Synthesis of novel chiral cholic acid-based molecular tweezers containing unsymmetrically disubstituted urea units using microwave irradiation

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An efficient procedure has been developed for the synthesis of new chiral cholic acid molecular tweezer artificial receptors by linking an unsymmetrically disubstituted urea to methyl deoxycholate via a carbonate chain using microwave irradiation. The structures of these new receptors were confirmed by ^{1}H NMR, IR, MS spectra and elemental analysis. Their binding properties were examined by UV-Vis spectra titration. The preliminary results indicate that these molecular tweezers not only recognised anions, but also showed good enantioselectivity for *D*-amino acid methyl esters.

Keywords: molecular tweezer, microwave irradiation, deoxycholic acid, molecular recognition

The understanding of noncovalent intermolecular interactions has become the central focus of supramolecular chemistry.[1–3] The design and synthesis of molecular tweezer artificial receptors to recognise substrates of biochemical significance utilising these weak forces so that they mimic biological events are of major interest in molecular recognition research.[4–8] The natural rigid concave structure and inherent asymmetry of cholic acid suggests that it is an ideal building block for the construction of molecular tweezers. In recent years, molecular tweezers have been synthesised derived from steroidal cholic acid.[9–13] However, to our knowledge, the use of chiral unsymmetrical disubstitued ureas as building blocks for the construction of deoxycholic acid molecular tweezer has not been reported.

Furthermore, the application of microwave techniques for organic synthesis has attracted considerable interest in recent years.[14–15] This is because this method can greatly reduce reaction times, enhance conversions and simplify work-up. In continuation of our ongoing program to synthesise tweezer artificial receptors using microwave irradiation,[16–18] we report here a facile and rapid synthetic method for the preparation of chiral unsymmetrically disubstituted urea type molecular tweezer based on deoxycholic acid under microwave irradiation which, to the best of our knowledge, has not been attempted previously. At the sametime, we have made some preliminarily studies of the recognition properties of this kind of molecular tweezer for anions and chiral molecules. The synthetic route is shown in Scheme 1.

Results and discussion

As shown in Table 1, the microwave-enhanced method when compared with the conventional heating method, has the following advantages: (1) the reaction avoids the use of the very toxic phosgene, and reduces pollution of the environment; (2) the reaction rate increased 27–33 times, and greatly shortened the reaction time; (3) the yields of molecular tweezers have increased from 57–65% to 86–94%. Hence, the microwave assisted method is a safe, fast, efficient and green synthesis method for chiral molecular tweezers based on deoxycholic acid.

The recognition of molecular tweezers **9b**, **9c**, **9f** for anions and *D/L* –amino acid methyl esters has been investigated by UV-Vis spectra titration in $CHCl_3$ at 25 °C. We added aromatic amines and D/L –amino acid methyl esters solution of different concentrations to **9b**, **9c**, **9f** of fixed concentration of 1×10^{-4} ~ 10×10^{-4} mol L^{-1}, and measured the characteristic absorbance value of the host–guest complexes. As the guest molecules were added, the absorbance value rose in a regular pattern. It showed that these molecular tweezers possessed the ability to form a complex with the guest molecules under examination. The titration data were analysed by using the Hildebrand–Benesi equation.[19] Based on equation (1), when $[G]_0>>[H]_0$, the plots of $1/[G]_0$ versus $1/\Delta A$ were measured. The plot gave a straight line. We calculated with the association constants (*Ka*) from the intercept and the slope of the line, we calculated with the association constants (*Ka*). The free energy change ($-\Delta G^0$) was obtained according to equation (2). The association constants (*Ka*) and free energy changes ($-\Delta G^0$) for the inclusion complexes of anions and *D/L*–amino acid methyl esters with the molecular tweezers **9b**, **9c**, **9f** are listed in Tables 2 and 3. These show that these molecular tweezers possessed the ability to form a complex with these guest molecules. The supramolecular complexes consisted of 1:1 host and guest molecules. The association constants of molecular tweezer **9f**, for example, are 507.25, 16862.00, 13670.56 L mol^{-1} for NO_3^-, $H_2PO_4^-$, CH_3COO^-, respectively. At the same time, these receptors showed good chiral recognition for *D*-amino acid methyl esters, the maximum K_D/K_L of molecular tweezer **9c** reaches 4.02 for *D/L*–His–OMe. The details of molecular recognition of these molecular tweezers are under further studies.

$$\frac{1}{\triangle A} = \frac{1}{aKa[G]_0} + \frac{1}{a} \quad (1)$$

$$\triangle G^0 = -RTLnKa \quad (2)$$

Experimental

Melting points were determined on a micro-melting point apparatus and were uncorrected. IR spectra were obtained on 1700 Perkin-Elmer FTIR using KBr disks. ^{1}H NMR spectra were recorded on a Varian INOVA 400 MHz spectrometer using TMS as internal standard. Mass spectra were determined on Waters Q-TOF Premier instrument. Elemental analysis was performed on a Carlo-Erba-1106 auto analyser. Optical rotation was measured on a Wzz-2B polarimeter. All reactions were performed in a commercial microwave reactor (XH-100A, 100-1000 W, Beijing Xianghu Science and Technology Development Co. Ltd, Beijing, P. R. China). All the solvents were purified before use. Intermediates **3** and **7** was prepared according to reported procedures.[20–21] The physical constants of intermediates **3a–f** and **7** are listed in Table 4.

Microwave method for the preparation of molecular tweezers **9a–f**

Triphosgene (0.11 g, 0.37 mmol) was added to a solution of intermediate **7** (0.29 g, 0.5 mmol) in dry CH_2Cl_2 (10 mL) and dry pyridine (0.2 mL) at room temperature. Then the solution was placed in the microwave oven and the reaction mixture was irradiated for 10 min at 200 W. Intermediate **8** was formed and, without separation, the intermediate **3** (1.5 mmol) and dry pyridine (0.2 mL) were added directly

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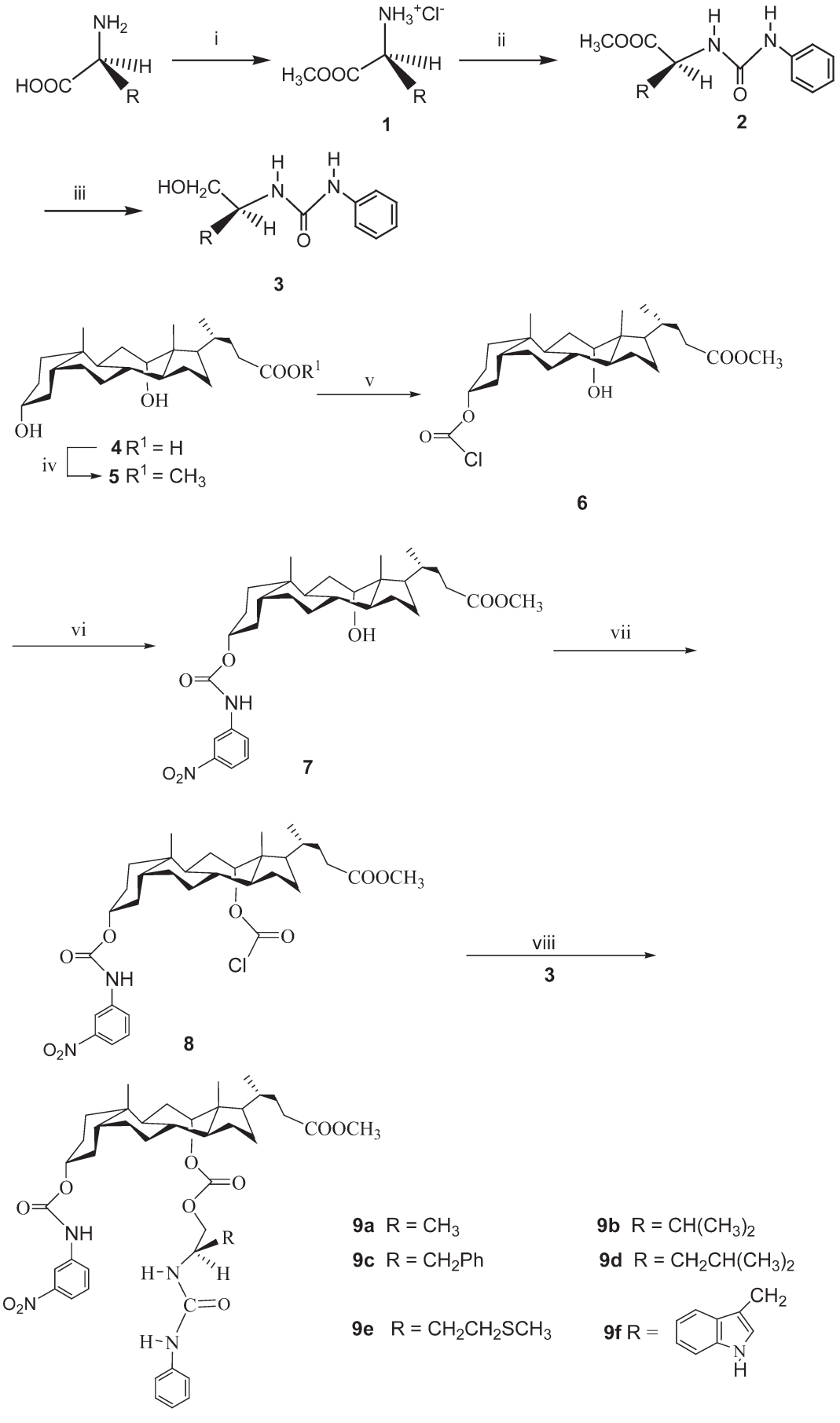

Scheme 1 Reagents and conditions (i) CH_3OH, $SOCl_2$; (ii) aniline, triphosgene, DIEA, CH_2Cl_2; (iii) $NaBH_4$, THF, H_2O; (iv) CH_3OH, CH_3COCl; (v) triphosgene, pyridine, MWI; (vi) *m*-nitroaniline, pyridine, MWI; (vii) triphosgene, CH_2Cl_2, pyridine, MWI; (viii) CH_2Cl_2, pyridine, MWI.

Table 1 Synthetic comparison of molecular tweezers **9a–f** between microwave irradiation and conventional heating

Compd.	Conventional method		Microwave method		t_c/t_w[a]
	Time/min	Yield/%	Time/min	Yield/%	
9a	600	57	21	93	29
9b	600	60	22	94	27
9c	660	63	23	90	29
9d	660	65	20	93	33
9e	720	61	24	87	30
9f	780	58	25	86	31

[a] t_c, Conventional heating method needs time; t_{MW}, microwave method needs time.

Table 2 Association constants (*Ka*) and Gibbs free energy changes ($-\Delta G^o$) for the inclusion complexes of anions with molecular tweezers **9b, 9c, 9f** in $CHCl_3$ at 25 °C

Host	Guest	*Ka*/L mol^{-1}	$-\Delta G^o$/kJ mol^{-1}
9b	NO_3^-	238.04	13.55
	$H_2PO_4^-$	12808.29	23.43
	CH_3COO^-	1691.34	18.42
9c	NO_3^-	2479.88	19.36
	$H_2PO_4^-$	14720.01	23.78
	CH_3COO^-	11053.51	23.07
9f	NO_3^-	507.25	15.43
	$H_2PO_4^-$	16862.00	24.10
	CH_3COO^-	13670.56	23.59

Table 3 Association constants(*Ka*) and Gibbs free energy changes ($-\Delta G^o$) for the inclusion complexes of amino acid methyl esters with molecular tweezers **9b**, **9c**, **9f** in $CHCl_3$ at 25 °C

Host	Guest	*Ka*/L mol^{-1}	$-\Delta G^o$/kJ mol^{-1}	K_D/K_L
9b	*D*-Try-OMe	268.12	13.85	2.36
	L-Try-OMe	113.56	11.72	
	D-His-OMe	586.17	15.78	3.57
	L-His-OMe	164.34	12.63	
9c	*D*-Try-OMe	301.06	14.13	2.47
	L-Try-OMe	121.65	11.89	
	D-His-OMe	858.78	16.73	4.02
	L-His-OMe	213.41	13.28	
9f	*D*-Try-OMe	286.42	14.01	2.66
	L-Try-OMe	107.66	11.59	
	D-His-OMe	645.48	16.02	2.40
	L-His-OMe	268.91	13.85	

Table 4 The physical constants of intermediates **3a–f** and 7

Compd	Formula	M.p./ °C	$[\alpha]_D^{20}$/ °C
3a	$C_{10}H_{14}N_2O_2$	125–127	–8.0 (c 0.5 CH_2Cl_2)
3b	$C_{12}H_{18}N_2O_2$	103–104	–44.0 (c 0.5 CH_2Cl_2)
3c	$C_{16}H_{18}N_2O_2$	133–134	–20.0 (c 0.5 CH_2Cl_2)
3d	$C_{13}H_{20}N_2O_2$	88–90	–28.0 (c 0.5 CH_2Cl_2)
3e	$C_{12}H_{18}N_2O_2S$	95–97	+ 18.4 (c 0.5 CH_2Cl_2)
3f	$C_{18}H_{19}N_3O_2$	167–168	+ 35.6 (c 0.5 CH_2Cl_2)
7	$C_{32}H_{46}N_2O_7$	184–185	+ 85.7 (c 0.5 CH_2Cl_2)

to the mixture and the irradiation continued for 10–15 min at the same power. The solvent was removed and the residue was diluted with ethyl acetate (20 mL) and washed with 10% $NaHCO_3$ (15 mL×3), brine (15 mL×3), and finally dried over anhydrous Na_2SO_4. The solvent was evaporated to give the crude product. The crude product was purified by column chromatography on silica gel H with dichloromethane/ethyl acetate as the eluant. The physical and spectra data of the compounds **9a–f** are as follows.

9a: Pale yellow solid, yield 93%, m.p. 82–84 °C, $[\alpha]_D^{20}$+74.4 (*c* 1.3, CH_2Cl_2); IR (KBr)(cm^{-1}): 3349, 2868, 1738, 1599, 1442, 1223, 1054; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.09 (s, 1H, 3-OCONH), 8.46 (s, 1H, PhNHCO), 8.41–6.85 (m, 9H, ArH), 6.17 (d, *J* = 8.0 Hz, 1H, CONH), 4.91 (brs, 1H, 12*3β-H*), 4.67–4.59 (m, 1H, 3β-H), 4.12–3.93 (m, 3H, NCH + OCH_2), 3.55 (s, 3H, $COOCH_3$), 1.10 (d, *J* = 6.4 Hz, 3H, CH_3), 0.92 (s, 3H, 19-**CH**$_3$), 0.78 (d, *J* = 6.4 Hz, 3H, 21-**CH**$_3$), 0.70 (s, 3H, 18-**CH**$_3$); HRMS (ESI) *m/z* Calcd for $C_{43}H_{58}N_4O_{10}$: 790.4153. Found: 791.4219 [M+H]$^+$. Anal. Calcd for $C_{43}H_{58}N_4O_{10}$: C, 65.30; H, 7.39; N, 7.08. Found: C, 65.20; H, 7.40; N, 7.06%.

9b: Pale yellow solid, yield 94%, m.p. 109–111 °C, $[\alpha]_D^{20}$+39.0 (*c* 1.6, CH_2Cl_2); IR (KBr)(cm^{-1}): 3385, 2870, 1736, 1596, 1441, 1227, 1061; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.12 (s, 1H, 3-OCONH), 8.46 (s, 1H, PhNHCO), 8.42–6.87 (m, 9H, ArH), 6.18 (d, *J* = 8.4 Hz, 1H, CONH), 4.91 (brs, 1H, 12*3β-H*), 4.67-4.60 (m, 1H, 3β-H), 4.18–4.14 (m, 1H, NCH), 4.09–3.73 (m, 2H, OCH_2), 3.55 (s, 3H, $COOCH_3$), 0.91 (s, 3H, 19-**CH**$_3$), 0.87–0.82 (m, 7H, $CH(CH_3)_2$), 0.77 (d, *J* = 6.4 Hz, 3H, 21-**CH**$_3$), 0.69 (s, 3H, 18-**CH**$_3$); HRMS(ESI) *m/z* Calcd for $C_{45}H_{63}N_4O_{10}$: 819.4544. Found: 819.4554 [M]$^+$. Anal. Calcd for $C_{45}H_{63}N_4O_{10}$: C, 65.91; H, 7.74; N, 6.83. Found: C, 65.70; H, 7.72; N, 6.81%.

9c: Pale yellow solid, yield 90%, m.p. 82–83 °C, $[\alpha]_D^{20}$+53.3 (*c* 1.3, CH_2Cl_2); IR (KBr)(cm^{-1}): 3387, 2869, 1737, 1598, 1447, 1225, 1065; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.06 (s, 1H, 3-OCONH), 8.46 (s, 1H, PhNHCO), 8.40–6.84 (m, 14H, ArH), 6.23 (d, *J* = 8.0 Hz, 1H, CONH), 4.92 (brs, 1H, 12*3β-H*), 4.65–4.59 (m, 1H, 3β-H), 4.18–3.99 (m, 3H, NCH + OCH_2), 3.55 (s, 3H, $COOCH_3$), 2.82–2.72 (m, 2H, $PhCH_2$), 0.92 (s, 3H, 19-**CH**$_3$), 0.79 (d, *J* = 6.4 Hz, 3H, 21-**CH**$_3$), 0.68 (s, 3H, 18-**CH**$_3$); HRMS(ESI) *m/z* Calcd for $C_{49}H_{62}N_4O_{10}$: 866.4466. Found: 867.4551 [M+H]$^+$. Anal. Calcd for $C_{49}H_{62}N_4O_{10}$: C, 67.88; H, 7.21; N, 6.46. Found: C, 67.71; H, 7.18; N, 6.48%.

9d: Pale yellow solid, yield 93%, m.p. 104–106 °C, $[\alpha]_D^{20}$+89.7 (*c* 1.6, CH_2Cl_2); IR (KBr)(cm^{-1}): 3354, 2889, 1742, 1591, 1438, 1217, 1077; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.12 (s, 1H, 3-OCONH), 8.45 (s, 1H, PhNHCO), 8.40–6.89 (m, 9H, ArH), 6.13 (d, *J* = 8.4 Hz, 1H, CONH), 4.92 (brs, 1H, 12*3β-H*), 4.68–4.60 (m, 1H, 3β-H), 4.15–4.11 (m, 1H, NCH), 4.03–3.94 (m, 2H, OCH_2), 3.55 (s, 3H, $COOCH_3$), 1.10 (d, *J* = 6.4 Hz, 3H, CH_3), 0.92 (s, 3H, 19-**CH**$_3$), 0.87–0.82 (m, 7H, $CH(CH_3)_2$), 0.79 (d, *J* = 6.4 Hz, 3H, 21-**CH**$_3$), 0.71 (s, 3H, 18-**CH**$_3$); HRMS(ESI) *m/z* Calcd for $C_{46}H_{64}N_4O_{10}$: 832.4622. Found: 833.4711 [M+H]$^+$. Anal. Calcd for $C_{46}H_{64}N_4O_{10}$: C, 66.32; H, 7.74; N, 6.73. Found: C, 66.20; H, 7.76; N, 6.76%.

9e: Pale yellow solid, yield 87%, m.p. 94–96 °C, $[\alpha]_D^{20}$+122.4 (*c* 1.3, CH_2Cl_2); IR (KBr)(cm^{-1}): 3348, 2948, 1738, 1590, 1468, 1221, 1090; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.14 (s, 1H, 3-OCONH), 8.46 (s, 1H, PhNHCO), 8.43–6.86 (m, 9H, ArH), 6.23 (d, *J* = 8.4 Hz, 1H, CONH), 4.91 (brs, 1H, 12*3β-H*), 4.68–4.57 (m, 1H, 3β-H), 4.25–4.18 (m, 1H, NCH), 4.07–3.98 (m, 2H, OCH_2), 3.55 (s, 3H, $COOCH_3$), 2.57–2.36 (m, 4H, CH_2CH_2S), 2.08 (s, 3H, SCH_3), 0.92 (s, 3H, 19-**CH**$_3$), 0.79 (d, *J* = 6.4 Hz, 3H, 21-**CH**$_3$), 0.70 (s, 3H, 18-**CH**$_3$); HRMS(ESI) *m/z* Calcd for $C_{45}H_{62}N_4O_{10}S$: 850.4187. Found: 851.4268 [M+H]$^+$. Anal. Calcd for $C_{45}H_{62}N_4O_{10}S$: C, 63.51; H, 7.34; N, 6.58. Found: C, 63.37; H, 7.32; N, 6.59%.

9f: Pale yellow solid, yield 86%, m.p. 115–117 °C, $[\alpha]_D^{20}$+218.2 (*c* 1.2, CH_2Cl_2); IR (KBr)(cm^{-1}): 3349, 2868, 1738, 1599, 1442, 1223, 1054; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.90 (s, 1H, indole-NH), 10.01 (s, 1H, 3-OCONH), 8.52 (s, 1H, PhNHCO), 8.40–6.90 (m, 14H, ArH), 6.22 (d, *J* = 8.4 Hz, 1H, CONH), 4.91 (brs, 1H, 12*3β-H*), 4.64–4.57 (m, 1H, 3β-H), 4.26–4.20 (m, 1H, NCH), 4.18–4.13 (m, 2H, OCH_2), 3.52 (s, 3H, $COOCH_3$), 2.94–2.85 (m, 2H, indole-CH_2), 0.94 (s, 3H, 19-CH_3), 0.77 (d, *J* = 6.4 Hz, 3H, 21-CH_3), 0.69 (s, 3H, 18-CH_3); HRMS(ESI) *m/z* Calcd for $C_{51}H_{63}N_5O_{10}$: 905.4575. Found: 906.4648 [M+H]$^+$. Anal. Calcd for $C_{51}H_{63}N_5O_{10}$: C, 67.60; H, 7.01; N, 7.73. Found: C, 67.43; H, 7.03; N, 7.70%.

Conventional method for the preparation of molecular tweezers **9a–f**
Triphosgene (0.11 g, 0.37 mmol)was added to a solution of intermediate **7** (0.29 g, 0.5 mmol) in dry CH_2Cl_2 (20 mL) and dry pyridine (0.2 mL) at room temperature. Then the solution was refluxed for 5 h. Intermediate **8** was formed and, without separation, intermediate **3** (1.5 mmol) and dry pyridine (0.2 mL) were added directly to the mixture which was refluxed for a further 5–8 h. The solvent was removed and the residue was diluted with ethyl acetate (20 mL) and washed with 10% $NaHCO_3$ (15 mL×3), brine (15 mL×3) and finally dried over anhydrous Na_2SO_4. The solvent was evaporated to give the crude product. The crude product was purified by column chromatography on silica gel H with dichloromethane/ethyl acetate as the eluant.

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