**Supporting Online Material**

**Materials and methods**

**2-Methylisoquinolinium iodide 4** was prepared following a literature procedure (SI).

**N-methylated morphine 5** was prepared by reacting morphine (0.50 g, 1.75 mmol) with methyl iodide (10 mL, 160 mmol) in 100 mL acetonitrile for 72 hrs at room temperature followed by recrystallization from acetonitrile. \(^1\text{H-NMR (500 MHz, D}_2\text{O)}: \delta 1.98(\text{d, 1H}); 2.47(\text{dt, 1H}); 2.83(\text{dd, 1H}); 3.22(\text{s, 3H}); 3.23-3.34(\text{m, 3H}); 3.30(\text{s, 3H}); 3.37(\text{t, 1H}); 3.44(\text{d, 1H}); 4.02(\text{t, 1H}); 4.27(\text{m, 1H}); 4.98(\text{dd, 1H}); 5.30(\text{dt, 1H}); 5.65(\text{dm, 1H}); 6.56(\text{d, 1H}); 6.65(\text{d, 1H}). \(^{13}\text{C-NMR (500 MHz, D}_2\text{O): \delta 23.49; 29.30; 33.32; 41.34; 50.21; 54.15; 56.08; 65.41; 69.89; 90.03; 117.90; 120.20; 122.50; 125.55; 129.01; 133.13; 138.44; 145.31. Anal. calcd. C: 50.60; H: 5.19; N: 3.28; found: C: 50.39; H: 5.19; N: 3.27.**

**Hosts 6 and 7** were isolated using preparative HPLC from DCLs that were biased towards their formation. The guest-templated library solution obtained using the procedure described in (24) was lyophilized. The solid (100 mg) was dissolved in 1.0 mL of a 20% aqueous solution of 2-propanol and filtered (0.45 μm syringe filter). Aliquots of 100 μL of this solution were chromatographed using preparative HPLC (250×10 mm 5 μm Hypersil SAX anion exchange column; mobile phases: A: 0.50 M ammonium formate in a 55:35:10 mixture of 2-propanol, acetonitrile and water; pH 3.5 (formic acid); B: water; C: 55:35:10 mixture of 2-propanol, acetonitrile and water. Gradient used for 6 (A:B:C): t=0-32 min. 5.8:34:60.2→6.9:34:59.1; t=32-35 min. 6.9:34:59.1→8.34:58; t=35-40 min. 8.34:58→70:0:30; t=40-45 min 70:0:30 t=45-48 min 70:0:30→5.8:34:60.2 ). Retention
time: 30-34 min. Gradients used for 7 (A:B:C): t=0-9 min. 13:35:52; t=9-14 min. 13:35:52→65:35:0; t=14-20 min. 65:35:0; t=20-25 min 65:35:0→13:35:52 ). Retention time: 11.5-13.5 min.

After collection of each fraction 0.1 mL formic acid was added and the solution was stored at -78°C. After combining the fractions, the solvents were removed under reduced pressure keeping the temperature below 40°C. The last traces of solvent were removed under high vacuum for 2-3 hours. Water was then added and the turbid solutions were sonicated for 1 minute and lyophilized. This procedure was repeated 3-4 times to remove all ammonium formate until a pale yellow solid was obtained. The crude host (2.0 mg) was dissolved in 1.5 mL borate buffer (10mM pH 9.0) and sonicated for 2 minutes. The resulting turbid solution was centrifuged. Hydrochloric acid (100 µl of a 2.0M solution) was added to the supernatant. The resulting suspension was centrifuged and the pellet washed with dilute hydrochloric acid (0.5 mL of a 5mM solution) and centrifuged. The solid was dried under vacuum overnight. Analyses: Host 6 (major diastereomer): ¹H-NMR (500 MHz, CD₃OD): δ 5.62(s, 2H); 5.67(s,2H); 7.11(d,2H); 7.19(d,2H); 7.24(m,4H); 7.56(s,2H); 7.61(s,2H); 7.91(s,2H); 8.07(s,1H). Anal. calcd. for 6·4H₂O: C: 53.51; H: 3.34; found: C:53.27; H: 3.39. Exact mass: calcd. for M+Na⁺ 914.9591; found: 914.9602. Host 7 (mixture of stereoisomers): ¹H-NMR (500 MHz, CD₃OD): δ 5.81 (s, 6H ddd/l1l + 2H dld/l1l ); 5.90(s, 2H dld/l1l); 5.92(s,2H dld/l1l); 6.93(m); 7.19(m); 7.37(s,6H ddd/l1l); 7.39(s,2H dld/l1l); 7.51(s,2H dld/l1l); 7.60(s,2H dld/l1l). Anal. calcd. for 7·6H₂O: C: 55.37; H: 3.61; found: C:55.49; H: 3.92. Exact mass: calcd. for M+Na⁺ 1084.9954; found: 1084.9928.
Figure S1. Part of the ESI-mass spectrum of DCLs made from (A) 1 (6.6 mM) and 2 (3.3 mM) in the presence of 4 (10 mM); and (B) 1 (10 mM) in the presence of 5 (5 mM) showing the amplified hosts as the major peaks accompanied by the host-guest complexes.
**Figure S2.** Representative example of the calorimetric determination of the equilibrium constants and thermodynamic parameters for host-guest binding showing (A) heat effects; and (B) enthalpies resulting from the titration of guest 4 into a solution of host 6 at 298K. All solutions were made in 10 mM borate buffer pH 9.0.

**References**