

Stereoselective Synthesis of a Topologically Chiral Molecule: The Trefoil Knot

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Bis-5,6-pinene bipyridine-[*m*-phenyl]^[1]

Under argon atmosphere, in a 50 mL two-necked round-bottomed flask equipped with a reflux condenser and a wisp, 400 mg (1.21 mmol) of 6'-bromo-5,6-pinene-bipyridine were dissolved in 10 mL toluene and 100 mg (0.64 mmol) of 1,4 phenylenediboronic acid were dissolved in 5 mL of EtOH. Beside, 3.18 mg of Na₂CO₃ were dissolved in 15 mL H₂O under argon too. The solution of NaCO₃ was put into the mixture with a syringe and 88 mg (0.76 mmol) of Pd(PPh₃)₄ was added as catalyst. The mixture was heated at 100°C during 20 h and the reaction was followed by TLC. After addition of 10 drops of H₂O₂ 30%, 10 mL of CH₂Cl₂ and 10 mL of H₂O was added. The aqueous phase was extracted 3x with CH₂Cl₂. After drying over MgSO₄ and evaporation of the solvent 200 mg of a white product were obtained after several purifications by chromatography (SiO₂, hexane: AcOEt: NEt₃, 5:1:0.1) (yield: 29%). ¹H NMR (300 MHz, CDCl₃): 8.90 (s, 1H, H_(a) normally triplet), 8.40-8.36 (m, 2H, H_(b), H₍₃₎), 8.23 (d, 1H, H_(3')), 7.93-7.83 (m, 2H, H₍₄₎,

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H_(c)), 7.65 (dxd, 1H, H_(4')); ³J_{4'-3}=7.5 Hz, ³J_{4'-5'}=7.5 Hz, 7.38 (d, 1H, H_(5'); ³J_{5'-4'}=7.8 Hz), 3.20 (d, 2H, H₍₈₎), ³J₈₋₇=2.7 Hz), 2.85 (dxd, 1H, H₍₅₎); ³J_{5-9exo}=5.4 Hz, ³J_{5-9endo}=5.7 Hz, 2.82-2.71 (m, 1H, H_(9exo)), 2.41-2.43 (m-sept., 1H, H₍₇₎; ³J=3 Hz), 1.44 (s, 3H, H₍₁₀₎), 1.38 (d, 1H, H_(9endo); ³J_{9endo-9exo}=9.3 Hz), 0.7 (s, 3H, H₍₁₁₎). **¹³C-NMR (300 MHz, CDCl₃):** 156.22, 156.17, 153.47, 142.34, 137.67, 133.95, 129.11, 127.65, 127.57, 125.60, 123.13, 119.89, 119.83, 119.28, 46.57, 40.29, 39.63, 32.02, 30.74, 26.12, 21.38. **HR-MS:** calc. 575.3114; found 575.3157.

3,6,9,12-tetraoxanone-14-en-1-ol^[2]

In a 250 mL flask fitted with condenser, dropping funnel and argon inlet was flushed with argon and then charged with tetraethylene glycol (30g, 0.1544 mol), grinded sodium hydroxide (8g, 0.2mol) and dry THF (100mL). Allyl bromide (18.49g, 0.153mol) in THF (50mL) was added slowly and the mixture heated to reflux for 3h. The solution was then cooled, filtered and the solvent was removed to leave a yellow oil. This oil was dissolved in water (100mL) which was first washed with toluene (2x50mL to remove the disubstituted product) and then extracted with CH₂Cl₂ (8x50mL). The organic phase was dried over MgSO₄, filtered off and evaporated to dryness. A colorless oil was obtained in 43% yield (15.78g).

NMR ¹H (CDCl₃, 300 MHz): 6.02-5.85 (m, 1H, H_(f)); 5.35-5.15 (m, 2H, H_(g)); 4.19-4.03 (m, 2H, H_(e)); 3.78-3.61 (m, 16H, H_(a,b,c,d,e,f,g)); 2.68 (br s, 1H, -OH).

Mesylate derivative^[3]

A solution of the alcohol (10g, 0.0426mol) in presence of freshly distilled triethylamine (37.34 mL, 0.268mol) was cooled to -5°C under argon. A solution of mesyl chloride (4.64mL, 0.06mol) in 20mL of anhydrous CH₂Cl₂ was added dropwise to the previous solution. The temperature was maintained below 0°C as the reaction is very exothermic. After 3h stirring at -5°C, the mixture was brought to room temperature. The reaction mixture was washed with H₂O and dried over MgSO₄. After evaporation of the solvent,

the crude product was filtered off over Al_2O_3 (eluent CH_2Cl_2) to give the mesylate derivative in 65% yield (8.8g).

NMR ^1H (CDCl_3 , 300 MHz): 6.05-5.80 (m, 1H, $\text{H}_{(\text{f})}$); 5.30-5.15 (m, 2H, $\text{H}_{(\text{g})}$); 4.21 (m, 2H, $\text{H}_{(\text{a})}$), 4.02 (m, 2H, $\text{H}_{(\text{e})}$); 3.78 (m, 2H, $\text{H}_{(\text{b})}$); 3.75-3.40 (m, 10H, $\text{H}_{(\text{b,c,d,e,f})}$); 3.08 (s, 3H, $-\text{CH}_3$).

Iodide derivative^[4]

The mesylate (5g, 0.0157mol) was dissolved in acetone (100mL) and the solution was refluxed in presence of sodium iodide (22g, 0.152mol) under argon. The reaction was monitored by TLC and was finished after 4h. After removal of the solvent, the crude mixture was taken up in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$. The organic layers were combined, dried over MgSO_4 and the solvent evaporated to give a colorless oil with good purity in 82% yield (4.42g).

NMR ^1H (CDCl_3 , 300 MHz): 6.05-5.80 (m, 1H, $\text{H}_{(\text{f})}$); 5.30-5.15 (m, 2H, $\text{H}_{(\text{g})}$); 4.02 (m, 2H, $\text{H}_{(\text{e})}$); 3.78 (t, 2H, $\text{H}_{(\text{b})}$ $^3\text{J}= 4.5$ Hz); 3.65 (m, 10H, $\text{H}_{(\text{b,c,d,e,f})}$); 3.25 (t, 2H, $\text{H}_{(\text{a})}$, $^3\text{J}=4.5$ Hz)).

Alkylation

10mL of dry THF (distilled over Na/benzophenone) were cooled down to -40°C and 0.45mL (2.35 mmol) of dry diisopropylamine (distilled over KOH) followed by 1.8mL (2.13mmol, 1.6 M in hexane) of n-BuLi were added. The solution was allowed to warm up to 0°C and then stirred for 15 min. The solution was cooled down again to -40°C and bis-5,6-pinene bipyridine-[*m*-phenyl] (410mg, 0.713mmol) dissolved in 10mL dry THF was slowly added via a syringe during 1h. The resulting dark blue solution was stirred at -40°C for 2h. Then a solution of the iodo derivative (737mg, 2.13mmol) in 10mL of dry THF was added via a syringe during 1h. This resulting reaction mixture was allowed to warm up to room temperature overnight. It was quenched with 10mL of water. After removal of THF, the water phase was extracted with CH_2Cl_2 (100mL). The combined organic phases were dried over MgSO_4 , filtered off and evaporated to yield a yellow oil,

which was purified by column chromatography (Alox, CH₂Cl₂/MeOH 1%). A pale yellow oil was isolated in 79% yield (573mg).

NMR ¹H (CDCl₃, 300 MHz): 8.90 (s, 1H, H_(a) normally triplet), 8.40-8.36 (m, 2H, H_(b), H₍₃₎), 8.23 (d, 1H, H_(3')), 7.93-7.83 (m, 2H, H₍₄₎, H_(c)), 7.65 (dxd, 1H, H_(4')); ³J_{4'-3}=7.5 Hz, ³J₄₋₅=7.5 Hz, 7.38 (d, 1H, H_(5')); ³J_{5'-4'}=7.8 Hz, 5.98-5.81 (m, 1H, H_(d)), 5.50-5.17 (m, 2H, H_(cis, trans)), 4.05 (2H, H_(e)), 3.95-3.60 (m, 14H, H₍₁₃₋₁₉₎), 3.20 (d, 1H, H₍₈₎), 2.85 (dxd, 1H, H₍₅₎); ³J_{5-9exo}=5.4 Hz, ³J_{5-9endo}=5.7 Hz, 2.80-2.55 (m, 2H, H_(12a, 9exo)), 2.41-2.43 (m-sept., 1H, H₍₇₎); ³J=3 Hz, 1.44 (s, 3H, H₍₁₀₎), 1.90-1.75 (m, 1H, H_(12b)), 1.48 (s, 3H, H₍₁₀₎), 1.38 (d, 1H, H_(9endo)); ³J_{9endo-9exo}=9.3 Hz, 0.7 (s, 3H, H₍₁₁₎). **¹³C-NMR (300 MHz, CDCl₃):** 158.94, 155.99, 154.89, 147.52, 139.91, 139.03, 136.35, 135.96, 130.65, 128.25, 125.21, 122.21, 121.39, 118.56, 118.36, 116.89, 72.49, 71.18, 71.10, 70.73, 70.63, 70.40, 69.76, 47.65, 43.83, 42.21, 40.43, 31.29, 28.53, 27.96, 26.07, 22.63.

ES-MS : *m/z* 1007.60 (M⁺), **HR-MS :** calc. 1007.58435; found 1007.58829.

Copper(I) complex with ligand

A degassed solution of copper(I) hexafluorophosphate (36.8 mg, 0.99 mmol) in acetonitrile (2mL) was added at room temperature and under argon to a solution of ligand (100mg, 0.099mmol) in acetonitrile (1mL). The resulting dark red mixture was stirred for one our. The solvent was evaporated and the residue washed with water and dried under vacuum. The pure double helix was obtained in 50% yield as a dark red solid (119mg).

NMR ¹H (CD₃CN, 300 MHz): 10.19 (s, 1H, H_(a) normally triplet), 8.10-7.98 (m, 2H, H_(b), H₍₃₎), 7.77 (d, 1H, H_(3')), ³J_{3'-4}=7.5 Hz ; 7.57 (d, 1H, H₍₄₎), ³J_{4'-3}=7.5 Hz, 7.30 (s, 1H, H_(5')), 7.18 (d, 1H, H_(c)); ³J_{c'-b'}=7.7 Hz, 6.09-5.91 (m, 1H, H_(d)), 5.40-5.21 (m, 2H, H_(cis, trans)), 4.05 (2H, H_(e)), 3.70-3.40 (m, 14H, H₍₁₃₋₁₉₎), 3.22 (d, 1H, H₍₈₎), 2.85 (dxd, 1H, H₍₅₎); ³J_{5-9exo}=5.4 Hz, ³J_{5-9endo}=5.7 Hz, 2.80-2.55 (m, 2H, H_(12a, 9exo)), 2.41-2.43 (m-sept., 1H,

H₍₇₎; ³J=3 Hz), 1.44 (s, 3H, H₍₁₀₎), 1.90-1.75 (m, 1H, H_(12b)), 1.38 (s, 3H, H₍₁₀₎), 1.15 (d, 1H, H_(9endo); ³J_{9endo-9exo}=9.3 Hz), 0.2 (s, 3H, H₍₁₁₎).

ESI-MS: *m/z* 1070.53 (M²⁺)

HR-MS : calc. 1069.50632; found 1069.51100.

Copper(I) complex of the knot

Double helix (119 mg, 0.055mmol) was dissolved in dry deuterated dichloromethane (5.5mL) at room temperature and under argon to obtain a 0.01M solution. The catalyst (Grubbs ruthenium (IV) carbene, 9 mg, 20%mol) was then added. The reaction could be monitored by ¹H NMR, the chemical shift of the cyclic olefins being strongly different from that of the terminal olefins. After 8 days, the solvent was evaporated and the crude extract was chromatographed (Alox, CH₂Cl₂/MeOH 1%) to give in 74% yield (85mg) a mixture of isomers *E* and *Z*.

NMR ¹H (CD₃CN, 300 MHz): 10.19 (s, 1H, H_(a) normally triplet), 8.10-7.98 (m, 2H, H_(b), H₍₃₎), 7.77 (d, 1H, H_(3')), ³J_{3'-4}=7.5 Hz; 7.57 (d, 1H, H₍₄₎), ³J_{4'-3'}=7.5 Hz, 7.30 (s, 1H, H_(5')), 7.18 (d, 1H, H_(c); ³J_{c'-b}=7.7 Hz), 5.72 (s, 2H, H_(olefin)). Broad signals.

ESI-MS: *m/z* 1042.50 (M²⁺)

HR-MS : calc. 1041.47971; found 1041.48283.

Reduction of the cyclic olefins of the knot

The dicopper(I) trefoil knot (85mg, 0.039mmol) was dissolved in a 1:1 mixture of CH₂Cl₂/ethanol (20mL). The catalyst (Pd/C, 5% mol in Pd) was then added. At room temperature and under vigorous stirring, the solution was maintained under a 3 bar hydrogen atmosphere for 16h. The reaction could also be monitored by ¹H NMR, since

the signal of the olefin progressively disappeared. After filtration on alumina and evaporation of the solvent, the reduced metallated knot was obtained in a quantitative yield as a dark red solid. The mass spectrum indicates a high purity of this intermediate product. No further characterization was attempted.

NMR ^1H (CD_3CN , 300 MHz): 10.19 (s, 1H, $\text{H}_{(\text{a})}$ normally triplet), 8.10-7.98 (m, 2H, $\text{H}_{(\text{b})}$, $\text{H}_{(\text{3})}$), 7.77 (d, 1H, $\text{H}_{(\text{3}')$), $^3\text{J}_{\text{3'-4}}=7.5$ Hz; 7.57 (d, 1H, $\text{H}_{(\text{4})}$), $^3\text{J}_{\text{4'-3}}=7.5$ Hz, 7.30 (s, 1H, $\text{H}_{(\text{5}')$), 7.18 (d, 1H, $\text{H}_{(\text{c})}$); $^3\text{J}_{\text{c'-b}}=7.7$ Hz). Broad signals.

ESI-MS: m/z 1038.50 (M^{2+})

Free knot

To a solution of the metallated knot (33 mg, 0.015 mmol) in a $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ mixture (1:1) was added potassium cyanide (0.5g, large excess). The mixture was stirred at room temperature for 6 hours, during which time the dark red colour of the copper(I) complex progressively disappeared. The solvent was evaporated and the residue was dissolved in dichloromethane. The crude mixture was washed 3 times with 0.1M ammonia in water, dried over MgSO_4 , and filtered to give the free knot in quantitative yield (29.46 mg, 0.015 mmol). The ^1H -NMR spectrum is quite complicated and broad signals due to a mixture of conformers in reptation, are observable.

ESI-MS: m/z 1964.22 (M^+)

Remetallation was achieved by adding a degassed solution of $\text{Cu}(\text{CH}_3\text{CN})_4.\text{PF}_6$ (11.18 mg, 0.03 mmol) in acetonitrile (10ml) to a solution of the free knot (29.46 mg, 0.015 mmol) at room temperature and under argon atmosphere. The dark red solution was stirred for 1 hour. The solvent was then evaporated and the residue was washed with water and dried under vacuum to give the knot in a quantitative yield (11 mg, 0.028 mmol).

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