Notes

Nucleophilic Cleavage of 4,5-Dihydro-3*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepinium Quaternary Salts. A Convenient Approach to New Axially Dissymmetric and Axially Asymmetric Ligands

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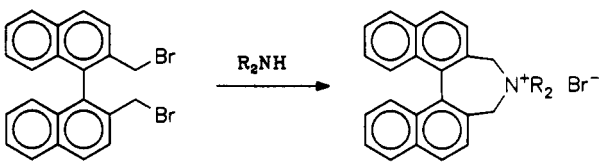
The axially dissymmetric derivatives of 2,2′-dihydroxy-, 2,2′-diphosphino-, and 2,2′-diamino-1,1′-binaphthalene have proved to be remarkably effective auxiliaries in enantioselective catalysis,[1-10] with the optical yields approaching 100% ee in several preparatively important reactions.[2,3,7-10] The synthesis of analogous ligands, in which the donor sites would be insulated from the aromatic moiety by a methylene unit and replaced eventually by other heteroatoms, presents accordingly a problem of a considerable interest.

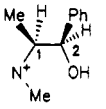
The easily accessible[11,12] 2,2′-bis(bromomethyl)-1,1′-binaphthalene (1) has been considered to be a promising building block for such purposes; however, intramolecular cyclization[11-16] involving the donor atom has been found to be a serious obstacle. Thus, in the reaction of the dibromide 1, with secondary amines, the biaminated binaphthyls are not formed,[13] with the dihydroazepinium quaternary salt being the exclusive product even when a large excess of amine is present (Scheme I).

In the present paper, we report a simple resolution of the synthetic problem, which rests on the nucleophilic cleavage of the dihydroazepinium salts (Scheme II). We have found that the quaternary salts **2–6** react under reasonably mild conditions with a surprisingly wide range of uncharged as well as charged nucleophiles involving, for example, amines, azide, malonate, mercaptide, phosphide, and selenide ions. Significantly, the benzylic carbon in **2–6** is attacked preferentially[17] in the reaction, leading to the 2,2′-bifunctional 1,1′-binaphthalenes **7–11**, in most instances in very satisfactory chemical yields.

Scheme I



1 2–6

Compound[i]	N^+R_2	Yield[ii] (%)
2	N^+Me_2	90 (44)[iii]
3		91 (53)[iv]
4		95 (45)
5		(72)
(S,1S,2R)-6		ref. 11
(R,1S,2R)-6	"	ref. 11

[i]**2–5** are racemic compounds. [ii]Isolated according to procedure A or B (procedure B in parentheses); cf. the Experimental Section. [iii]Reference 13. [iv]Reference 21.

The structures of the resulting products **7–11** were unambiguously determined from their ^1H NMR, MS, and IR spectra. The absence of configurational scrambling of the binaphthyl moiety under the experimental conditions has been inferred[19] from the formation of a single diastereoisomeric product (*S*,1*S*,2*R*)-**11** or (*R*,1*S*,2*R*)-**11** in the nucleophilic cleavage of the respective diastereoisomeric quaternary salts (*S*,1*S*,2*R*)-**6** or (*R*,1*S*,2*R*)-**6**.

Two anomalous results have been recorded during the course of the study. Firstly, the reaction of the quaternary

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(3) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597.
(4) Tomioka, K. *Synthesis* **1990**, 541.
(5) Bruner, H. *Synthesis* **1988**, 645.
(6) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.
(7) Narasaka, K. *Synthesis* **1991**, 1.
(8) Kaufmann, D.; Boese, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 545.
(9) Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187.
(10) Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *Tetrahedron Lett.* **1992**, *33*, 635.
(11) Maigrot, N.; Mazaleyrat, J. P. *Synthesis* **1985**, 317.
(12) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153.
(13) Cottineau, F.; Maigrot, N.; Mazaleyrat, J. P. *Tetrahedron Lett.* **1985**, *26*, 421.
(14) Hawkins, J. M.; Fu, G. C. *J. Org. Chem.* **1986**, *51*, 2820.
(15) Maigrot, N.; Mazaleyrat, J. P.; Welvart, T. *J. Org. Chem.* **1985**, *50*, 3916.
(16) Mazaleyrat, J. P.; Cram, J. D. *J. Am. Chem. Soc.* **1981**, *103*, 4585.
(17) To our knowledge, reaction of benzylic quaternary salts with nucleophiles has not been the subject of a systematic study, although preferential nucleophilic attack at the benzylic carbon has been noted in a few instances (see refs 13 and 18).
(18) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Wagatsuma, N.; Wakisaka, K. *Tetrahedron Lett.* **1969**, 635.
(19) Evidence concerning diastereoisomeric purity of the ligands (*S*,1*S*,2*R*)-**11** and (*R*,1*S*,2*R*)-**11** as well as (*R*,*R*)-**13** is based on the NMR spectra of the isolated products. The isolation procedure consisted of a flash chromatography or a simple extractive workup (cf. the Experimental Section). A selective loss of only one diastereoisomer under such conditions is highly improbable. During the course of revision of the manuscript we have used the (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol as a chiral shift reagent to demonstrate that the formation of the ligands **7a** and **7b** from the corresponding optically active quaternary salt **2** is enantiomerically uniform.[20] In spite of the unambiguous additional evidence, we share a reviewer's caution that "with varying nucleophiles, temperatures, and lengths of reaction times, enantiomerization (diastereoisomerization) can occur in every one of the reactions, and should be ascertained individually".

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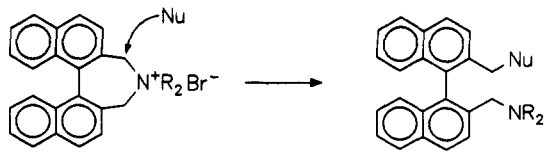
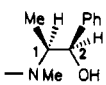
Scheme II

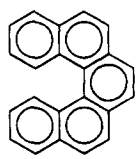


2–6 7–11

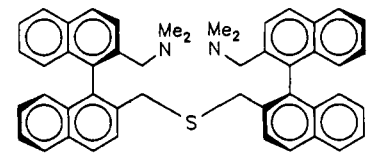
Compound[i]	$-NR_2$	-Nu	Yield[ii] (%)
7a	$-NMe_2$	-N⌒O	72
7b	"	-SBu^n	73
7c	"	$-CH(CO_2Et)_2$	41
8a	-N⌒	-N⌒O	92
8b	"	$-N_3$	87
8c	"	$-PPh_2$	41
9a	-N⌒O	-N⌒O	99
9b	"	$-N_3$	98
9c	"	-SePh	83
10	-N⌒NH	-N⌒NH	96
(S,1S,2R)-11		$-N_3$	95
(R,1S,2R)-11	"	$-N_3$	87

[i] 7a–10 are racemic compounds. [ii] Isolated; no attempt to optimize the yields has been made. For reaction conditions see the Experimental Section.

salt **2** with the strongly basic nucleophile lithium pyrrolidide (in pyrrolidine) or *n*-butyllithium (in THF) afforded, instead of the corresponding substitution product, an aromatic hydrocarbon, which could be assigned the structure of pentahelicene[20] **12**. Secondly, the reaction of the optically active quaternary salt[20] (*R*)-**2** with sodium sulfide gave, instead of the expected bidentate ligand, the tridentate ligand (*R,R*)-**13**. Interestingly, a single diastereoisomer[22] was obtained as the sole product in 89% yield. This provides more evidence[19] that diastereoisomerization does not occur during the course of the reaction.



12



(R,R)-**13**

The nucleophilic cleavage of the quaternary salts **2–6** provides a straightforward access to a new class of bi- and oligodentate binaphthyl ligands **7–11** exhibiting either axial dissymmetry (C_2 axis)[23] or axial asymmetry (C_1 axis), in dependence on identity or nonidentity of the donor groups in the 2,2′-positions. A simple synthesis of the optically pure precursors of type **2** from the racemic dibromide **1** will be reported elsewhere.[20]

(20) Stará, I. G.; Starý, I.; Závada, J. Unpublished work.
(21) Hall, D. M.; Turner, E. E. *J. Chem. Soc.* **1955**, 1242.
(22) The racemic quaternary salt yields an unseparable mixture of diastereoisomeric products.
(23) In the majority of scenarios for absolute stereochemical control, the presence of C_2 symmetry axis within the chiral auxiliary has been tacitly assumed to serve the important function of reducing the number of possible competing diastereoisomeric transition states (cf. ref 6). A comparison between akin dissymmetric and asymmetric bidentate binaphthyl ligands might shed interesting light on this assumption.

Experimental Section

General. All chemicals were of reagent grade. THF was distilled from $LiAlH_4$ before use; DMF, from P_2O_5 or calcium hydride. Ethanol was dried using sodium. Melting points were taken on a Kofler block and are uncorrected. Optical rotations were measured in chloroform with an accuracy of 0.2%. ^1H NMR spectra (200.06 MHz, FT mode) were recorded in $CDCl_3$, benzene-d_6, or DMSO-d_6 using TMS, C_6H_6, or DMSO as the internal reference, respectively. EI mass spectra were obtained at 70 eV, FAB spectra were measured in a thioglycerol/glycerol (3:1) matrix using MeOH or $CHCl_3$ as solvents. Flash chromatography was performed with silica gel Silpearl (5–40 μm, Kavalier Votice, Czechoslovakia).

Preparation of Quaternary Salts. Procedure A. A solution of racemic dibromide[11] **1** (1.0 equiv) and a secondary amine (2.0–2.1 equiv) in a mixture of benzene and acetonitrile (1:1) was stirred at 60 °C for 12 h. Removal of the solvent gave a solid residue which was digested subsequently with benzene (2 × 10 mL) and water (25 mL), filtered, washed with water (2 × 15 mL), and dried in vacuo over KOH.

Procedure B. The procedure in ref 21 was followed.

4,5-Dihydrospiro[3*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine-4,4′-morpholinium] bromide (4): yield 95% (procedure A); 45% (procedure B); mp 249–51 °C dec (water); ^1H NMR (DMSO-d_6) δ 3.35–3.51 and 3.53–3.69 (m, 4 H, $N^+CH_2CH_2O$), 3.87 (d, AB system, J = 13.3 Hz, 2 H, $ArCH_2N^+$), 3.88–4.04 and 4.18–4.33 (m, 4 H, $N^+CH_2CH_2O$), 5.09 (d, AB system, J = 13.3 Hz, 2 H, $ArCH_2N^+$), 7.33–8.31 (m, 12 H, arom); IR (KBr) 2973 ν_{as}(CH_2 of $(CH_2)_4N^+$ and $(CH_2)_2O$), 2872 ν_s(CH_2 of $(CH_2)_4N^+$ and $(CH_2)_2O$), 1124 ν_{as}(C–O–C) cm^{-1}; FAB MS m/z (relative intensity) 446 (M^+ + 1, 1.6), 366 (M^+ – Br, 100), 281 (57), 266 (35), 252 (10). Anal. Calcd for $C_{28}H_{24}BrNO\cdot 2H_2O$: C, 64.73; H, 5.89; N, 2.90. Found: C, 64.47; H, 5.63; N, 2.79.

4,5-Dihydrospiro[3*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine-4,1′-piperazinium] bromide (5): yield 72% (procedure B); mp 265–9 °C dec (water); ^1H NMR (DMSO-d_6) δ 2.68 (br s, 1 H, NH), 2.92–3.10 (m, 4 H, $N^+CH_2CH_2NH$), 3.19–3.49 (m, 4 H, $N^+CH_2CH_2NH$), 3.77 (d, AB system, J = 13.2 Hz, 1 H, $ArCH_2N^+$), 4.94 (d, AB system, J = 13.2 Hz, 1 H, $ArCH_2N^+$), 7.26–8.27 (m, 12 H, arom); IR (KBr) 3340 ν(NH), 2971 ν_{as}(CH_2 of $(CH_2)_4N^+$), 2885 ν_s(CH_2 of $(CH_2)_4N^+$) cm^{-1}; FAB MS m/z (relative intensity) 445 (M^+ + 1, 1.4), 365 (M^+ – Br, 100), 281 (32), 266 (32), 252 (9). Anal. Calcd for $C_{28}H_{25}N_2Br\cdot 2H_2O$: C, 64.87; H, 6.07; N, 5.81. Found: C, 64.71; H, 6.18; N, 5.76.

Cleavage of Quaternary Salts. 2-[(*N*,*N*-Dimethylamino)methyl]-2′-(4-morpholinylmethyl)-1,1′-binaphthyl (7a). A mixture of 100 mg (0.247 mmol) of quaternary salt[18] **2** and 1 mL of morpholine was heated at 120 °C for 3 h. The reaction mixture was then poured into water and extracted with $CHCl_3$ (3 × 10 mL). The organic layer was washed with water (2 × 10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography (pentane–ether–acetone–methanol (60:25:13:2)) to yield 73 mg (72%) of **7a** as an oil: ^1H NMR ($CDCl_3$) δ 2.09 (s, 6 H, CH_3), 2.17 (m, $W/2$ = 6.3 Hz, 4 H, NCH_2CH_2O), 2.93 and 3.05 (AB q, J_{AB} = 14.2 Hz, 2 H, benzyl H), 3.23 and 3.30 (AB q, J_{AB} = 14.4 Hz, 2 H, benzyl H), 3.56 (t, J = 4.2 Hz, 4 H, NCH_2CH_2O), 6.94–8.07 (m, 12 H, arom); IR (CCl_4) 2818 and 2771 ν_s(CH_2), 1119 ν_{as}(C–O–C) cm^{-1}; EI MS m/z (relative intensity) 410 (M^+, 23), 365 (23), 323 (25), 279 (100), 265 (27), 252 (6). Anal. Calcd for $C_{28}H_{30}N_2O$: C, 81.91; H, 7.37; N, 6.82. Found: C, 81.86; H, 7.61; N, 6.77.

2-[1-(Butylthio)methyl]-2′-[(*N*,*N*-dimethylamino)-methyl]-1,1′-binaphthyl (7b). To a mixture of 42 mg (0.374 mmol, 2.2 equiv) of potassium *tert*-butoxide and 40 μL (0.373 mmol, 2.2 equiv) of 1-butanethiol in 3 mL of absolute ethanol was added 70 mg (0.173 mmol) of quaternary salt[18] **2**. The mixture was heated at 65 °C for 2 h under argon. After removal of solvent in vacuo, flash chromatography (pentane–ether–acetone (80:10:10)) afforded 52 mg (73%) of **7b** as an oil: ^1H NMR ($CDCl_3$) δ 1.01

(m, $W/2$ = 3.0 Hz, 7 H, $CH_2CH_2CH_3$), 1.31 (s, 2 H, SCH_2), 2.07 (s, 6 H, CH_3), 2.92 (d, AB system, J = 14.4 Hz, 1 H, $ArCH_2N$), 3.41 (s, 2 H, $ArCH_2S$), 3.45 (d, AB system, J = 14.4 Hz, 1 H, $ArCH_2N$), 7.01–8.01 (m, 12 H, arom); IR (CCl_4) 2819 and 2772 ν_s(CH_3 or $(CH_3)_2N$) cm^{-1}; FAB MS m/z (relative intensity) 414 (M^+ + 1, 100), 356 (11), 313 (42), 279 (99), 267 (76), 252 (22). Anal. Calcd for $C_{28}H_{31}NS$: C, 81.31; H, 7.55; N, 3.39; S, 7.75. Found: C, 81.14; H, 7.67; N, 3.31; S, 7.84.

Diethyl [[2-[(*N*,*N*-Dimethylamino)methyl]-1,1′-binaphthyl-2′-yl]methyl]propanedioate (7c). To a mixture containing 15 mg (0.494 mmol, 2.9 equiv) of NaH (80% suspension in mineral oil) and 80 μL (0.527 mmol, 3.0 equiv) of diethyl malonate in 2 mL of DMF under argon was added a solution of 70 mg (0.173 mmol) of quaternary salt[13] **2**. After refluxing for 3 h, the mixture was poured into water (30 mL), extracted with ether (2 × 10 mL), washed with water (2 × 10 mL), and dried over anhydrous Na_2SO_4. The extract was concentrated in vacuo and purified by flash chromatography (pentane–ether–acetone (80:10:10)) to yield 34 mg (41%) of **7c** as an oil: ^1H NMR ($CDCl_3$) δ 1.03 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.13 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 2.13 (s, 6 H, NCH_3), 2.36–2.73 (m, 2 H, $ArCH_2CH$), 2.96 (d, AB system, J = 6.0 Hz, 1 H, $ArCH_2N$), 3.00 (d, AB system, J = 6.0 Hz, 1 H, $ArCH_2N$), 3.37 (dd, J = 8.0 Hz, 7.0 Hz, 1 H, EtO_2CCH), 3.90 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 4.07 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 6.76–8.11 (m, 12 H, arom); IR (CCl_4) 2819 and 2771 ν_s(CH_3 of $(CH_3)_2N$), 1752 and 1734 ν(C=O) cm^{-1}; FAB MS m/s (relative intensity) 484 (M^+ + 1, 100), 412 (21), 366 (5), 319 (10), 291 (16), 279 (94), 266 (36), 252 (10). Anal. Calcd for $C_{31}H_{33}NO_4$: C, 76.99; H, 6.88; N, 2.90. Found: C, 76.92; H, 6.64; N, 2.87.

2-(4-Morpholinylmethyl)-2′-(1-piperidinylmethyl)-1,1′-binaphthyl (8a). A procedure similar to that described for the preparation of **7a** was followed. Starting from 50 mg (0.113 mmol) of quaternary salt[21] **3** and 1 mL of morpholine, the mixture was heated for 80 min. After workup, the product was purified by flash chromatography (pentane–ether–acetone (60:25:15)) to give 47 mg (92%) of **8a** as an oil: ^1H NMR ($CDCl_3$) δ 1.20–1.55 (m, 6 H, $NCH_2CH_2CH_2CH_2CH_2$), 2.00–2.30 (m, 8 H, $NCH_2CH_2CH_2CH_2CH_2$ and NCH_2CH_2O), 3.00 (d, AB system, J = 10.3 Hz, 1 H, $ArCH_2N_{piper}$), 3.06 (d, AB system, J = 10.3 Hz, 1 H, $ArCH_2N_{piper}$), 3.25 (d, AB system, J = 14.0 Hz, 1 H, $ArCH_2N_{morph}$), 3.27 (d, AB system, J = 14.0 Hz, 1 H, $ArCH_2N_{morph}$), 3.56 (t, J = 4.5 Hz, 4 H, NCH_2CH_2O), 6.90–8.07 (m, 12 H, arom); IR (CCl_4) 2807 and 2758 ν(CH_2 of $(CH_2)_3N$), 1120 ν_{as}(C–O–C) cm^{-1}; EI MS m/z (relative intensity) 450 (M^+, 34), 365 (37), 363 (56), 280 (100), 265 (51), 252 (10). Anal. Calcd for $C_{31}H_{34}N_2O$: C, 82.63; H, 7.61; N, 6.22. Found: C, 82.51; H, 7.95; N, 6.10.

2-(Azidomethyl)-2′-(1-piperidinylmethyl)-1,1′-binaphthyl (8b). A mixture of 100 mg (0.225 mmol) of quaternary salt[20] **3** and 22 mg (0.338 mmol, 1.5 equiv) of sodium azide in 2 mL of DMF was stirred under heating at 110 °C for 2.5 h. The reaction mixture was then treated with water (20 mL) and extracted with ether (3 × 20 mL). The ethereal layer was washed with water (10 mL) and dried over anhydrous Na_2SO_4. The removal of solvent under reduced pressure left the residue which was purified by flash chromatography (petroleum ether–ether–acetone (96:2:2)) to give 80 mg (87%) of **8b** as an oil: ^1H NMR ($CDCl_3$) δ 1.18–1.53 (m, 6 H, $NCH_2CH_2CH_2CH_2CH_2$), 1.92–2.29 (m, 4 H, $NCH_2CH_2CH_2CH_2CH_2$), 3.01 (d, AB system, J = 14.2 Hz, 1 H, $ArCH_2N$), 3.15 (d, AB system, J = 14.2 Hz, 1 H, $ArCH_2N$), 4.06 (d, AB system, J = 14.2 Hz, 1 H, $ArCH_2N_3$), 4.16 (d, AB system, J = 14.2 Hz, 1 H, $ArCH_2N_3$), 6.97–8.24 (m, 12 H, arom); IR (CCl_4) 2801 and 2757 ν(CH_2 of $(CH_2)_3N$), 2099 ν_{as}(N_3) cm^{-1}; FAB MS m/z (relative intensity) 407 (M^+ + 1, 100), 366 (14), 294 (35), 280 (36), 266 (58), 252 (24); EI MS m/z (relative intensity) 378 (M^+ – N_2, 13), 364 (2), 350 (4), 294 (19), 280 (100), 265 (31), 252 (18). Anal. Calcd for $C_{27}H_{26}N_4$: C, 79.77; H, 6.45; N, 13.78. Found: C, 79.63; H, 6.68; N, 13.70.

2-[(Diphenylphosphino)methyl]-2′-(1-piperidinylmethyl)-1,1′-binaphthyl (8c). To a solution of 390 μL (2.24 mmol, 2.0 equiv) of diphenylphosphine in 2 mL of dry THF was added dropwise 930 μL (2.24 mmol, 2.0 equiv) of *n*-butyllithium (2.4 M solution in hexane) at 0 °C under argon. After being stirred for 10 min at 0 °C, the resulting orange solution was added to a stirred suspension of 500 mg (1.13 mmol) of quaternary salt[20] **3** in 5 mL of dry THF. Stirring was continued at room temperature overnight. The solvent was then removed in vacuo, and the residue was purified by flash chromatography (alumina, solvent system pentane–benzene (1:1)) to furnish the crude product. Purification by filtration through a column of alumina (eluent pentane–benzene (1:1)) gave 254 mg (41%) of **8c** as an amorphous solid: ^1H NMR (benzene-d_6) δ 0.79–1.49 (m, 6 H, $NCH_2CH_2CH_2CH_2CH_2$), 1.97–2.25 (m, 4 H, $NCH_2CH_2CH_2CH_2CH_2$), 3.18 (d, AB system, J = 14.6 Hz, 1 H, $ArCH_2N$), 3.37 (s, 2 H, $ArCH_2P$), 3.62 (d, AB system, J = 14.6 Hz, 1 H, $ArCH_2N$), 6.82–8.25 (m, 22 H, arom); IR (KBr) 2797 and 2755 ν(CH_2 of $(CH_2)_3N$), 1433 ν_{ring}(Ph of Ph_2P) cm^{-1}; FAB MS m/z (relative intensity) 550 (M^+ + 1, 15), 497 (19), 465 (71), 366 (100), 276 (48), 265 (75), 252 (32). Anal. Calcd for $C_{39}H_{36}NP$: C, 85.22; H, 6.60; N, 2.55; P, 5.63. Found: C, 85.50; H, 6.53; N, 2.52; P, 5.40.

2,2′-Bis(4-morpholinylmethyl)-1,1′-binaphthyl (9a). A stirred mixture of 100 mg (0.224 mmol) of quaternary salt **4** and 1 mL of morpholine was heated at 120 °C for 1 h. After cooling, the reaction mixture was poured into water (20 mL) and the white precipitate filtered, washed with water (10 mL), and dried in vacuo over KOH to provide **9a** in quantitative yield (101 mg): mp 168 °C (petroleum ether–chloroform); ^1H NMR ($CDCl_3$) δ 2.19 (m, $W/2$ = 12 Hz, 8 H, NCH_2CH_2O), 3.05 (d, AB system, J = 14.0 Hz, 2 H, $ArCH_2N$), 3.27 (d, AB system, J = 14.0 Hz, 2 H, $ArCH_2N$), 3.56 (t, J = 4.2 Hz, 8 H, NCH_2CH_2O), 6.93–8.02 (m, 12 H, arom); IR (CCl_4) 2810 and 2764 ν(CH_2 of $(CH_2)_3N$), 1120 ν_{as}(C–O–C) cm^{-1}; FAB MS m/z (relative intensity) 453 (M^+ + 1, 76), 366 (52), 281 (100), 266 (77), 252 (32). Anal. Calcd for $C_{30}H_{32}N_2O_2$: C, 79.61; H, 7.13; N, 6.19. Found: C, 79.59; H, 7.18; N, 6.11.

2-(Azidomethyl)-2′-(4-morpholinylmethyl)-1,1′-binaphthyl (9b). A procedure similar to that described for the preparation of **8b** was followed. Starting from 100 mg (0.224 mmol) of quaternary salt **4**, 90 mg (98%, oil) of **9b** was isolated by flash chromatography (petroleum ether–ether–acetone (90:5:5)): ^1H NMR ($CDCl_3$) δ 2.00–2.36 (m, 4 H, NCH_2CH_2O), 3.06 (d, AB system, J = 14.0 Hz, 1 H, $ArCH_2N$), 3.22 (d, AB system, J = 14.0 Hz, 1 H, $ArCH_2N$), 3.55 (m, $W/2$ = 11.0 Hz, 4 H, NCH_2CH_2O), 4.10 (s, 2 H, $ArCH_2N_3$), 6.98–8.08 (m, 12 H, arom); IR (CCl_4) 2811 and 2765 ν(CH_2 of $(CH_2)_3N$), 2099 ν_{as}(N_3), 1120 ν_{as}(C–O–C) cm^{-1}; EI MS m/z (relative intensity) 380 (M^+ – N_2, 17), 366 (1), 352 (4), 294 (27), 280 (100), 265 (32), 252 (13). Anal. Calcd for $C_{26}H_{24}N_4O$: C, 76.45; H, 5.92; N, 13.72. Found: C, 76.20; H, 6.01; N, 13.58.

2-(4-Morpholinylmethyl)-2′-[(phenylseleno)methyl]-1,1′-binaphthyl (9c). A solution of 50 mg (0.160 mmol, 1.0 equiv) of diphenyl diselenide in 1 mL of absolute ethanol under argon was treated (stirring) with 13 mg (0.397 mmol, 2.1 equiv) of sodium borohyride at room temperature for 10 min. The resulting colorless solution was then added to the suspension of 75 mg (0.168 mmol) of quaternary salt **4** in 2 mL of dry THF, and stirring was continued overnight. Solvents were removed under reduced pressure. Flash chromatography (petroleum ether–ether–acetone (85:10:5)) provided 73 mg (83%) of **9c** as an oil: ^1H NMR ($CDCl_3$) δ 2.20 (m, $W/2$ = 13.0 Hz, 4 H, NCH_2CH_2O), 3.06 (d, AB system, J = 14.5 Hz, 1 H, $ArCH_2N$), 3.36 (d, AB system, J = 14.5 Hz, 1 H, $ArCH_2N$), 3.55 (m, $W/2$ = 11.2 Hz, 4 H, NCH_2CH_2O), 3.88 (s, 2 H, $ArCH_2Se$), 6.78–8.02 (m, 17 H, arom); IR (CCl_4) 2810 and 2765 ν(CH_2 of $(CH_2)_3N$), 1579 ν_{ring}(Ph of PhSe), 1119 ν_{as}(C–O–C) cm^{-1}; EI MS m/z (relative intensity) 523 (M^+, 18), 436 (2), 366 (69), 353 (8), 314 (15), 281 (100), 266 (55), 252 (11). Anal. Calcd for $C_{32}H_{29}NOSe$: C, 73.55; H, 5.59; N, 2.68. Found: C, 73.43; H, 5.38; N, 2.64.

2,2′-Bis(1-piperazinylmethyl)-1,1′-binaphthyl (10). A mixture of 800 mg (1.66 mmol) of quaternary salt **5** (dihydrate) and 716 mg (8.31 mmol, 5.0 equiv) of piperazine was heated at 150 °C for 6 h in a sealed tube. The solid residue was crushed, treated with water (25 mL), filtered and washed with water (2 × 10 mL), taken up in refluxing benzene (80 mL), and filtered. Evaporation of solvent in vacuo gave 719 mg (96%) of **10**: mp 155–7 °C (petroleum ether–chloroform); ^1H NMR ($CDCl_3$) δ 1.84 (s, 2 H, NH), 2.16 (br s, 8 H, NCH_2CH_2NH), 2.75 (t, J = 4.7 Hz, 8 H, NCH_2CH_2NH), 3.02 (d, AB system, J = 14.2 Hz, 2 H,

ArCH_2N), 3.22 (d, AB system, J = 14.2 Hz, 2 H, ArCH_2N), 6.95–8.05 (m, 12 H, arom); IR ($CHCl_3$) 3338 ν(NH), 2817 ν_s(CH_2 of $(CH_2)_3N$) cm^{-1}; FAB MS m/z (relative intensity) 451 (M^+ + 1, 48), 365 (64), 281 (100), 279 (94), 266 (99), 252 (26). Anal. Calcd for $C_{30}H_{34}N_4$: C, 79.96; H, 7.61; N, 12.43. Found: C, 80.05; H, 7.80; N, 12.37.

(*S*,1*S*,2*R*)-2-Azido-2′-[[*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylamino]methyl]-1,1′-binaphthyl [(*S*,1*S*,2*R*)-11]. A procedure similar to that described for the preparation of **8b** was followed. Starting from 1 g (1.75 mmol) of quaternary salt[11] (*S*,1*S*,2*R*)-**6** (crystallized with 1 EtOH), 810 mg (95%, oil) of (*S*,1*S*,2*R*)-**11** was separated by flash chromatography (petroleum ether–ether–acetone (90:5:5 and then 85:5:10)): $[\alpha]^{26}_D$ −84° (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.65 (d, J = 7.0 Hz, 3 H, CCH_3), 2.06 (s, 3 H, NCH_3), 2.53–2.69 (m, 1 H, C*H*CH_3), 3.29 (d, AB system, J = 14.0 Hz, 1 H, ArCH_2N), 3.45 (d, AB system, J = 14.0 Hz, 1 H, ArCH_2N), 4.01 (d, AB system, J = 14.0 Hz, 1 H, ArCH_2N_3), 4.11 (d, AB system, J = 14.0 Hz, 1 H, ArCH_2N_3), 4.69 (br s, 1 H, Ph(OH)C*H*), 6.95–8.11 (m, 17 H, arom); IR (CCl_4) 3619 ν(OH), 2791 ν_s(CH_3 of CH_3N), 2099 ν_{as}(N_3), 1496 ν_{ring}(Ph) cm^{-1}; EI MS m/z (relative intensity) 379 (M^+ − C_7H_7O, 52), 351 (48), 294 (100), 266 (69), 252 (22). Anal. Calcd for $C_{32}H_{30}N_4O$: C, 78.98; H, 6.21; N, 11.51. Found: C, 78.75; H, 6.31; N, 11.45.

(*R*,1*S*,2*R*)-2-Azido-2′-[[*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylamino]methyl]-1,1′-binaphthyl [(*R*,1*S*,2*R*)-11]. A procedure similar to that described for the preparation of **8b** was followed except that the reaction mixture was heated for 4 h. With 1 g (1.91 mmol) of quaternary salt[11] (*R*,1*S*,2*R*)-**6** as starting material, 809 mg (87%, oil) of (*R*,1*S*,2*R*)-**11** was obtained by flash chromatography (petroleum ether–ether–acetone (80:10:10)): $[\alpha]^{26}_D$ +72° (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.56 (d, J = 6.8 Hz, 3 H, CCH_3), 2.08 (s, 3 H, NCH_3), 2.63 (dq, J = 6.8, 4.4 Hz, 1 H, C*H*CH_3), 3.18 (d, AB system, J = 13.9 Hz, 1 H, ArCH_2N), 3.44 (d, AB system, J = 13.9 Hz, 1 H, ArCH_2N), 4.00 (d, AB system, J = 14.0 Hz, 1 H, ArCH_2N_3), 4.09 (d, AB system, J = 14.0 Hz, 1 H, ArCH_2N_3), 4.61 (d, J = 4.4 Hz, 1 H, Ph(OH)C*H*), 6.98–8.08 (m, 17 H, arom); IR (CCl_4) 3619 ν(OH_{free}), 3484 ν(OH_{assoc}), 2790 ν_s(CH_3 of CH_3N), 2099 ν_{as}(N_3), 1494 ν_{ring}(Ph) cm^{-1}; EI MS m/z (relative intensity) 379 (M^+ − C_7H_7O, 45), 351 (44), 294 (100), 266 (52), 252 (23). Anal. Calcd for $C_{32}H_{30}N_4O$: C, 78.98; H, 6.21; N, 11.51. Found: C, 79.13; H, 6.08; N, 11.40.

(*R*,*R*)-Bis[[2-[(*N*,*N*-dimethylamino)methyl]-1,1′-binaphthyl-2′-yl]methyl] Sulfide [(*R*,*R*)-13]. Treatment of 300 mg (0.741 mmol) of quaternary salt[19] (*R*)-**2** in 3 mL of DMF with 534 mg (2.22 mmol, 3.0 equiv) of $Na_2S{\cdot}9H_2O$ at 100 °C for 10 min under N_2, followed by pouring into brine, yielded a precipitate which was filtered, washed with brine, and extracted with benzene (2 × 20 mL) under reflux. The benzene solution was filtered, and the solvent was evaporated in vacuo to give 225 mg (89%) of (*R*,*R*)-**13** as an amorphous solid: $[\alpha]^{20}_D$ +91° (*c* 0.27, benzene); ^1H NMR ($CDCl_3$) δ 1.98 (s, 12 H, CH_3), 2.84 (d, AB system, J = 14.2 Hz, 2 H, ArCH_2N), 3.13 (d, AB system, J = 13.9 Hz, 2 H, ArCH_2S), 3.23 (d, AB system, J = 13.9 Hz, 2 H, ArCH_2S), 3.26 (d, AB system, J = 14.2 Hz, 2 H, ArCH_2N), 6.80–8.00 (m, 24 H, arom); IR (CCl_4) 2819 and 2771 ν_s(CH_3), 676 and 669 ν_s(C–S–C) cm^{-1}; FAB MS m/z (relative intensity) 681 (M^+ + 1, 53), 638 (8), 358 (17), 324 (58), 279 (100), 266 (91), 252 (35). Anal. Calcd for $C_{48}H_{44}N_2S$: C, 84.66; H, 6.51; N, 4.11; S, 4.71. Found: C, 84.54; H, 6.70; N, 3.98; S, 4.58.

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Registry No. (±)-**1**, 64091-25-4; (±)-**2**, 97781-19-6; (*R*)-**2**, 144068-74-6; (±)-**3**, 144068-75-7; (±)-**4**, 143970-96-1; (±)-**5**, 143970-97-2; (*S*,1*S*,2*R*)-**6**, 86593-80-8; (*R*,1*S*,2*R*)-**6**, 86631-57-4; (±)-**7a**, 143970-98-3; (±)-**7b**, 143970-99-4; (±)-**7c**, 143971-00-0; (±)-**8a**, 143971-01-1; (±)-**8b**, 143971-02-2; (±)-**8c**, 143971-03-3; (±)-**9a**, 143971-04-4; (±)-**9b**, 143971-05-5; (±)-**9c**, 143971-06-6; (±)-**10**, 143971-07-7; (*S*,1*S*,2*R*)-**11**, 143971-08-8; (*R*,1*S*,2*R*)-**11**, 144068-76-8; (*R*,*R*)-**13**, 143971-09-9; $HSBu^n$, 109-79-5; $CH_2(CO_2Et)_2$, 105-53-3; Ph_2PH, 829-85-6; morpholine, 110-91-8; piperazine, 110-85-0.

Medium-Sized Cyclophanes. 24.[1] Bromination of 8-Substituted [2.2]Metaparacyclophanes

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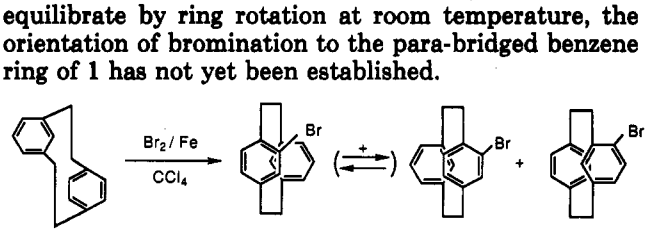
Introduction

The meta-bridged benzene ring of [2.2]metaparacyclophane (MPCP = metaparacyclophane) (**1**) has been shown to undergo conformational flipping[2-7] with a substantial energy barrier (ca. 20 kcal mol^{-1}). According to X-ray crystallographic studies of **1**,[8] the deformations of benzene rings are similar to those of the corresponding rings in [2.2]para- and -metacyclophanes, with para- and meta-bridged rings bent in a boat- and a chairlike form, respectively. The angle between the two aromatic planes defined by the carbon atoms 3, 4, 6, and 7 on one hand and 12, 13, 15, and 16, on the other, is about 13°. It should be noted that the angle between the 11,12,16-plane and 10,11-bond vector (or between 13,14,15-plane and 1,14-bond vector) is even larger than the analogous angle in [2.2]paracyclophane. The para-bridged moiety of **1** is thus more strongly tilted than those of the isomeric compound. Introduction of the substituents at the 8-position increases the strain in the molecule in comparison with the unsubstituted [2.2]MPCP (**1**); the deformation of the para-bridged benzene ring of 8-methyl[2.2]MPCP was estimated to be 15° by our recent X-ray crystallography.[9]

Cram et al. reported[10] the bromination of [2.2]MPCP with bromine in the presence of ferric bromide to afford three kinds of monobromides. However, since **2** and **3** equilibrate by ring rotation at room temperature, the orientation of bromination to the para-bridged benzene ring of **1** has not yet been established.



1 2 3 4

Thus there is substantial interest in investigating the bromination of 8-substituted [2.2]MPCPs, which might afford single monobromides because the ring rotation of the meta-bridged benzene ring is impossible at room temperature. And also in order to study the orientation of bromination of the para-bridged benzene ring in detail, we have attempted to protect the 5-position of [2.2]MPCPs by the bulky *tert*-butyl group. We report here on the bromination of 5-*tert*-butyl-8-substituted-[2.2]MPCPs (**5**).

Results and Discussion

Bromination of 5-*tert*-butyl-8-methyl[2.2]MPCP (**5a**) with 1.1 equiv of bromine in a carbon tetrachloride solution in the presence of iron powder afforded 15-bromo substitution product **6a** in 61% yield along with starting compound. No bromo substitution at the 12-position was observed. In contrast, 8-methoxy derivative **5b** exclusively afforded 12-bromo substitution product **7b** in 85% yield.

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