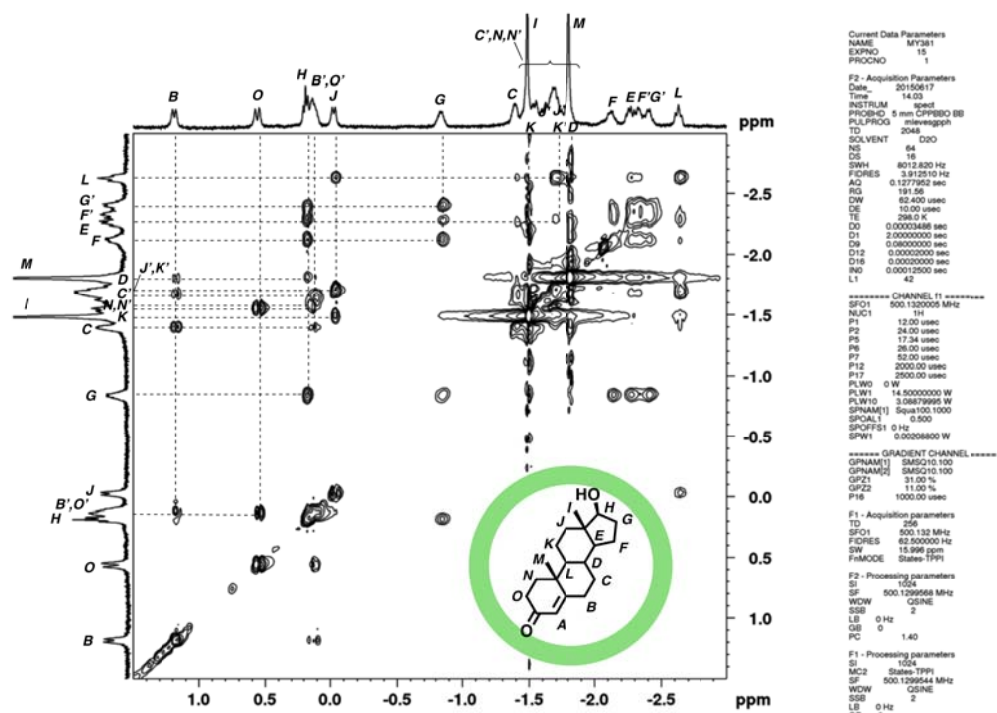


Fig. S8. Homonuclear Hartmann-Hahn spectrum of **1•2a**. HOHAHA spectrum (500 MHz, D₂O, room temperature) of **1•2a**.

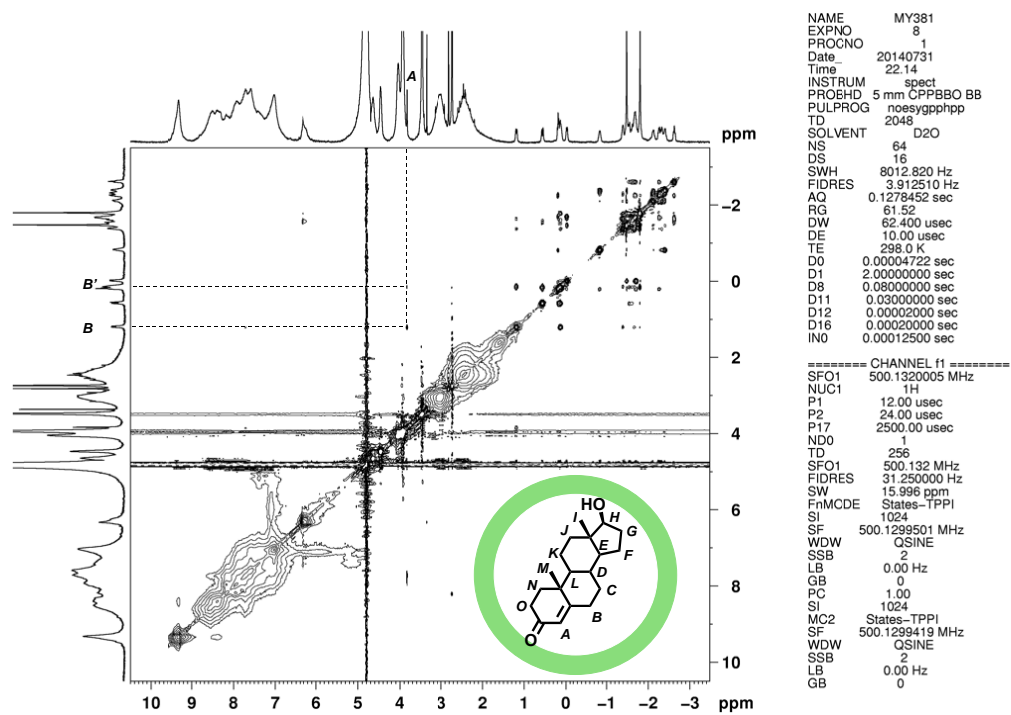


Fig. S9. Nuclear Overhauser effect spectroscopy spectrum of **1•2a**. NOESY spectrum (500 MHz, D₂O, room temperature) of **1•2a**.

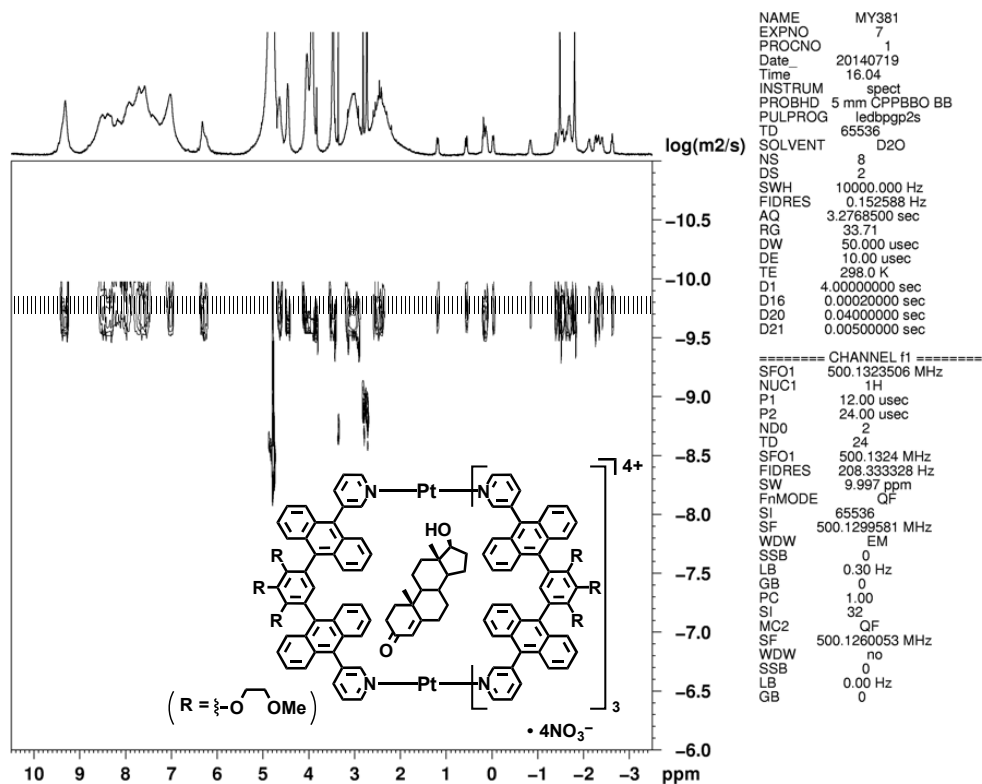


Fig. S10. Diffusion-ordered spectroscopy spectrum of **1•2a**. ¹H DOSY spectrum (500 MHz, D₂O, room temperature) of **1•2a**.

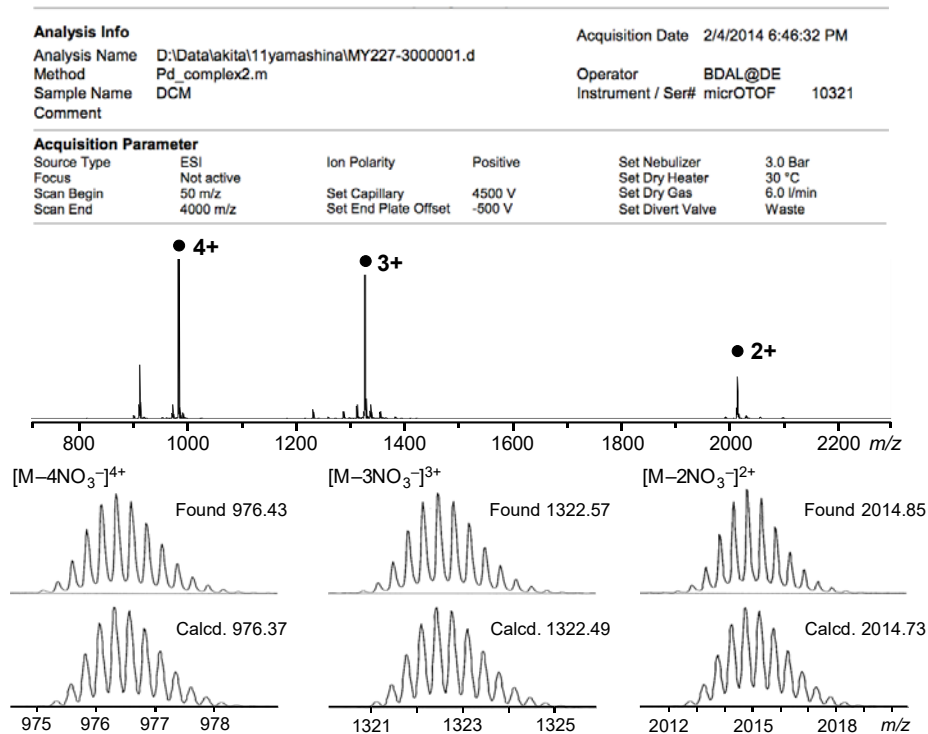


Fig. S11. MS spectrum of **1•2a**. ESI-TOF MS spectrum (H₂O, room temperature) of **1•2a**.

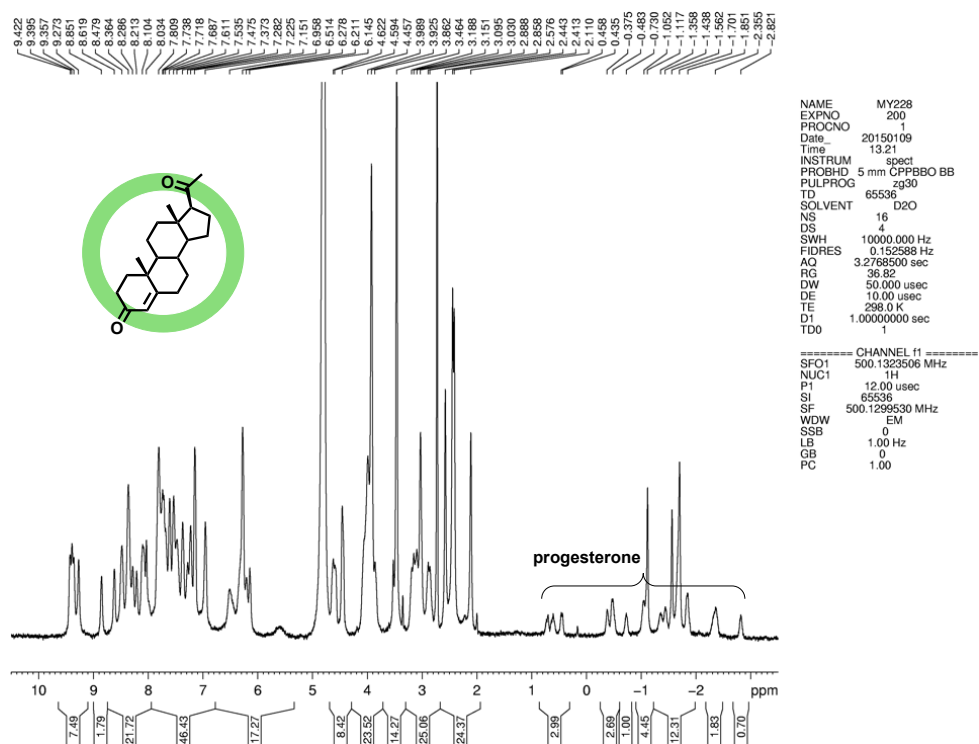


Fig. S12. NMR spectrum of **1•3a**. ¹H NMR spectrum (500 MHz, D₂O, room temperature) of **1•3a**.

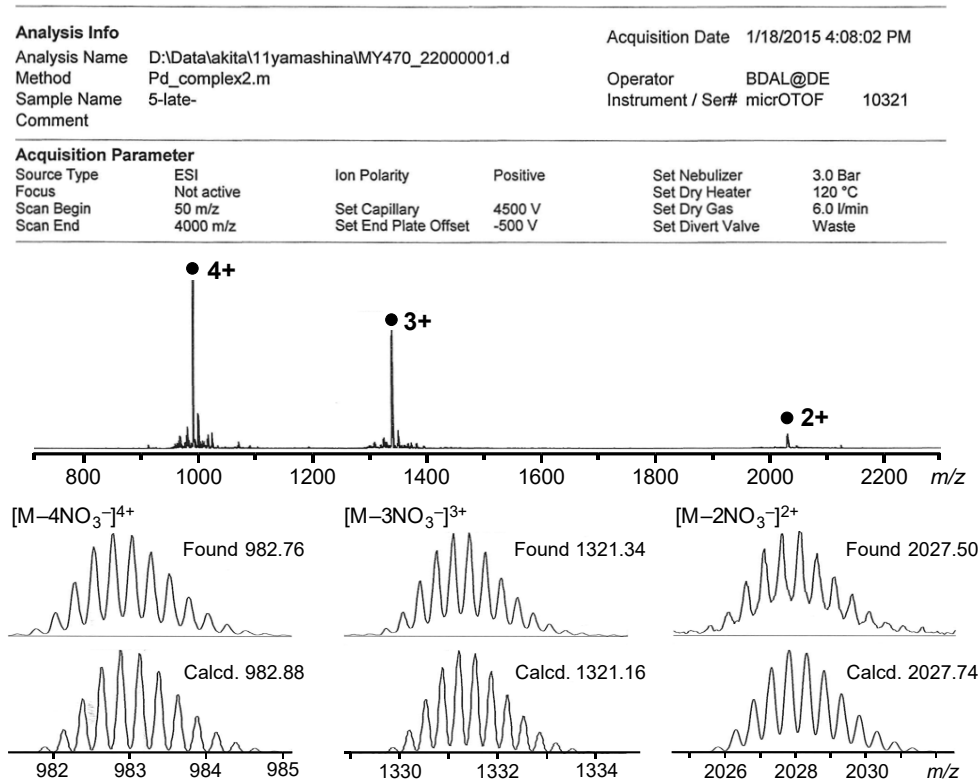


Fig. S13. MS spectrum of **1•3a**. ESI-TOF MS spectrum (H₂O, room temperature) of **1•3a**.

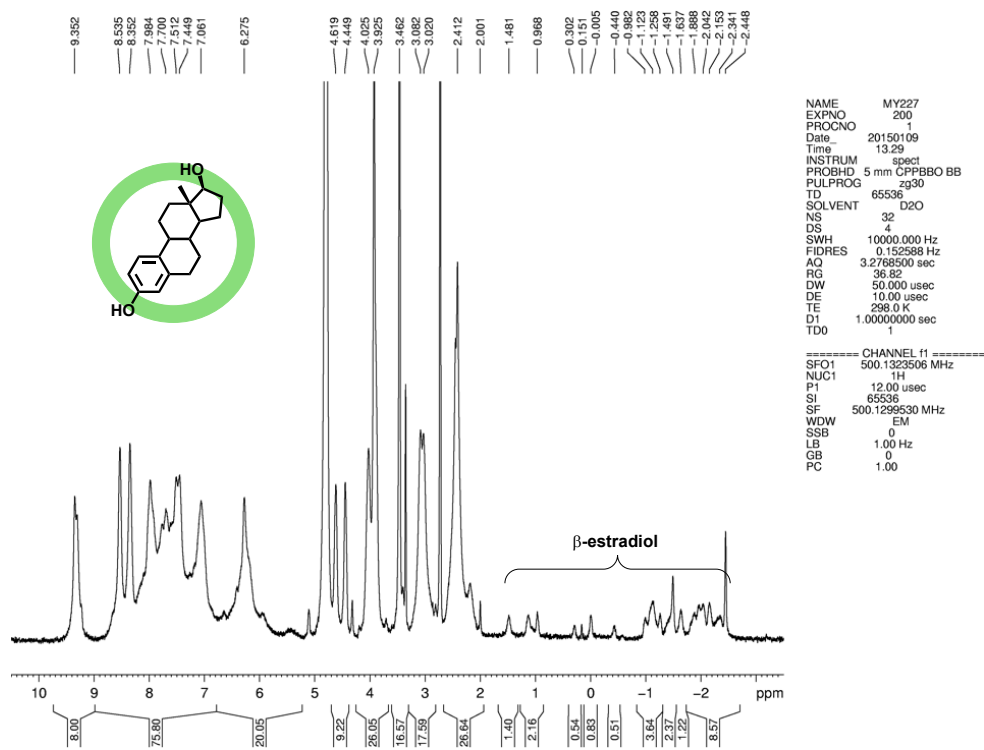


Fig. S14. NMR spectrum of **1•4a**. ¹H NMR spectrum (500 MHz, D₂O, room temperature) of **1•4a**.

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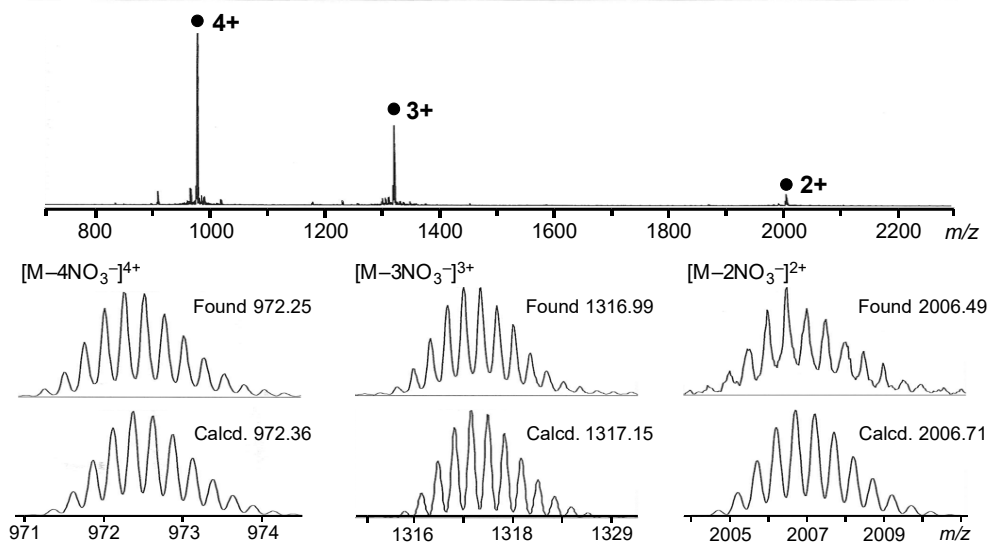


Fig. S15. MS spectrum of **1•4a**. ESI-TOF MS spectrum (H₂O, room temperature) of **1•4a**.

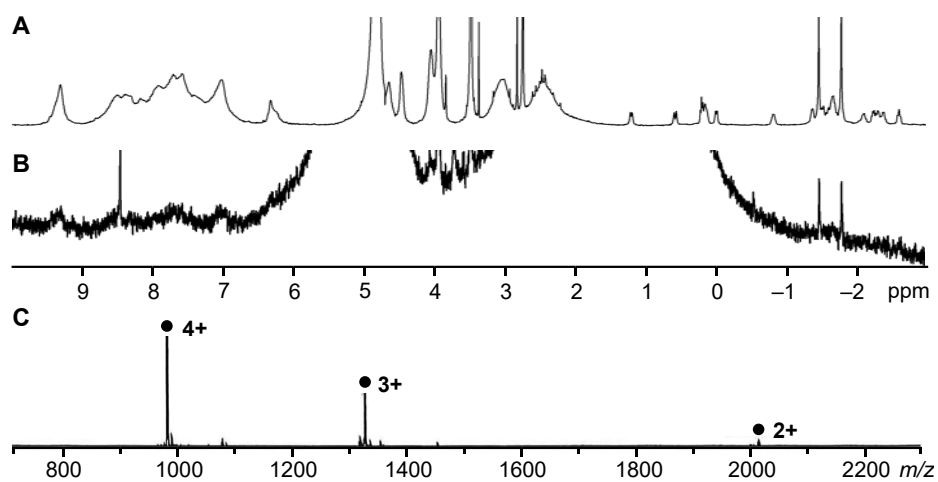


Fig. S16. Concentration-dependent binding experiment. ¹H NMR spectra (500 MHz, D₂O, room temperature) of **1•2a** at (A) 0.8 mM and (B) 5 μM. (C) ESI-TOF MS spectrum (H₂O, room temperature) of **1•2a** at 5 μM.

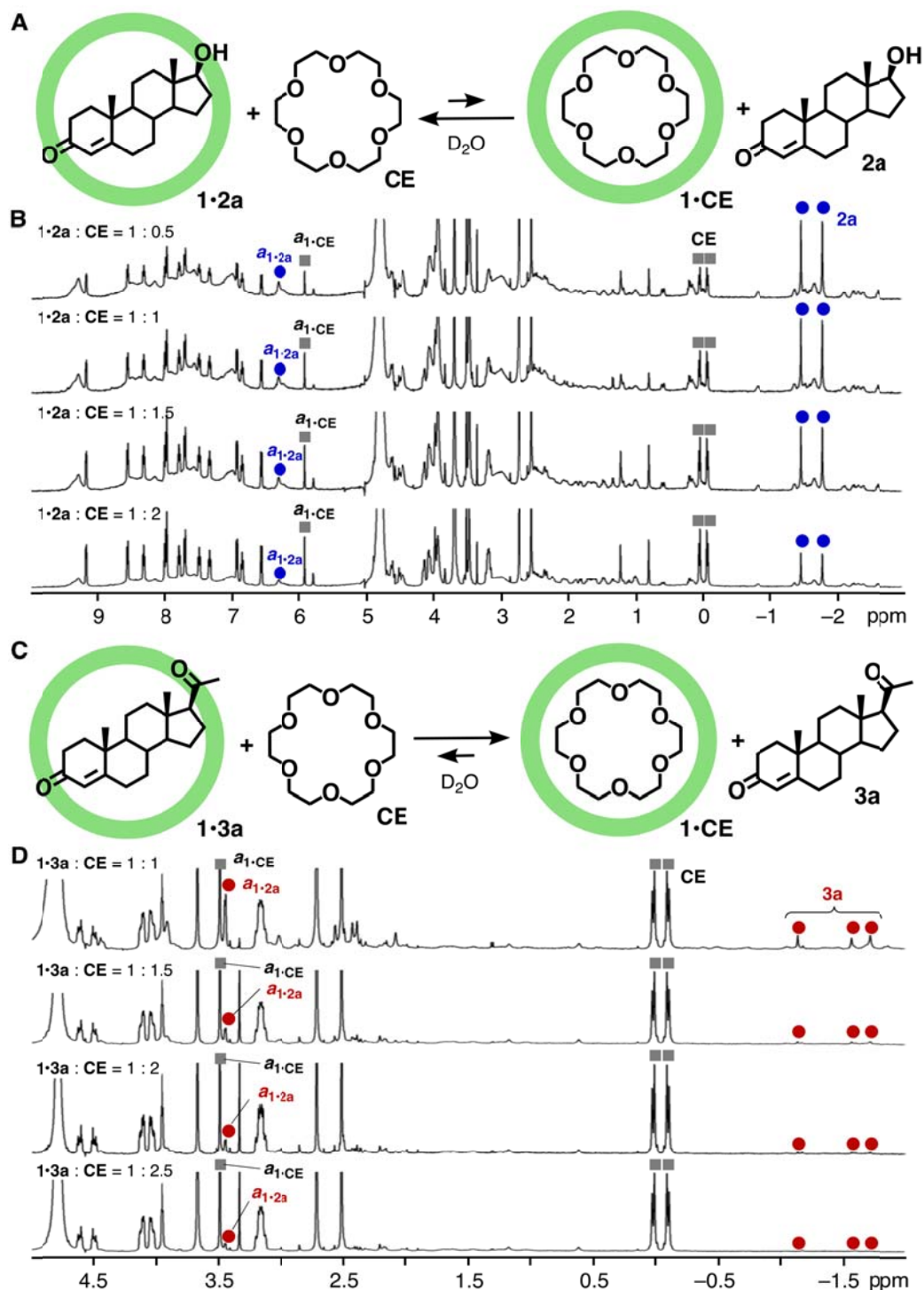


Fig. S17. Competitive binding experiment of 2a/3a and CE with 1. (A) Schematic representation of the competitive binding experiment of 2a and 18-crown-6 (CE) with 1 in water. (B) ^1H NMR spectra (500 MHz, D_2O , room temperature) of the products after mixing $1\cdot 2a$ with CE in various ratios at 60 °C for 3 h. (C) Schematic representation of the competitive binding experiment of 3a and CE with 1 in water. (D) ^1H NMR spectra (500 MHz, D_2O , room temperature) of the products after mixing $1\cdot 3a$ with CE in various ratios at 60 °C for 3 h.

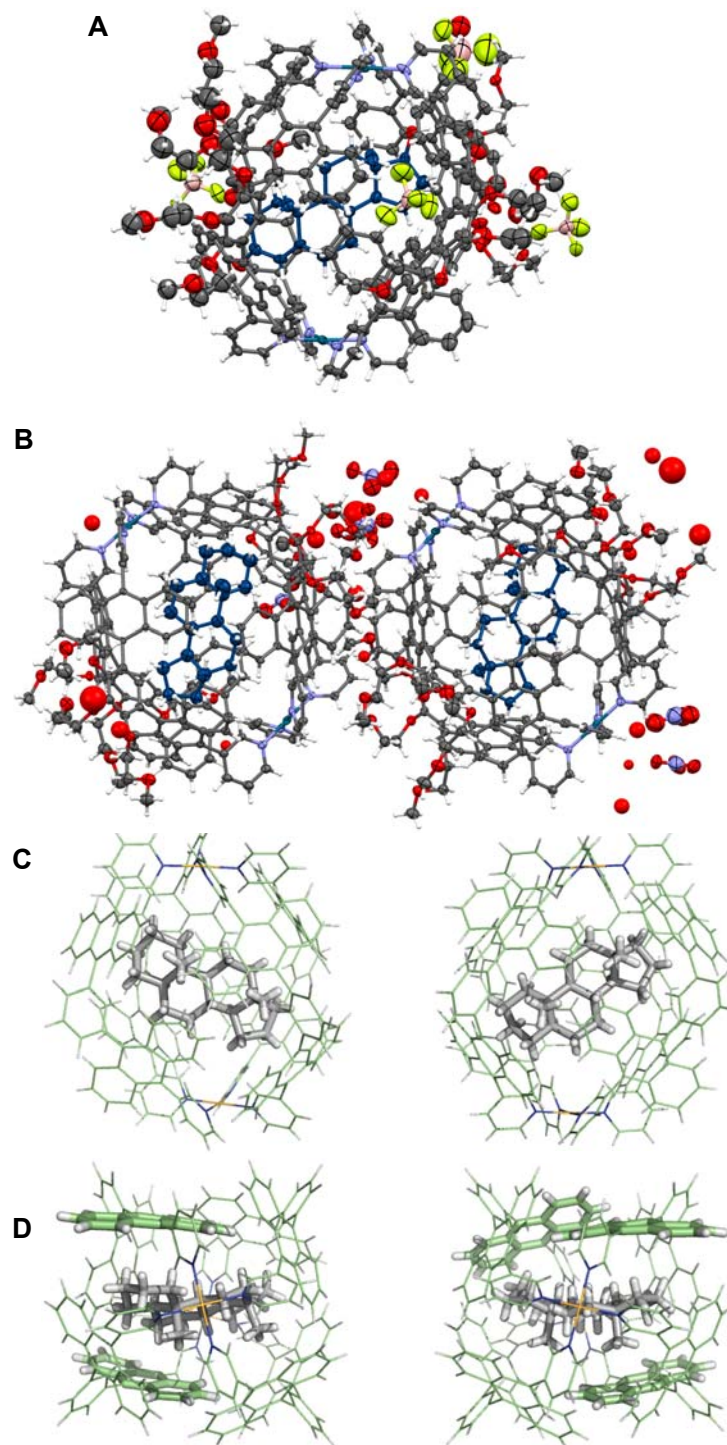


Fig. S18. Crystal structures of $1' \cdot 2a$ and $1'' \cdot 5c$. ORTEP drawing of **(A)** $1' \cdot 2a$ ($1'$ is an analogue of **1**, in which the Pt(II) and NO_3^- ions are replaced by Pd(II) and BF_4^- ions, respectively) and **(B)** $1'' \cdot 5c$ ($1''$ is an analogue of **1**, in which the Pt(II) ions are replaced by Pd(II) ions). Two crystallographically independent structures of $1'' \cdot 5c$ (R = -H): **(C)** side and **(D)** top views.

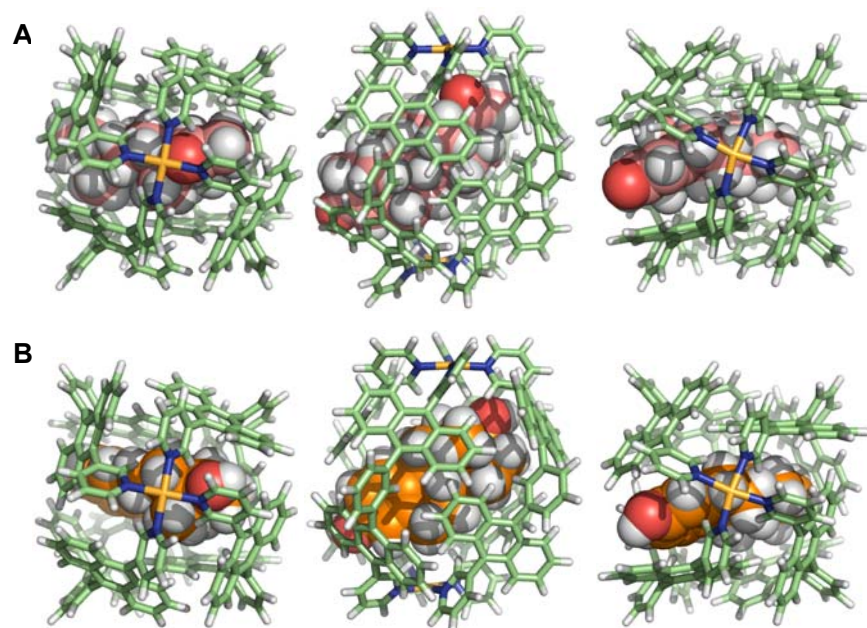


Fig. S19. Optimized structures of 1•3a and 1•4a. Optimized structures of (A) 1•3a and (B) 1•4a (top, side, and bottom views; R = -H).

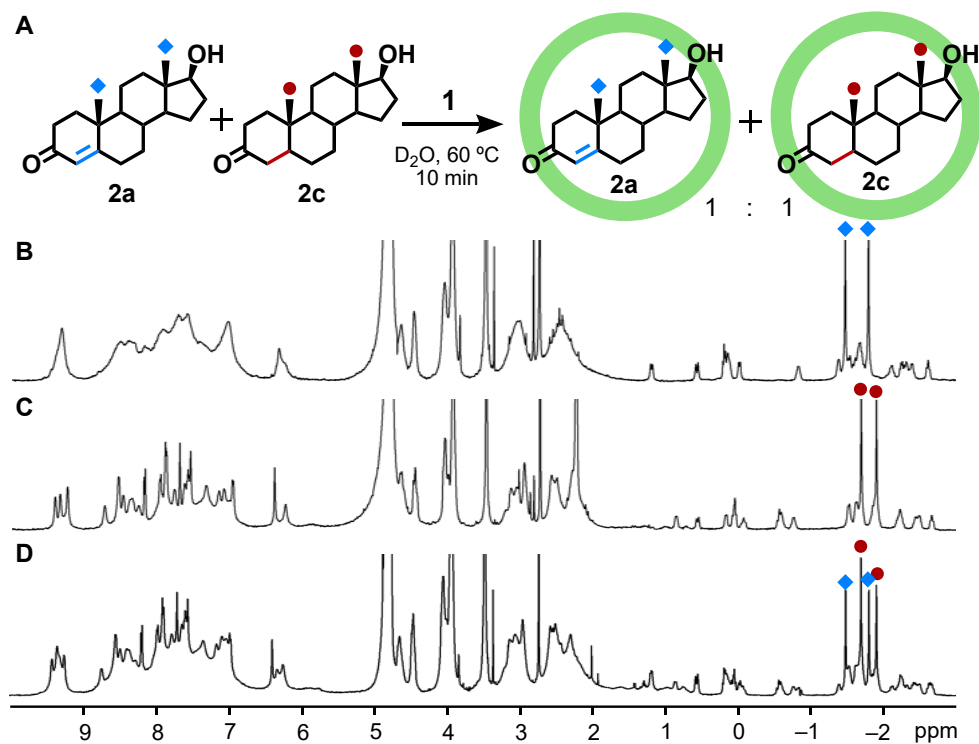


Fig. S20. Competitive binding experiment of 2a and 2c with 1. (A) Schematic representation of the competitive binding experiment of 2a and 2c with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) 1•2a, (C) 1•2c, and (D) products after mixing 2a and 2c with 1.

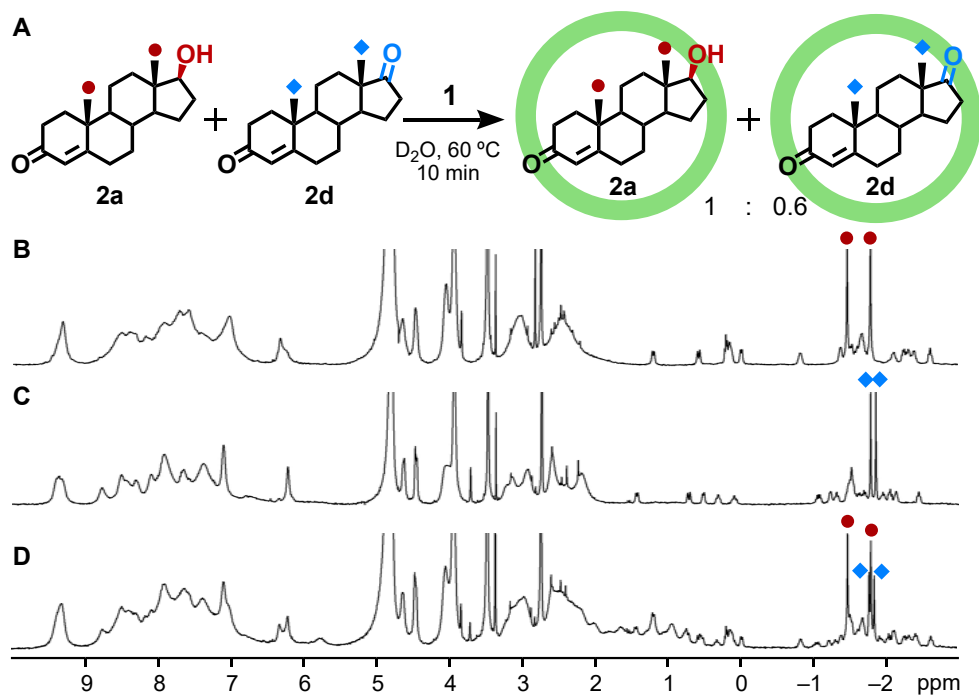


Fig. S21. Competitive binding experiment of 2a and 2d with 1. (A) Schematic representation of the competitive binding experiment of 2a and 2d with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) 1•2a, (C) 1•2d, and (D) products after mixing 2a and 2d with 1.

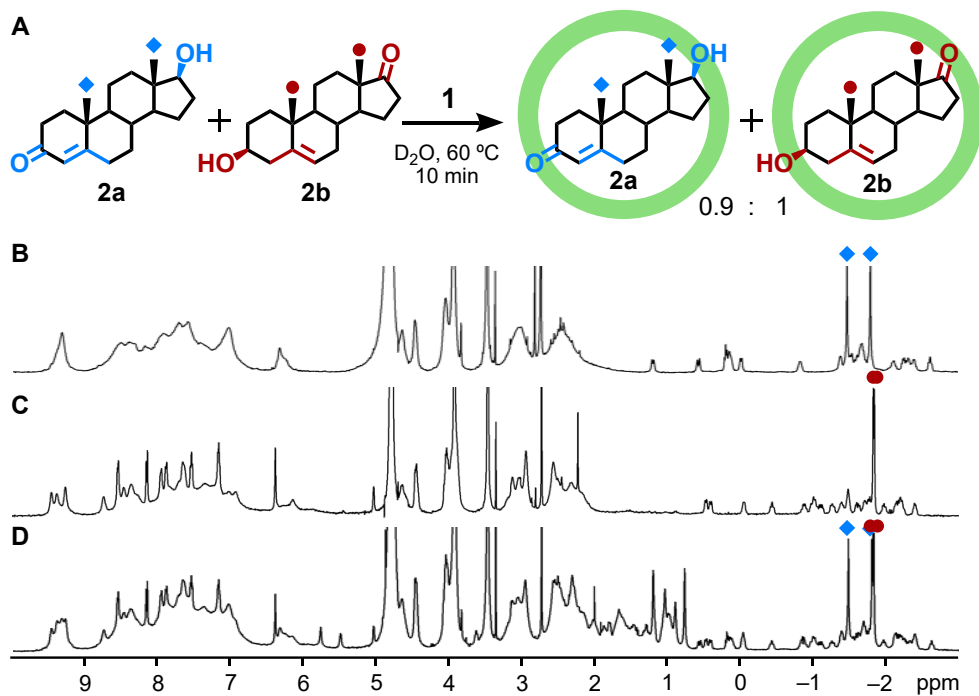


Fig. S22. Competitive binding experiment of 2a and 2b with 1. (A) Schematic representation of the competitive binding experiment of 2a and 2b with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) 1•2a, (C) 1•2b, and (D) products after mixing 2a and 2b with 1.

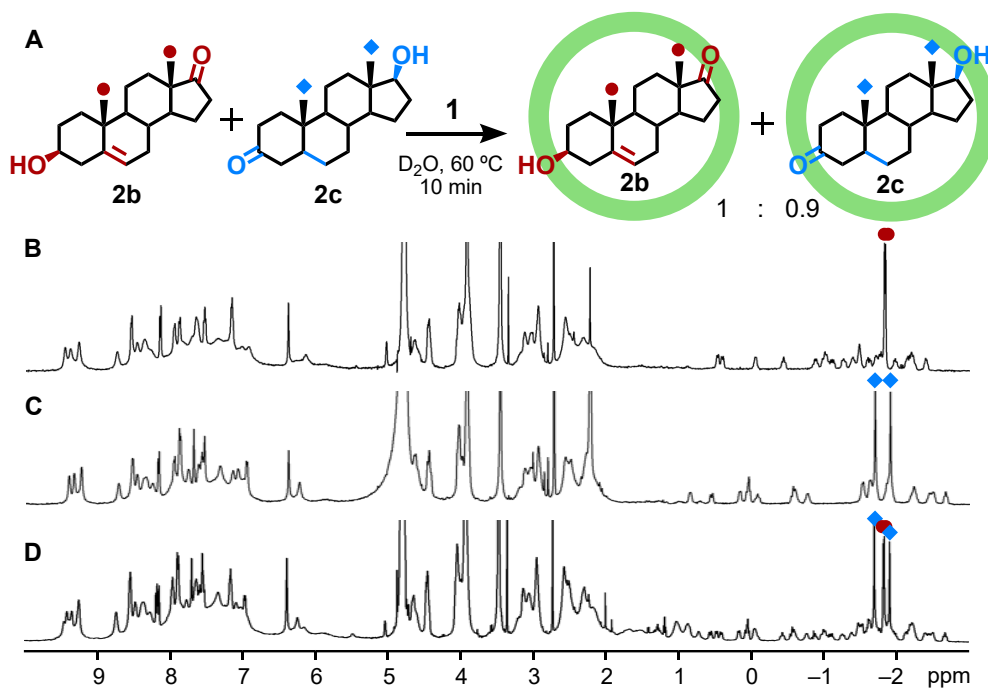


Fig. S23. Competitive binding experiment of 2b and 2c with 1. (A) Schematic representation of the competitive binding experiment of **2b** and **2c** with **1** in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) **1•2b**, (C) **1•2c**, and (D) products after mixing **2b** and **2c** with **1**.

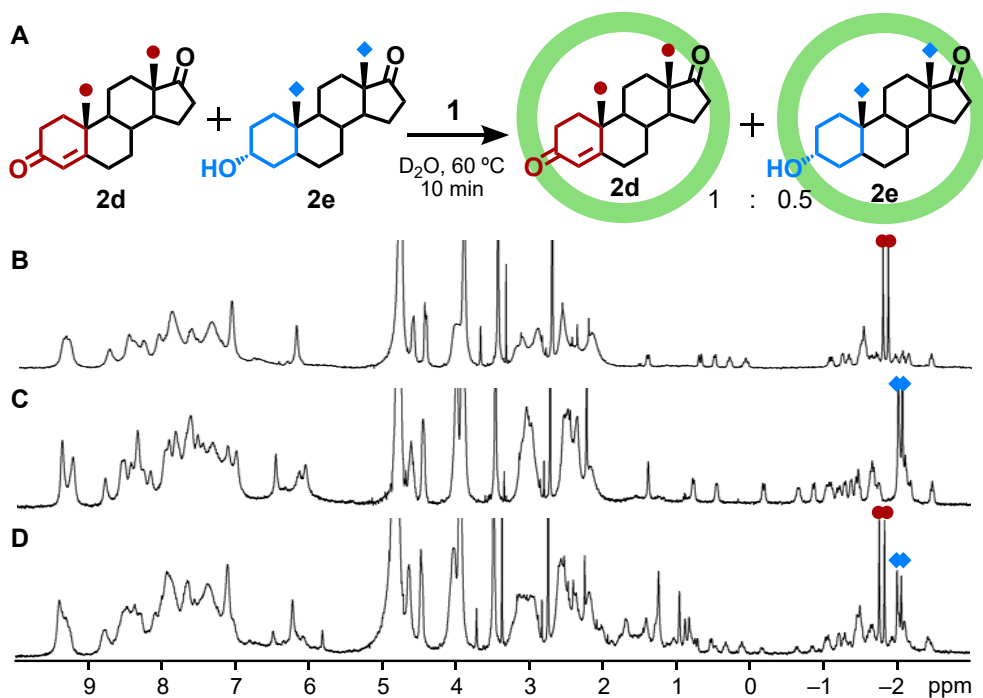


Fig. S24. Competitive binding experiment of 2d and 2e with 1. (A) Schematic representation of the competitive binding experiment of **2d** and **2e** with **1** in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) **1•2d**, (C) **1•2e**, and (D) products after mixing **2d** and **2e** with **1**.

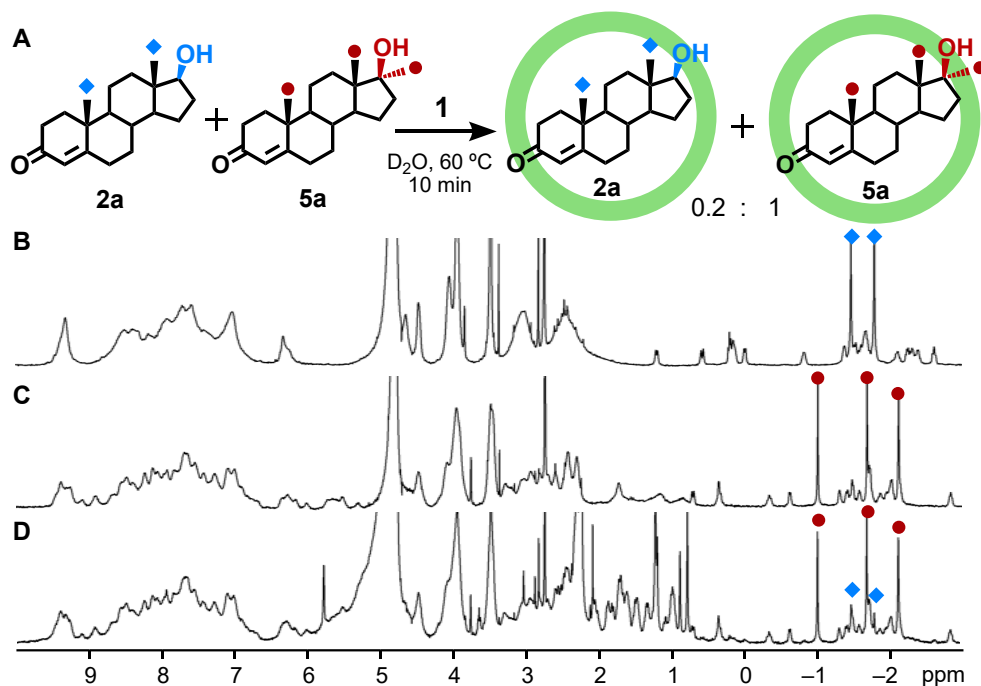


Fig. S25. Competitive binding experiment of 2a and 5a with 1. (A) Schematic representation of the competitive binding experiment of 2a and 5a with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) 1•2a, (C) 1•5a, and (D) products after mixing 2a and 5a with 1.

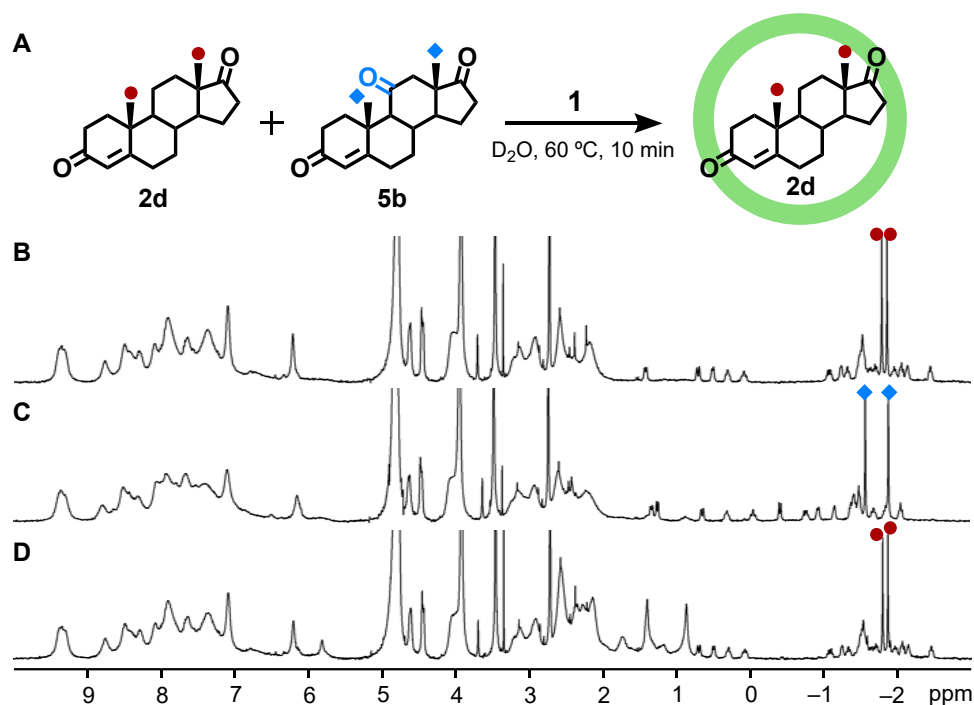


Fig. S26. Competitive binding experiment of 2d and 5b with 1. (A) Schematic representation of the competitive binding experiment of 2d and 5b with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) 1•2d, (C) 1•5b, and (D) products after mixing 2d and 5b with 1.

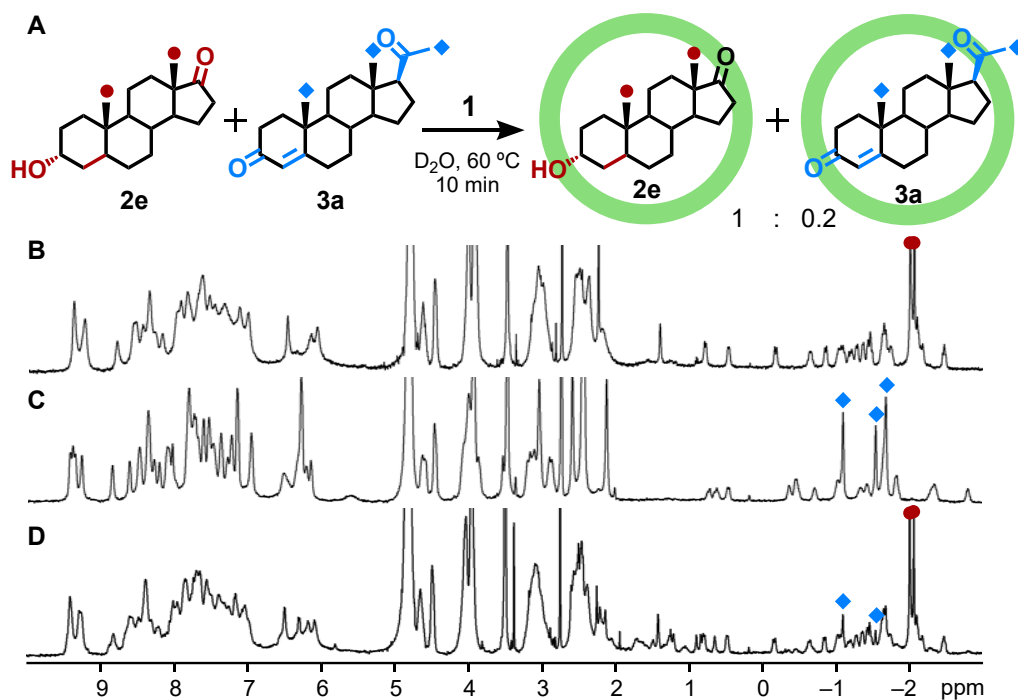


Fig. S27. Competitive binding experiment of 2e and 3a with 1. (A) Schematic representation of the competitive binding experiment of 2e and 3a with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) 1•2e, (C) 1•3a, and (D) products after mixing 2e and 3a with 1.

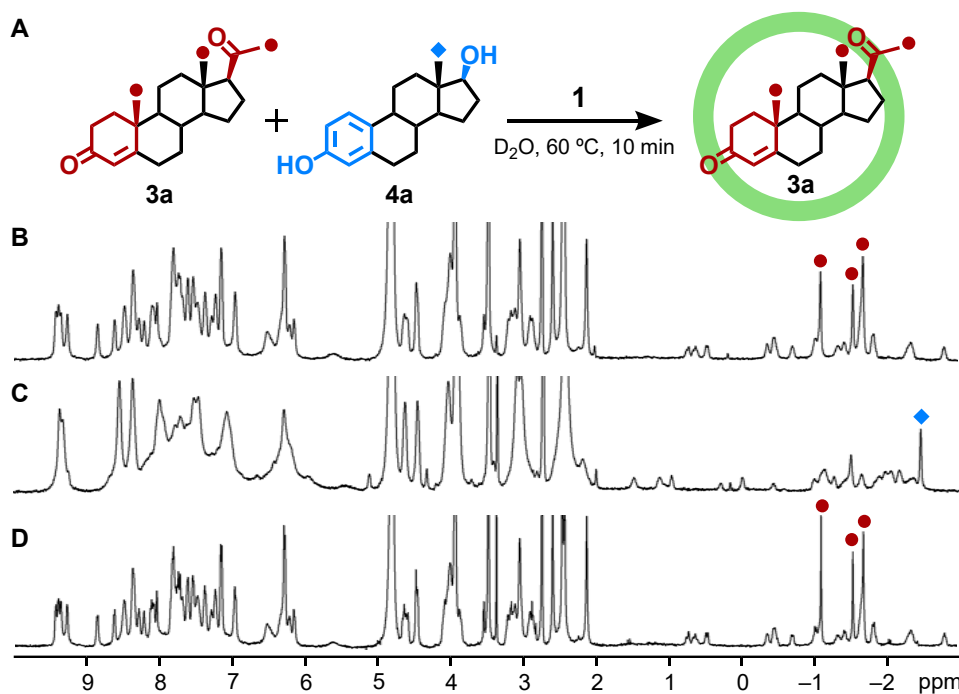


Fig. S28. Competitive binding experiment of 3a and 4a with 1. (A) Schematic representation of the competitive binding experiment of 3a and 4a with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) 1•3a, (C) 1•4a, and (D) products after mixing 3a and 4a with 1.

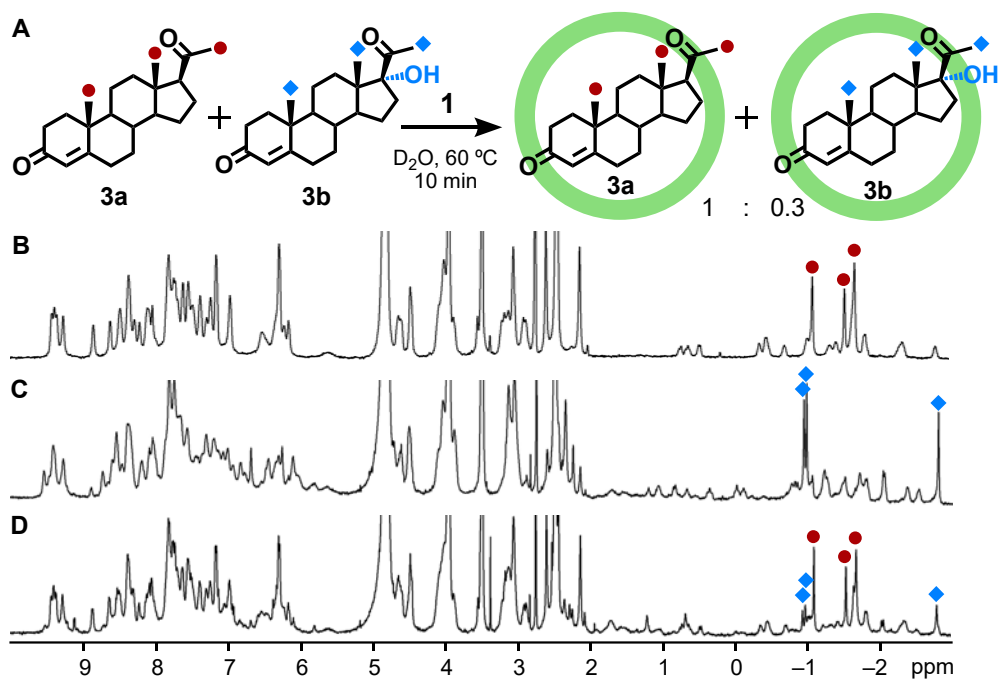


Fig. S29. Competitive binding experiment of 3a and 3b with 1. (A) Schematic representation of the competitive binding experiment of 3a and 3b with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) 1•3a, (C) 1•3b, and (D) products after mixing 3a and 3b with 1.

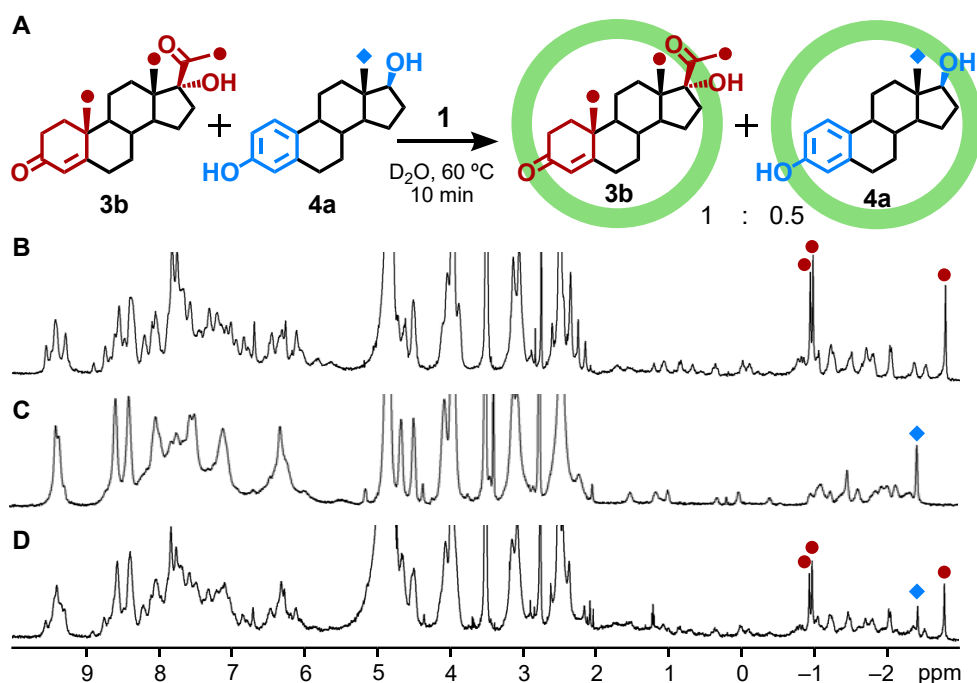


Fig. S30. Competitive binding experiment of 3b and 4a with 1. (A) Schematic representation of the competitive binding experiment of 3b and 4a with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) 1•3b, (C) 1•4a, and (D) products after mixing 3b and 4a with 1.

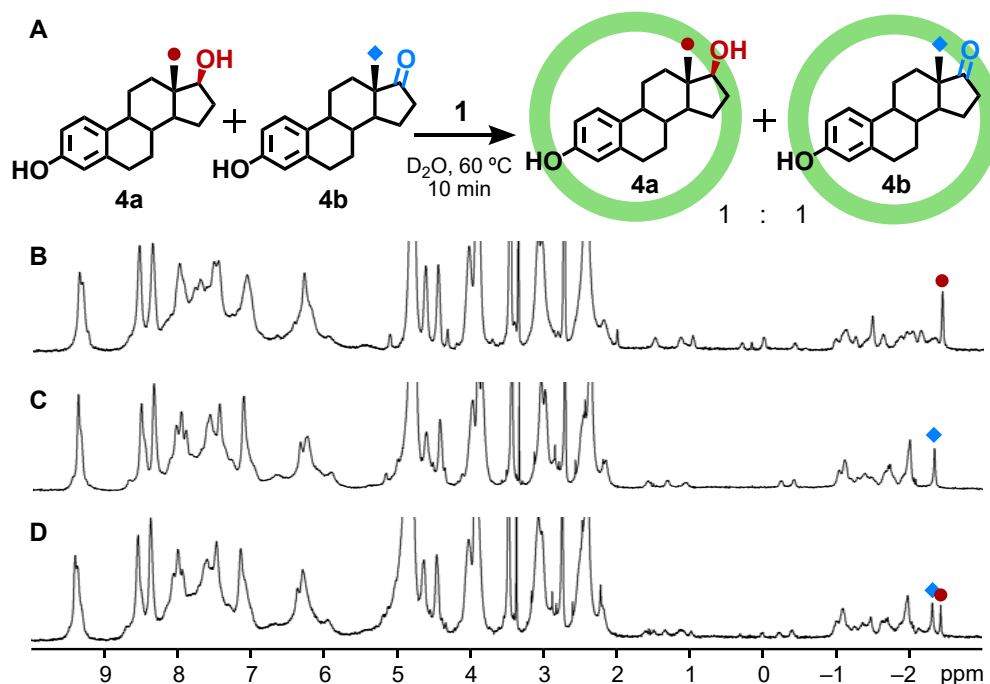


Fig. S31. Competitive binding experiment of 4a and 4b with 1. (A) Schematic representation of the competitive binding experiment of 4a and 4b with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) $1\cdot 4a$, (C) $1\cdot 4b$, and (D) products after mixing 4a and 4b with 1.

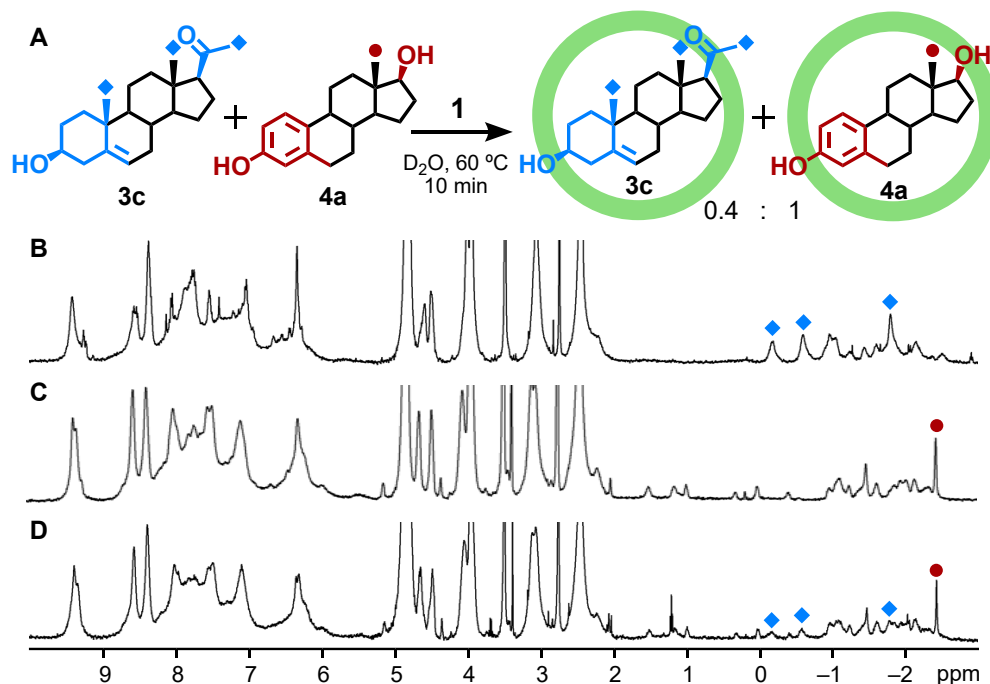


Fig. S32. Competitive binding experiment of 3c and 4a with 1. (A) Schematic representation of the competitive binding experiment of 3c and 4a with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) $1\cdot 3c$, (C) $1\cdot 4a$, and (D) products after mixing 3c and 4a with 1.

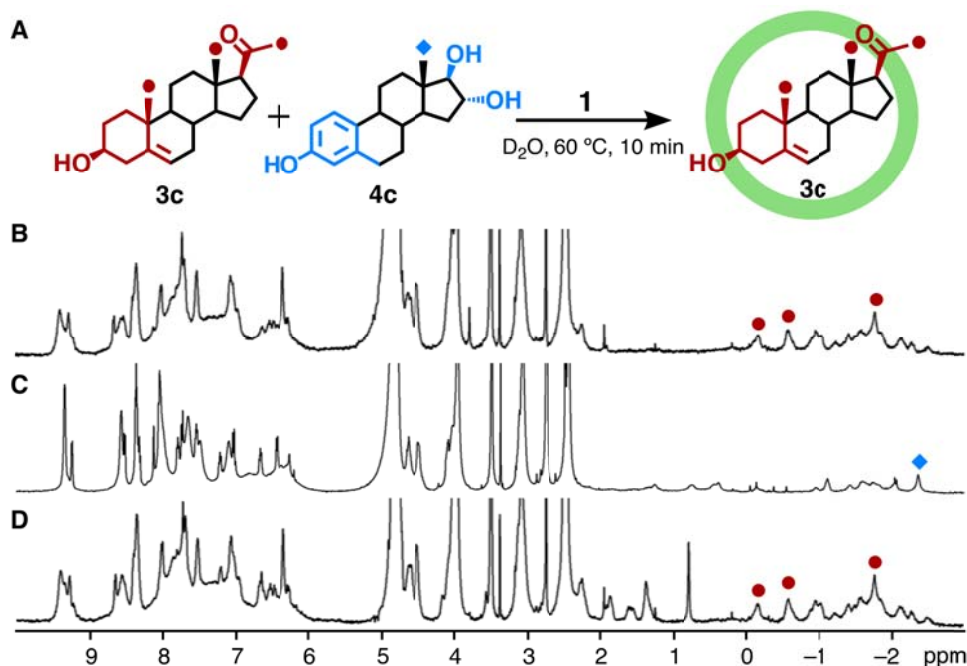


Fig. S33. Competitive binding experiment of 3c and 4c with 1. (A) Schematic representation of the competitive binding experiment of 3c and 4c with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) 1•3c, (C) 1•4c, and (D) products mixing 3c and 4c with 1.

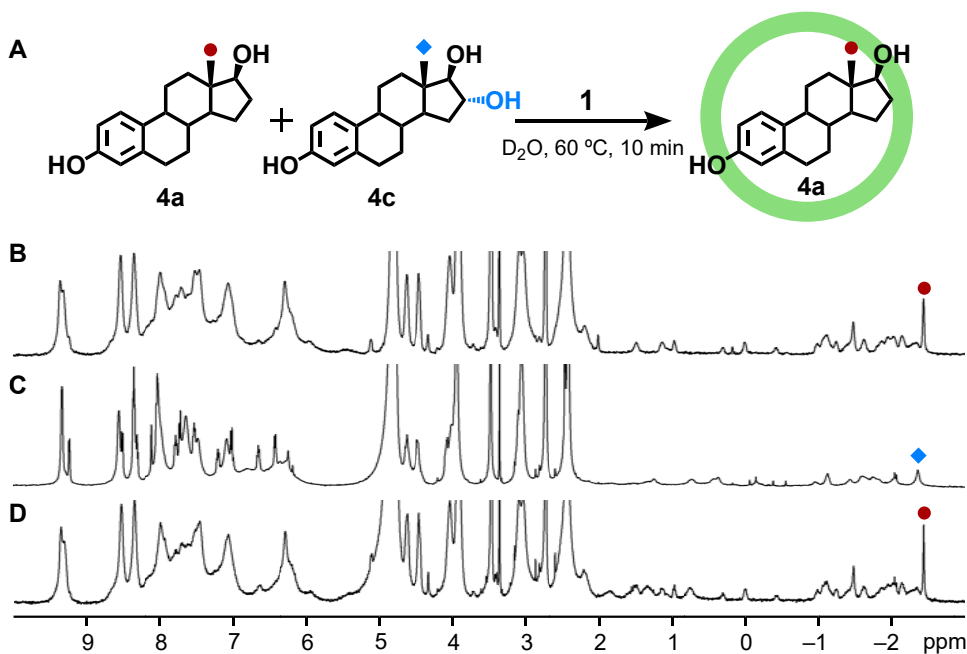


Fig. S34. Competitive binding experiment of 4a and 4c with 1. (A) Schematic representation of the competitive binding experiment of 4a and 4c with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) 1•4a, (C) 1•4c, and (D) after products mixing 4a and 4c with 1.

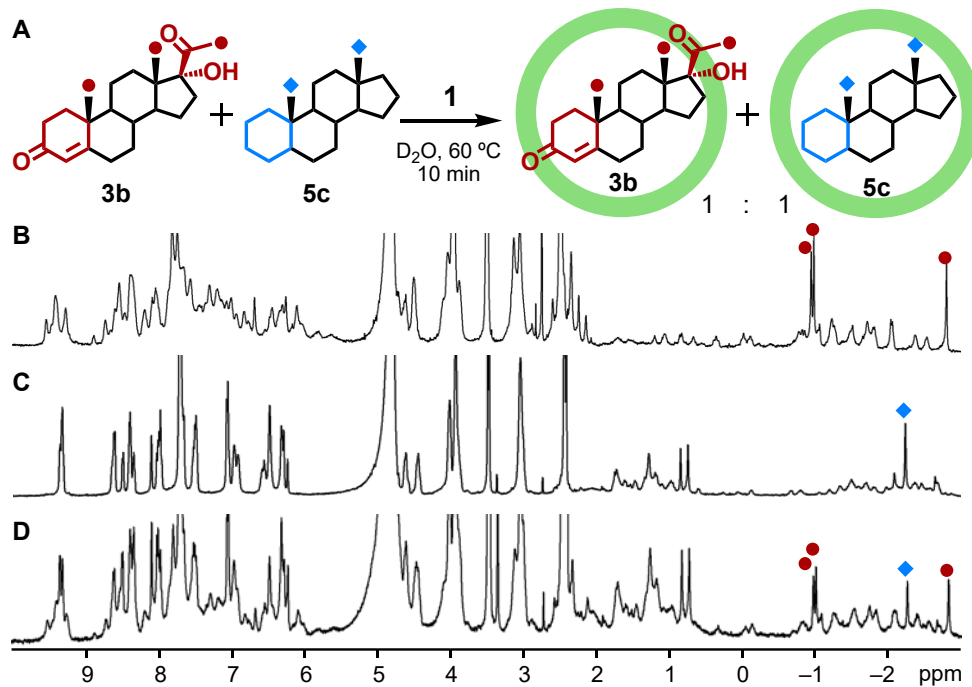


Fig. S35. Competitive binding experiment of 3b and 5c with 1. (A) Schematic representation of the competitive binding experiment of 3b and 5c with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) 1•3b, (C) 1•5c, and (D) products after mixing 3b and 5c with 1.

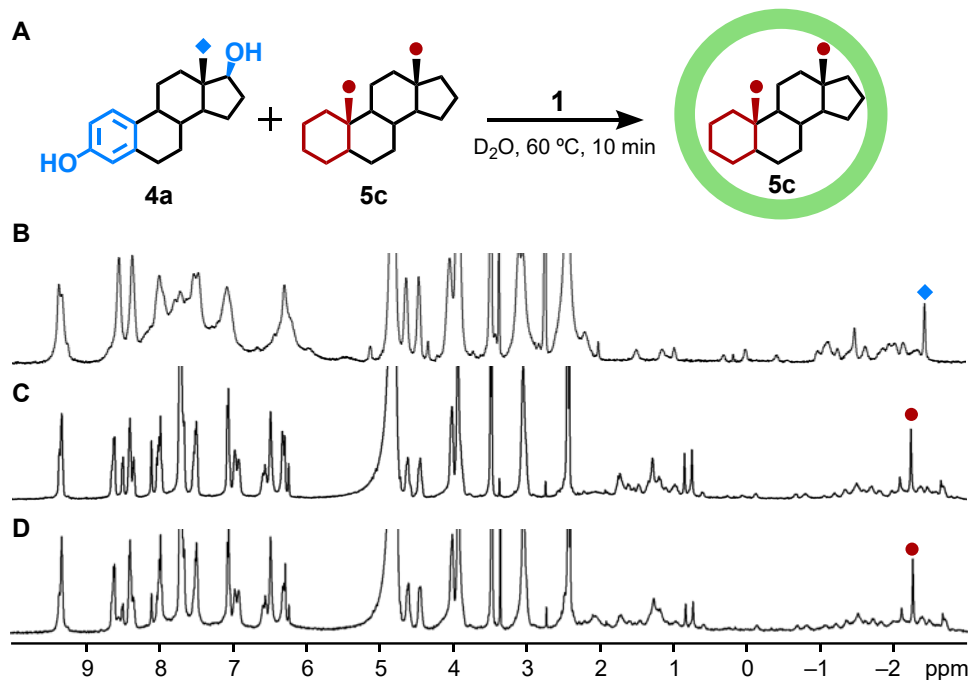
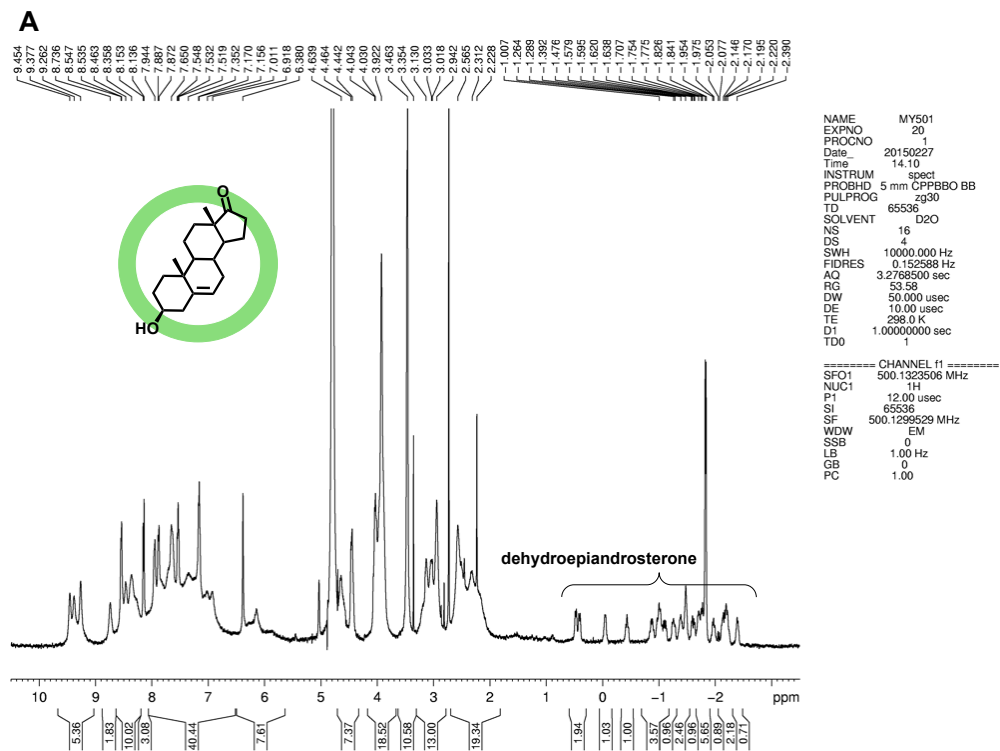


Fig. S36. Competitive binding experiment of 4a and 5c with 1. (A) Schematic representation of the competitive binding experiment of 4a and 5c with 1 in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) 1•4a, (C) 1•5c, and (D) products after mixing 4a and 5c with 1.



B

Analysis Info		Acquisition Date	
Analysis Name	D:\Data\akita\1yamashina\MY470_05000001.d	1/14/2015 6:27:14 PM	
Method	Pd_complex2.m	Operator	BDAL@DE
Sample Name	dcm	Instrument / Ser#	microTOF 10321
Comment			

Acquisition Parameter			
Source Type	ESI	Ion Polarity	Positive
Focus	Not active	Set Nebulizer	3.0 Bar
Scan Begin	50 m/z	Set Dry Heater	30 °C
Scan End	4000 m/z	Set Capillary	4500 V
		Set End Plate Offset	-500 V
		Set Dry Gas	6.0 l/min
		Set Divert Valve	Waste

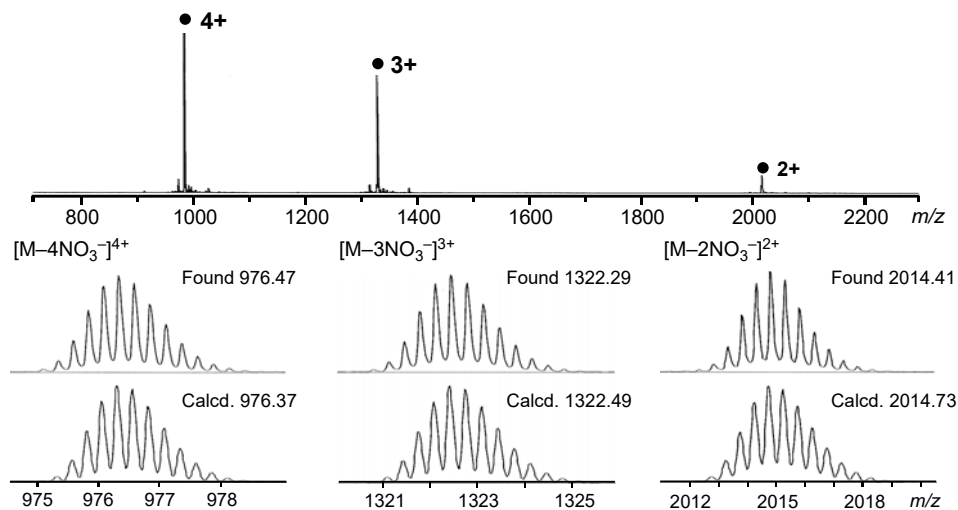


Fig. S37. NMR and MS spectra of **1•2b**. (A) 1H NMR (500 MHz, D_2O , room temperature) and (B) ESI-TOF MS (H_2O , room temperature) spectra of **1•2b**.

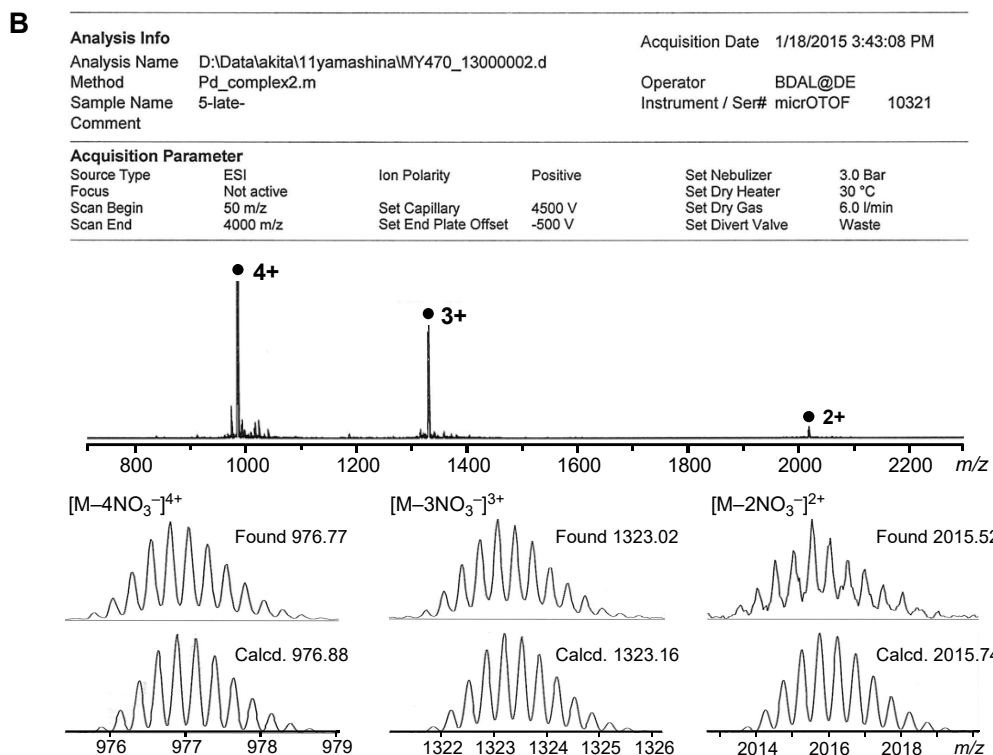
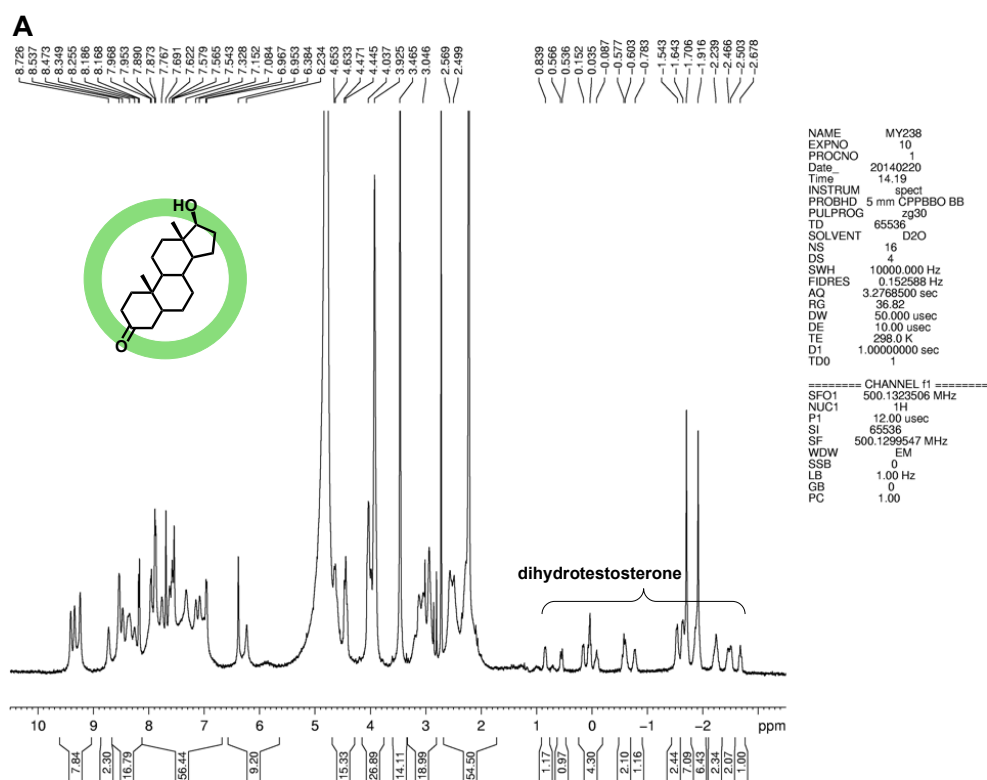


Fig. S38. NMR and MS spectra of **1·2c**. (A) 1H NMR (500 MHz, D_2O , room temperature) and (B) ESI-TOF MS (H_2O , room temperature) spectra of **1·2c**.

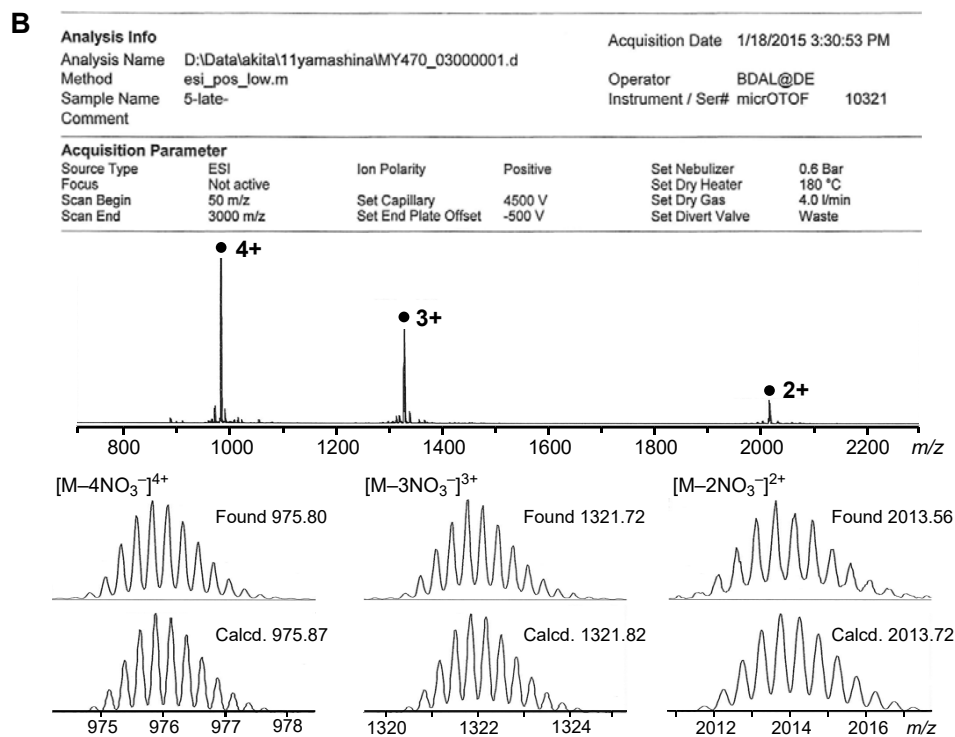
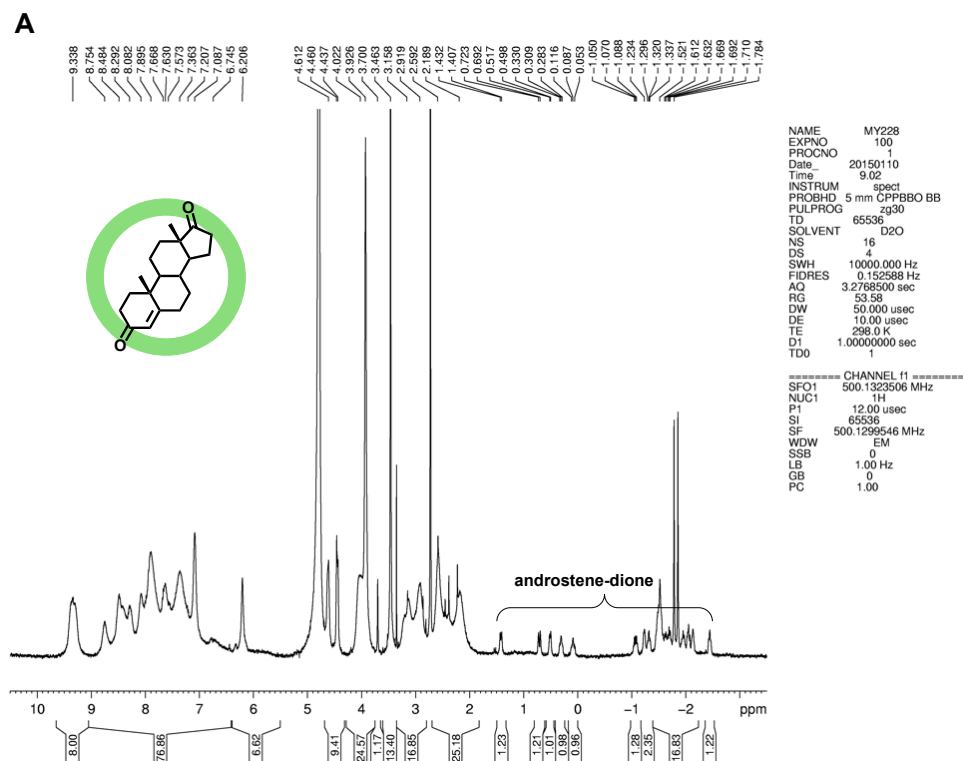
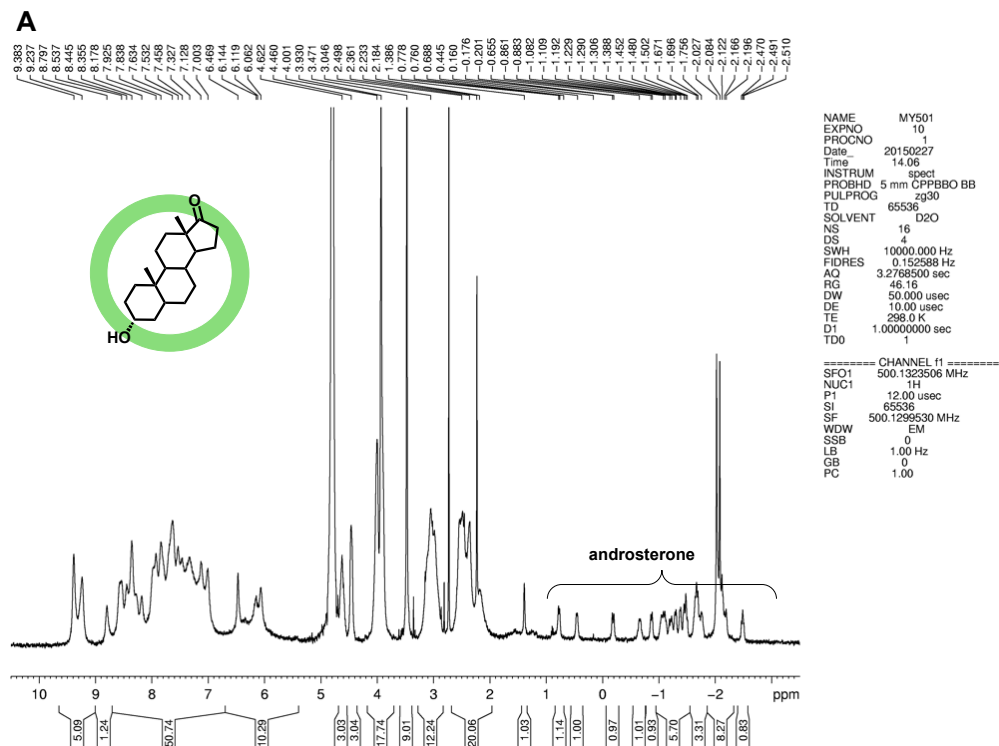


Fig. S39. NMR and MS spectra of 1•2d. (A) 1H NMR (500 MHz, D_2O , room temperature) and **(B)** ESI-TOF MS (H_2O , room temperature) spectra of 1•2d.



B

Analysis Info	Acquisition Date 1/14/2015 6:18:44 PM
Analysis Name D:\Data\akita\1yamashina\MY470_04000001.d	Operator BDAL@DE
Method Pd_complex2.m	Instrument / Ser# micrOTOF 10321
Sample Name dcm	
Comment	

Acquisition Parameter				
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer 3.0 Bar
Focus	Not active			Set Dry Heater 30 °C
Scan Begin	50 m/z	Set Capillary	4500 V	Set Dry Gas 6.0 l/min
Scan End	4000 m/z	Set End Plate Offset	-500 V	Set Divert Valve Waste

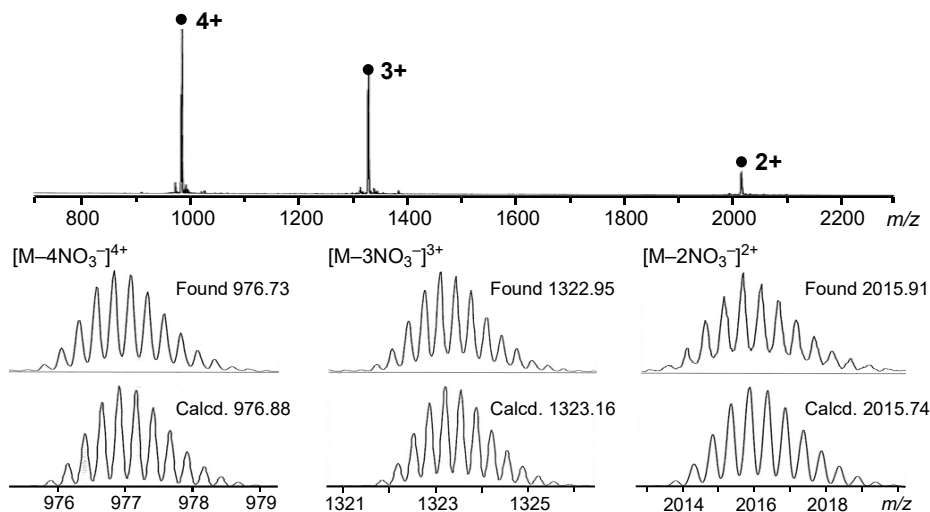
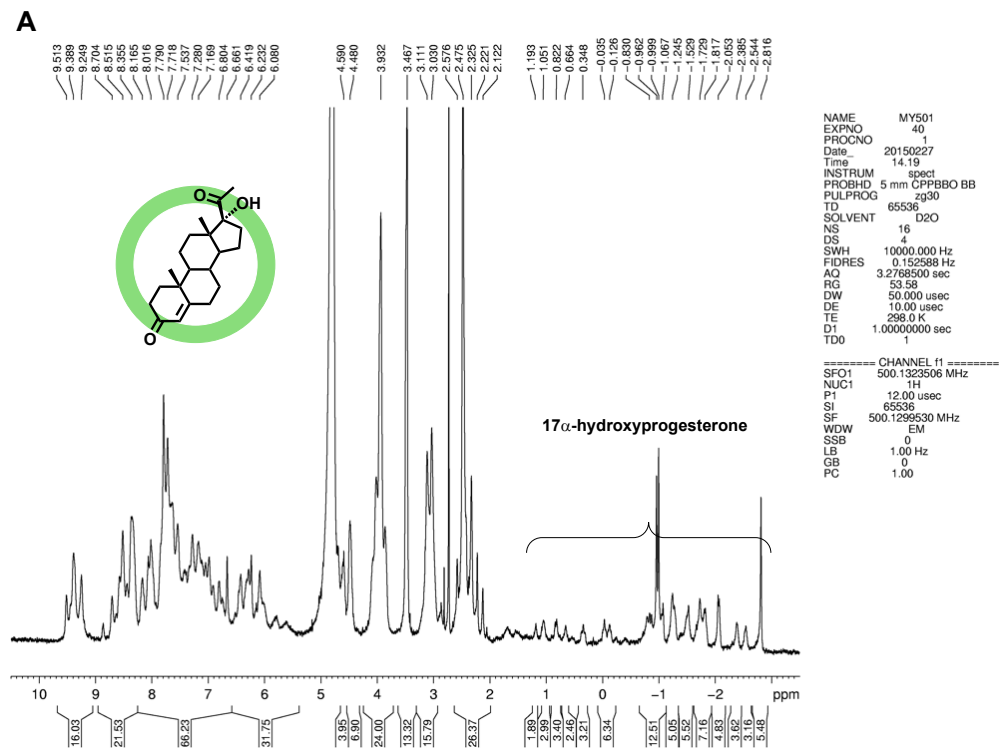


Fig. S40. NMR and MS spectra of 1•2e. (A) 1H NMR (500 MHz, D_2O , room temperature) and **(B)** ESI-TOF MS (H_2O , room temperature) spectra of 1•2e.



B

Analysis Info	Acquisition Date 2/27/2015 4:19:28 PM
Analysis Name D:\Data\akita\11yamashina\MY501_40000001.d	Operator BDAL@DE
Method Pd_complex2.m	Instrument / Ser# microTOF 10321
Sample Name	
Comment	

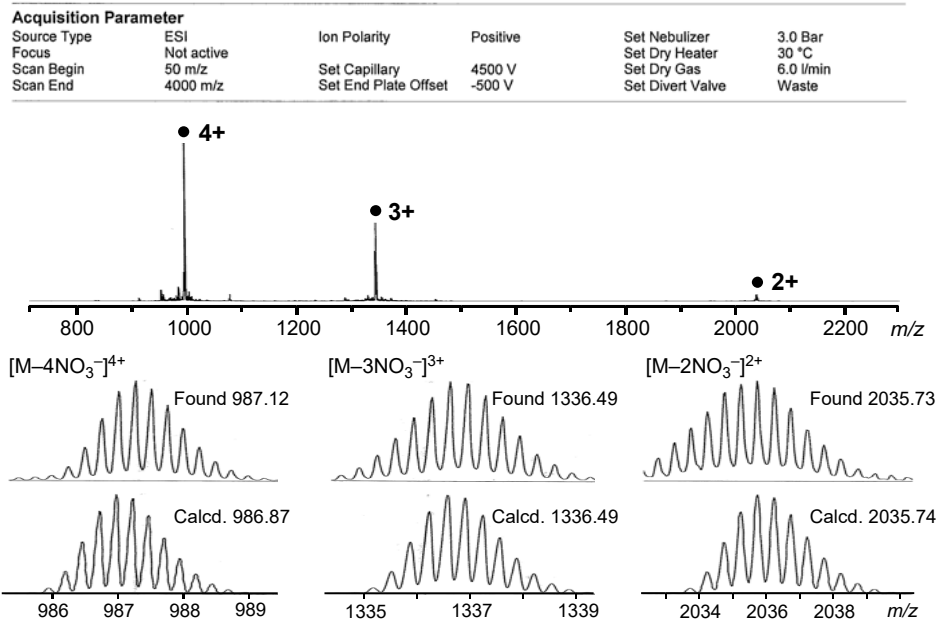


Fig. S41. NMR and MS spectra of 1•3b. (A) 1H NMR (500 MHz, D_2O , room temperature) and **(B)** ESI-TOF MS (H_2O , room temperature) spectra of 1•3b.

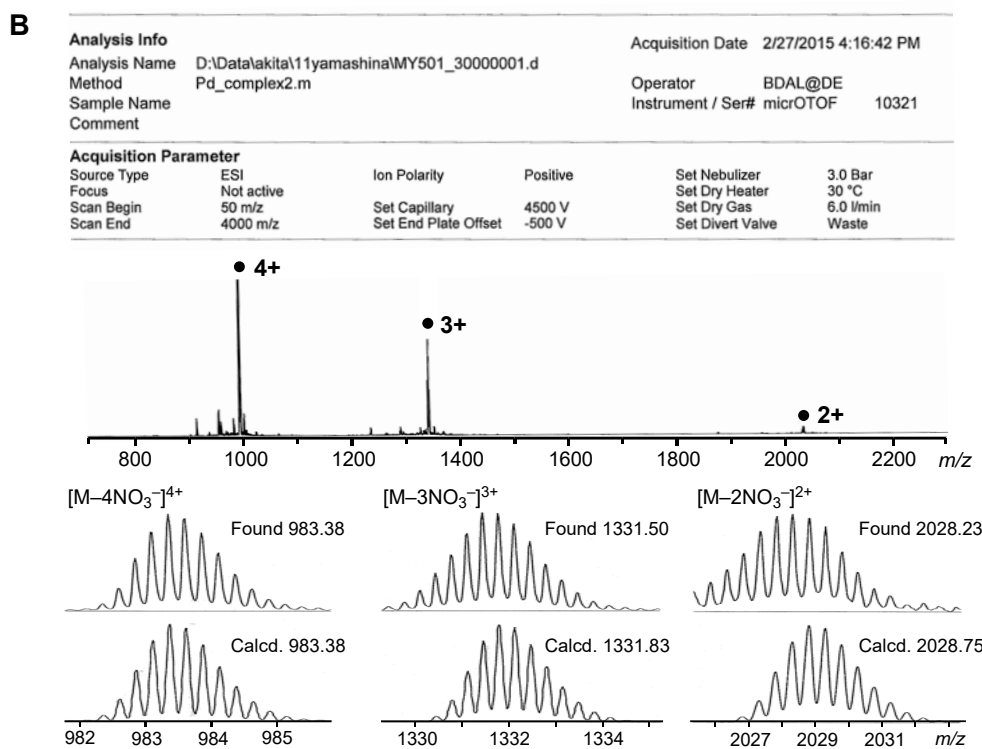
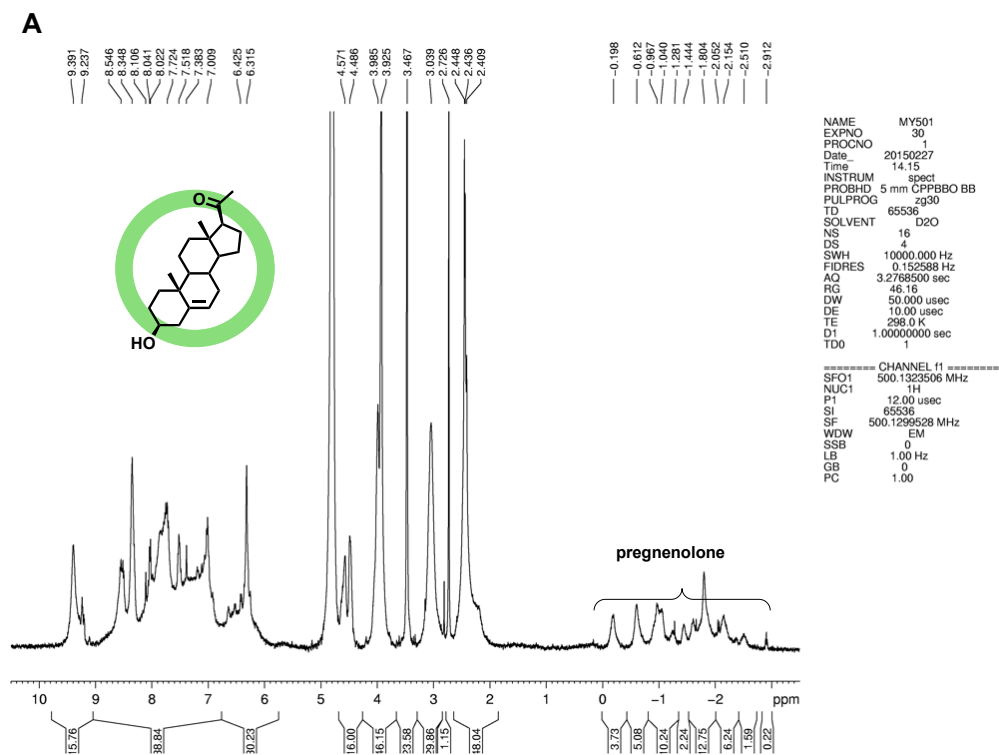


Fig. S42. NMR and MS spectra of 1•3c. (A) ¹H NMR (500 MHz, D₂O, room temperature) and **(B)** ESI-TOF MS (H₂O, room temperature) spectra of 1•3c.

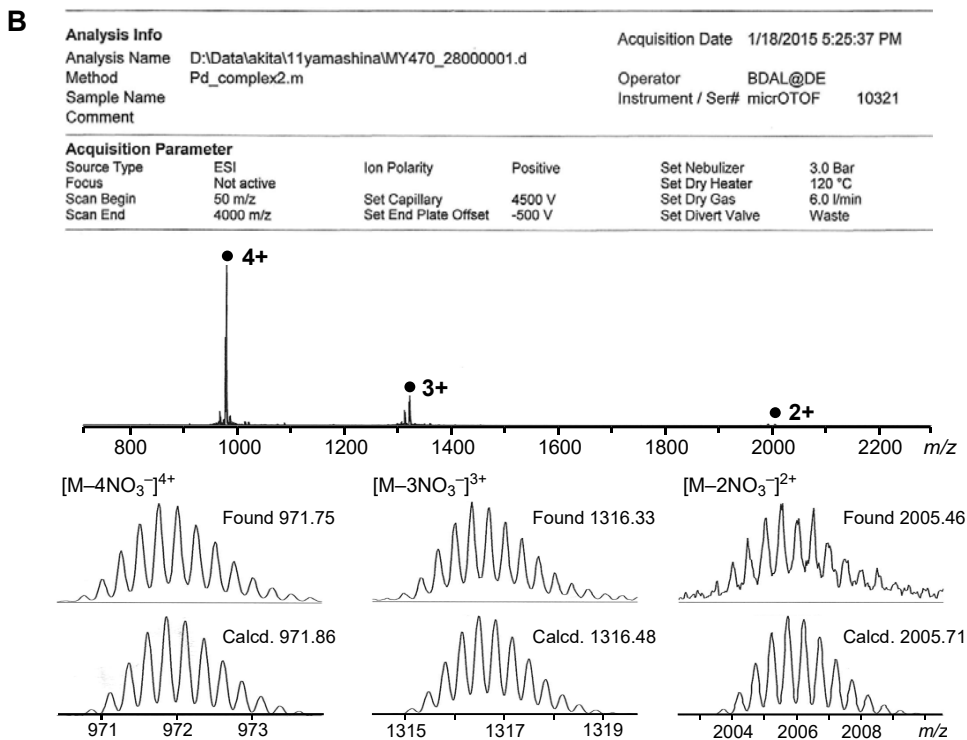
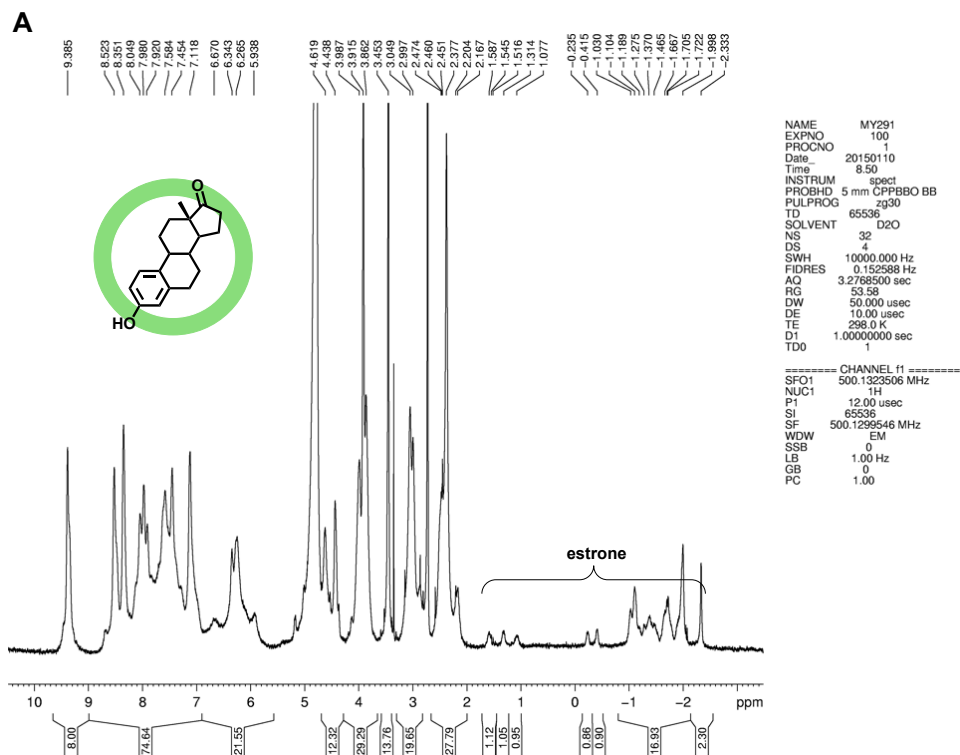


Fig. S43. NMR and MS spectra of 1•4b. (A) ^1H NMR (500 MHz, D_2O , room temperature) and **(B)** ESI-TOF MS (H_2O , room temperature) spectra of 1•4b.

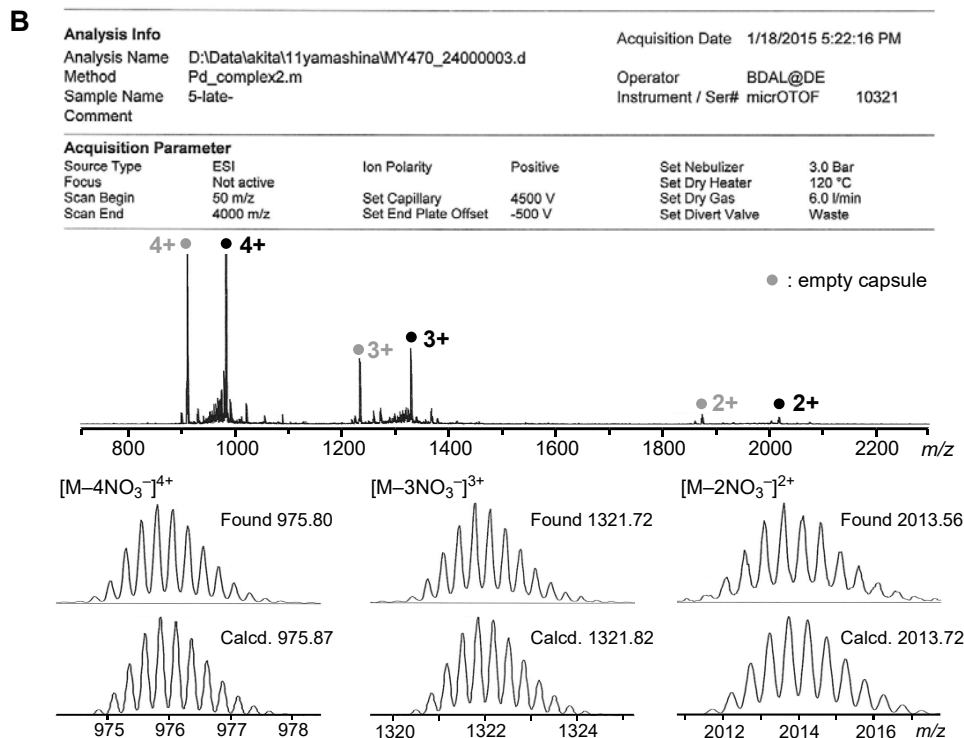
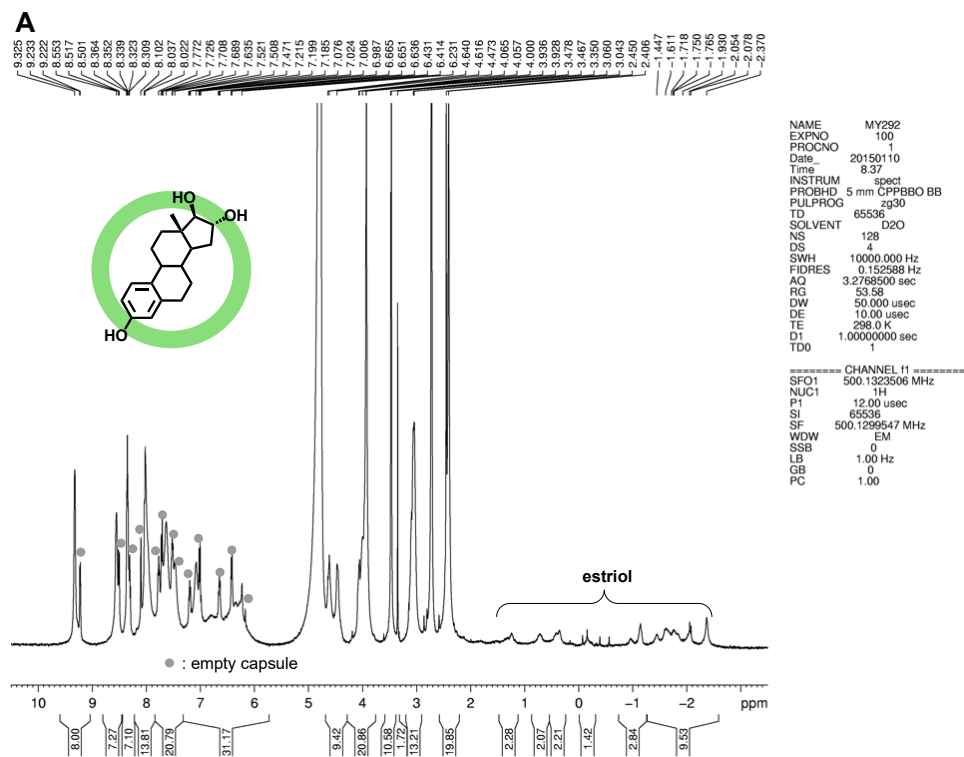


Fig. S44. NMR and MS spectra of 1•4c. (A) ^1H NMR (500 MHz, D_2O , room temperature) and **(B)** ESI-TOF MS (H_2O , room temperature) spectra of 1•4c (gray circle: empty 1).

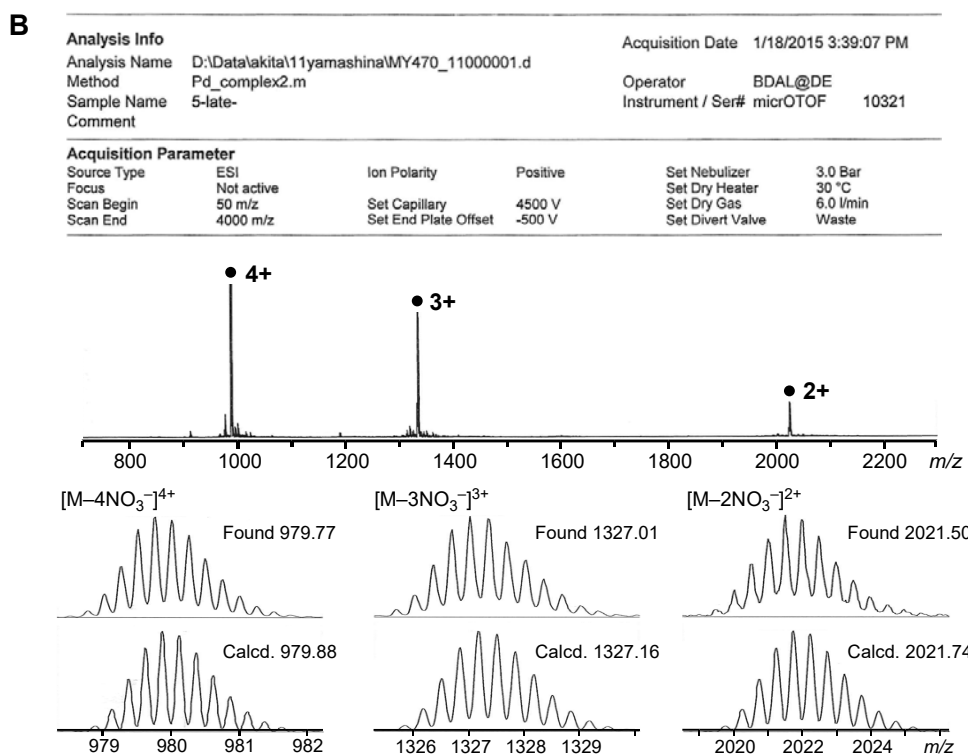
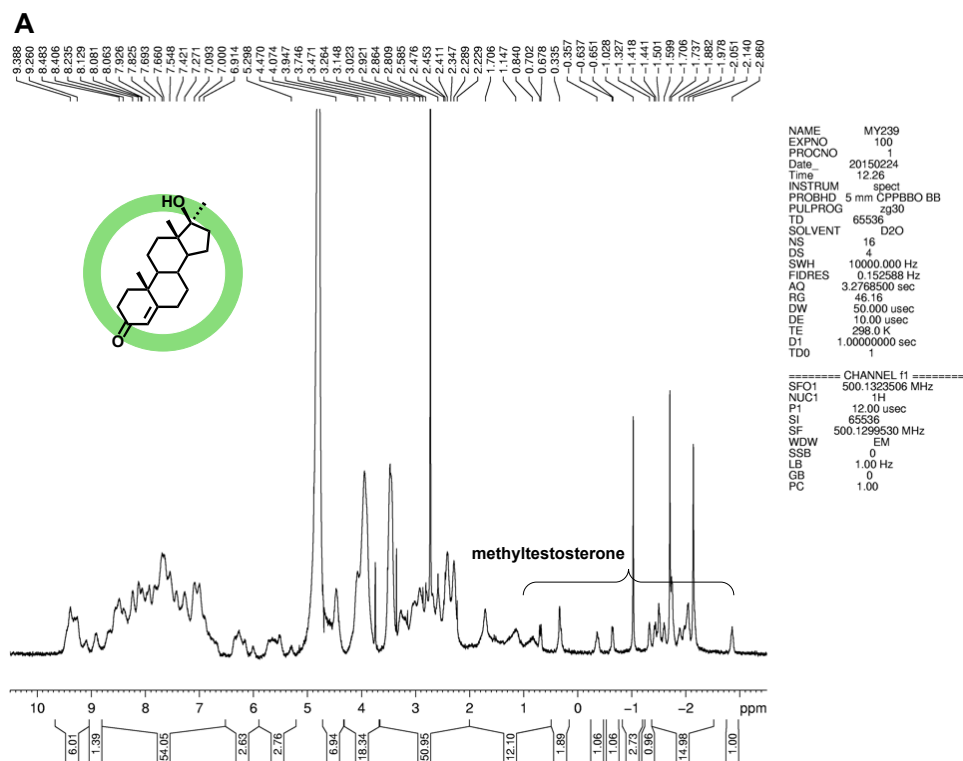


Fig. S45. NMR and MS spectra of 1•5a. (A) 1H NMR (500 MHz, D_2O , room temperature) and **(B)** ESI-TOF MS (H_2O , room temperature) spectra of 1•5a.

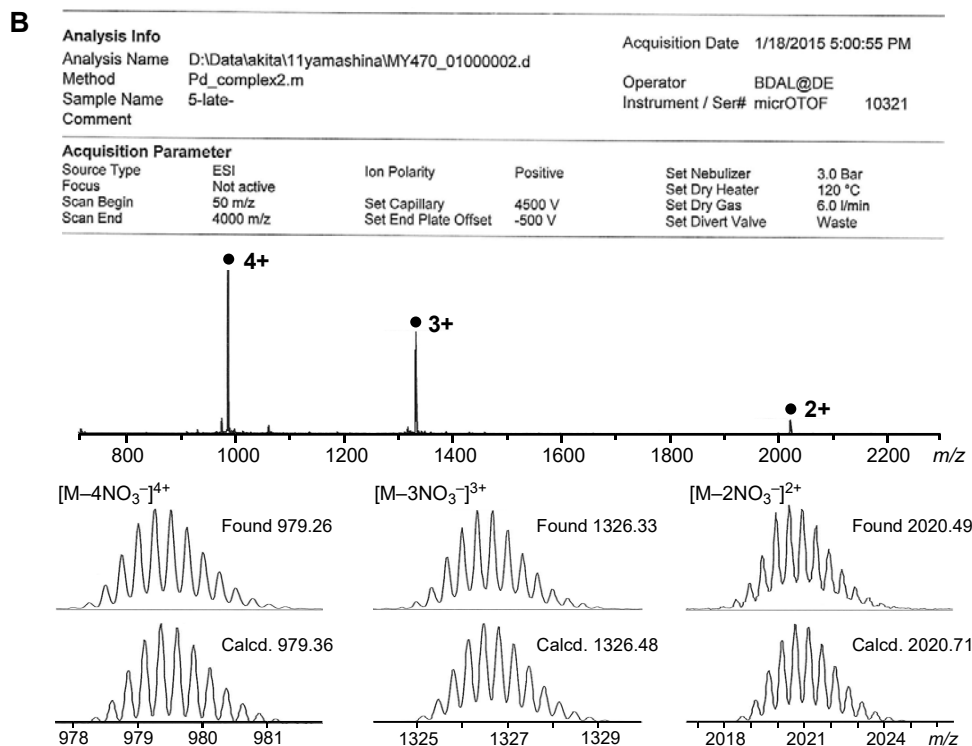
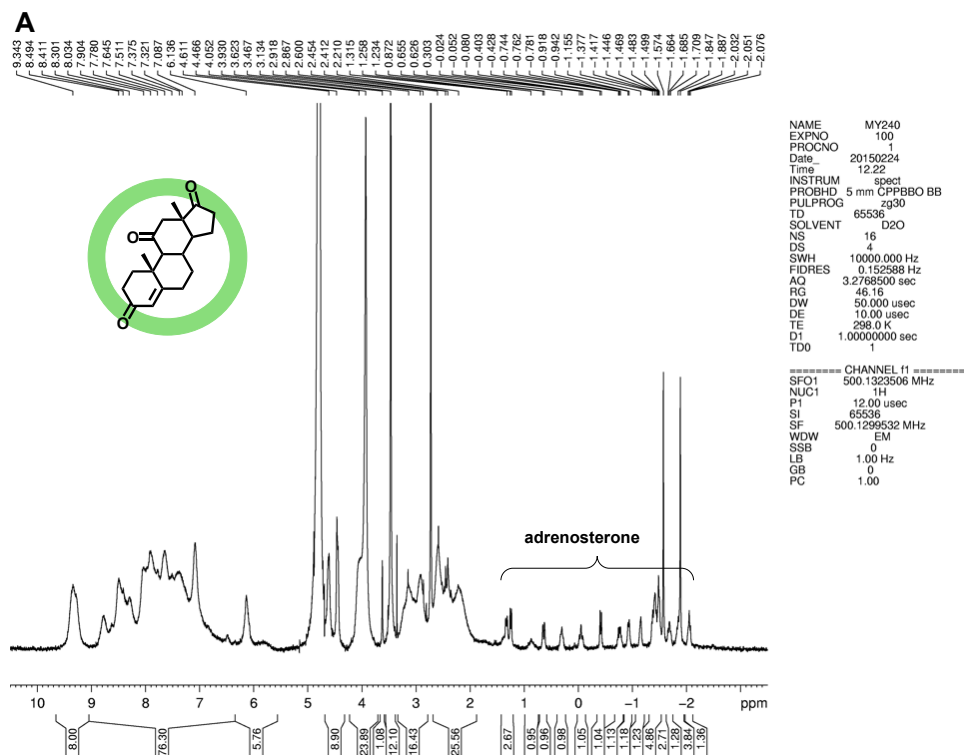


Fig. S46. NMR and MS spectra of **1•5b. (A) 1H NMR (500 MHz, D_2O , room temperature) and (B) ESI-TOF MS (H_2O , room temperature) spectra of **1•5b**.**

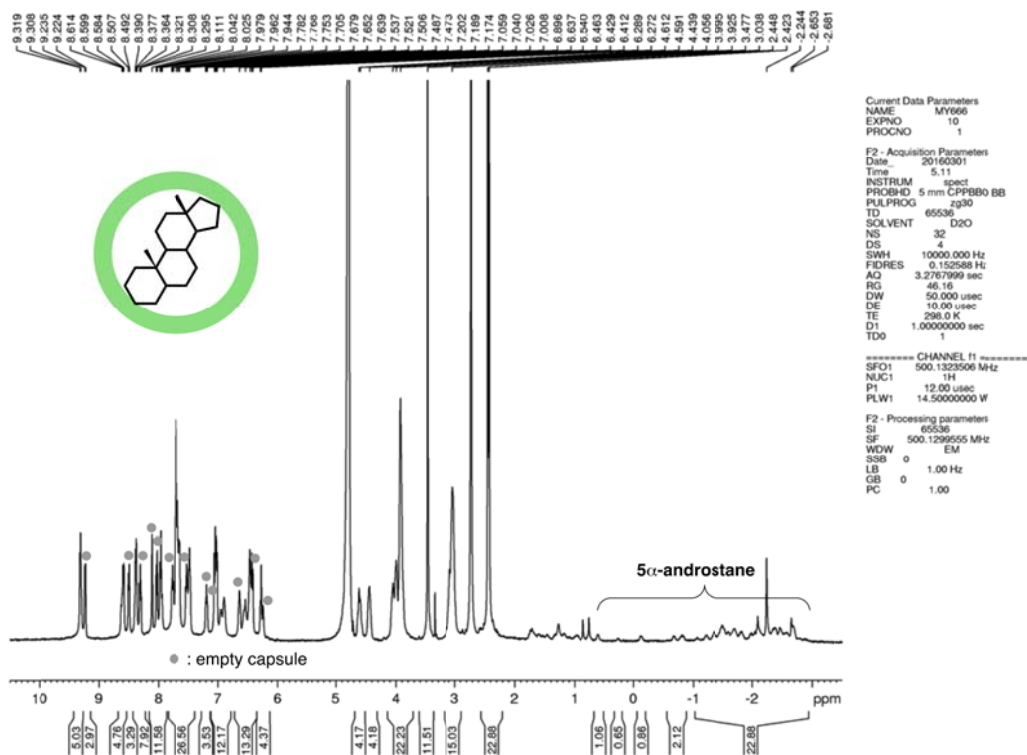


Fig. S47. NMR spectrum of **1•5c**. ^1H NMR (500 MHz, D_2O , room temperature) spectrum of **1•5c**.

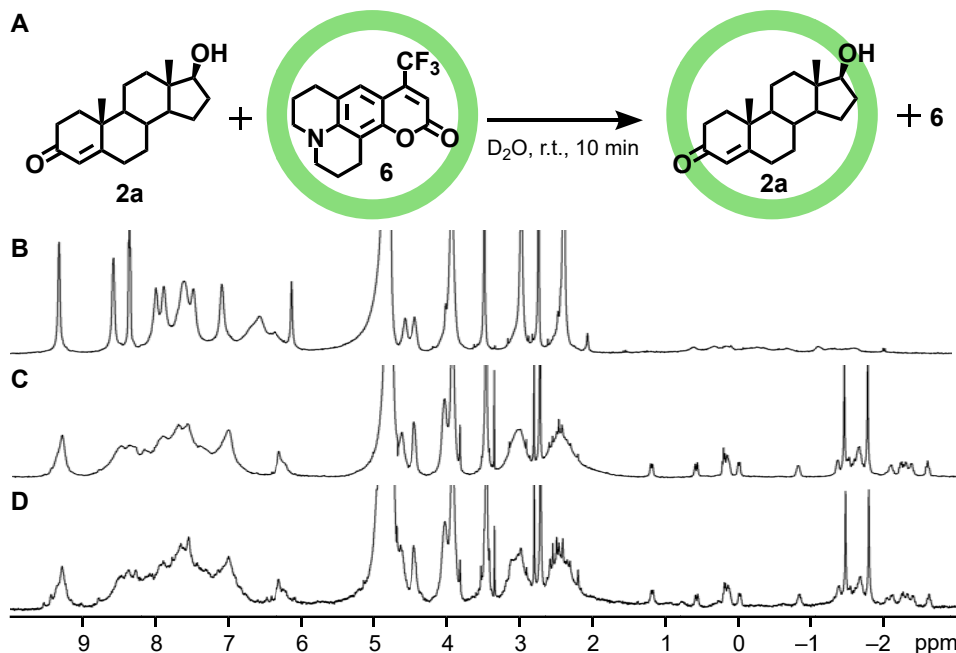


Fig. S48. Competitive binding experiment of **2a** and **6** with **1**. (A) Schematic representation of the competitive binding experiment of **2a** and **6** with **1** in water. ^1H NMR spectra (500 MHz, D_2O , room temperature) of (B) **1•6**, (C) **1•2a**, and (D) products after addition of **2a** ($0.45\ \mu\text{mol}$) to a D_2O solution of **1•6** ($0.8\ \text{mM}$, $0.5\ \text{mL}$).

Table S1. Binding constants of 1 toward 2a and 3a in water.

eq.	[1·2a] ₀ /mM	[CE] ₀ /mM	[1·2a] ^a /mM	[1·CE] ^b /mM	[2a _{free}] ^b /mM	[CE _{free}] ^c /mM	K _b ^d	K ^e /10 ⁷ M ⁻¹
0.5	0.388	0.194	0.338	0.050	0.050	0.144	19.0	4.4
1.0	0.388	0.388	0.316	0.072	0.072	0.316	19.5	4.5
2.0	0.388	0.776	0.288	0.100	0.100	0.676	19.5	4.5
4.0	0.388	1.552	0.254	0.134	0.134	1.418	19.9	4.6
average							19.5	4.5

^a [1·2a] = [1·2a]₀ · (a_{1·2a} / (a_{1·2a} + a_{1·CE})), ^b [1·CE] = [2a_{free}] = [1·2a]₀ - [1·2a], ^c [CE_{free}] = [CE]₀ - [1·CE],
^d K_b = ([1·2a] · [CE_{free}]) / ([1·CE] · [2a_{free}]), ^e K = K_a × K_b = 2.29 × 10⁶ × K_b (ref. 33)

eq.	[1·3a] ₀ /mM	[CE] ₀ /mM	[1·3a] ^a /mM	[1·CE] ^b /mM	[3a _{free}] ^b /mM	[CE _{free}] ^c /mM	K _b ^d	K ^e /10 ⁵ M ⁻¹
1.0	0.388	0.388	0.126	0.262	0.262	0.126	0.229	5.2
1.5	0.388	0.582	0.065	0.323	0.323	0.259	0.160	3.7
2.0	0.388	0.776	0.045	0.343	0.343	0.433	0.168	3.8
2.5	0.388	0.970	0.034	0.354	0.354	0.616	0.168	3.8
average							0.181	4.2

^a [1·3a] = [1·3a]₀ · (a_{1·3a} / (a_{1·3a} + a_{1·CE})), ^b [1·CE] = [3a_{free}] = [1·3a]₀ - [1·3a], ^c [CE_{free}] = [CE]₀ - [1·CE],
^d K_b = ([1·3a] · [CE_{free}]) / ([1·CE] · [3a_{free}]), ^e K = K_a × K_b = 2.29 × 10⁶ × K_b (ref. 33)

Table S2. Packing coefficients of host-guest complexes. (ref. 37)

	1·2a ¹	1·3a ¹	1·4a ¹	1·5a ¹	1·5c ²	1'·2a ³	1''·5c ³
guest volume (Å ³)	315	347	296	333	311	315	311
cavity volume (Å ³)	560	611	567	570	567	521	563
packing coefficient (%) ⁴	56	57	52	58	55	60	55

1: The optimized structures were generated based on the crystal structure of 1'·2a.

2: The optimized structure was generated based on the crystal structure of 1''·5c.

3: The cavity volumes were calculated without the optimization.

4: (the van der Waals volume of the guest)/(the cavity volume of the receptor) × 100.

Table S3. Water solubilities of steroid hormones. (ref. 10 and 39)

	2a	2b	2c	2d	2e	3a	3b	3c
solubility (μM)	114	76	-	200	40	33	20	95
temp. ($^{\circ}\text{C}$)	r.t.	23.5	-	25	23.5	r.t.	27.3	r.t.

	4a	4b	4c	5a	5b	5c
solubility (μM)	9	48	75	112	328	-
temp. ($^{\circ}\text{C}$)	r.t.	r.t.	r.t.	25	23.5	-

Table S4. Crystal data and structure refinement for 1'•2a.

Identification code	MY828
Empirical formula	C231 H212 B4 F16 N8 O29 Pd2
Formula weight	4123.11
Temperature	293 K
Wavelength	0.71073 Å
Crystal system	triclinic
Space group	P 1
Unit cell dimensions	$a = 17.1510 \text{ \AA}$ $\alpha = 107.080^\circ$ $b = 18.9830 \text{ \AA}$ $\beta = 109.420^\circ$ $c = 19.1610 \text{ \AA}$ $\gamma = 108.610^\circ$
Volume	4986.9 \AA^3
Z	1
Density (calculated)	1.373 Mg/m^3
Absorption coefficient	0.270 mm^{-1}
F(000)	2142
Crystal size	$0.120 \times 0.090 \times 0.070 \text{ mm}^3$
Theta range for data collection	1.266 to 28.907°
Index ranges	$-17 \leq h \leq 22$, $-24 \leq k \leq 22$, $-23 \leq l \leq 25$
Reflections collected	30433
Independent reflections	26230 [R(int) = 0.0365]
Completeness to theta = 25.242°	88.4 %
Absorption correction	multi-scan
Max. and min. transmission	0.981 and 0.860
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	26230 / 10956 / 2627
Goodness-of-fit on F^2	1.030
Final R indices [I > 2sigma(I)]	$R_1 = 0.0937$, $wR_2 = 0.2378$
R indices (all data)	$R_1 = 0.1623$, $wR_2 = 0.2806$
Largest diff. peak and hole	2.117 and $-1.303 \text{ e.\AA}^{-3}$

The supplementary crystallographic data (CCDC 1539560) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table S5. Crystal data and structure refinement for 1''•5c.

Identification code	MY666
Empirical formula	C231 H216 N11 O43 Pd2
Formula weight	4046.94
Temperature	273 K
Wavelength	1.54178 Å
Crystal system	triclinic
Space group	P 1
Unit cell dimensions	$a = 21.3972 (17) \text{ \AA}$ $\alpha = 71.570 (4)^\circ$ $b = 21.4356 (15) \text{ \AA}$ $\beta = 70.980 (4)^\circ$ $c = 27.389 (2) \text{ \AA}$ $\gamma = 60.886 (4)^\circ$
Volume	10185.4 (14) Å ³
Z	2
Density (calculated)	1.320 Mg/m ³
Absorption coefficient	2.087 mm ⁻¹
F(000)	4230
Crystal size	0.130 x 0.060 x 0.030 mm ³
Theta range for data collection	2.403 to 56.920°
Index ranges	-23<=h<=23, -19<=k<=23, -29<=l<=29
Reflections collected	64183
Independent reflections	39375 [R(int) = 0.1179]
Completeness to theta = 56.920°	99.2 %
Absorption correction	multi-scan
Max. and min. transmission	0.940 and 0.722
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	39375/ 9856 / 4808
Goodness-of-fit on F ²	1.185
Final R indices [I>2sigma(I)]	R ₁ = 0.1043, wR ₂ = 0.2494
R indices (all data)	R ₁ = 0.1716, wR ₂ = 0.2934
Largest diff. peak and hole	3.258 and -1.541 e.Å ⁻³

The supplementary crystallographic data (CCDC 1485686) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.