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OPTICALLY PURE (S)- AND (R)-4,5-DIHYDRO-3*H*-4-METHYLDINAPHTH[2,1-c;1',2'-e]AZEPINES. APPLICATION TO THE SYNTHESIS OF NEW BIDENTATE LIGANDS WITH AXIAL ASYMMETRY

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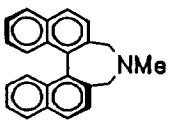
Abstract: Easily available ephedrinium salts (S,1R,2S)- and (R,1R,2S)-2 on treatment with alkoxide base afford enantiomerically pure dihydroazepines (S)- and (R)-1, respectively, in quantitative yields. Cleavage of the corresponding dihydroazepinium quaternary salts (S)- and (R)-4 with N- and S-nucleophiles provides a simple approach to a new series of 1,1'-binaphthalene ligands with two different donor groups in 2,2'-positions.

Axially dissymmetric 1,1'-binaphthyl ligands bearing two identical groups in 2,2'-positions proved to be remarkably useful in enantioselective catalysis, with optical yields close to 100% ee being obtained in several preparatively important reactions[1-7]. Somewhat paradoxically, few axially asymmetric analogues[8] with non-identical donor groups have been investigated so far, owing possibly to a lack of convenient optically active synthons and/or synthetic procedures.

In this paper, we report a simple synthesis of the optically pure (S)- and (R)-4,5-dihydro-3*H*-4-methyldinaphth[2,1-c;1',2'-e]azepines, (S)- and (R)-1 (Scheme 1), and of the corresponding quaternary salts, (S)- and (R)-2, which can serve as versatile building blocks for new optically active 1,1'-binaphthalenes with donor groups in 2,2'-positions.

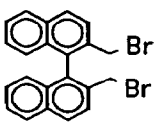
It is known that the easily accessible racemic 2,2'-bis(bromomethyl)-1,1'-binaphthalene 4 reacts smoothly with *l*-ephedrine yielding a diastereoisomeric mixture of the quaternary salts (S,1R,2S)- and (R,1R,2S)-5 which is readily separated by crystallization[9] (Scheme 2). As we have now found, treatment of the individual ephedrinium salts with alkoxide base leads quantitatively to the optically pure dihydroazepines (S)- and (R)-1 (Scheme 2)[10,11], which on alkylation afford the corresponding quaternary salts (S)- and (R)-2, respectively, again in very high yields (Table 1).

Scheme 1

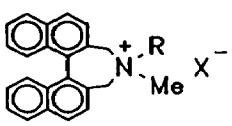


(S)-1

(R)-1

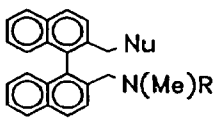


(±)-4



(S) or (R)-2

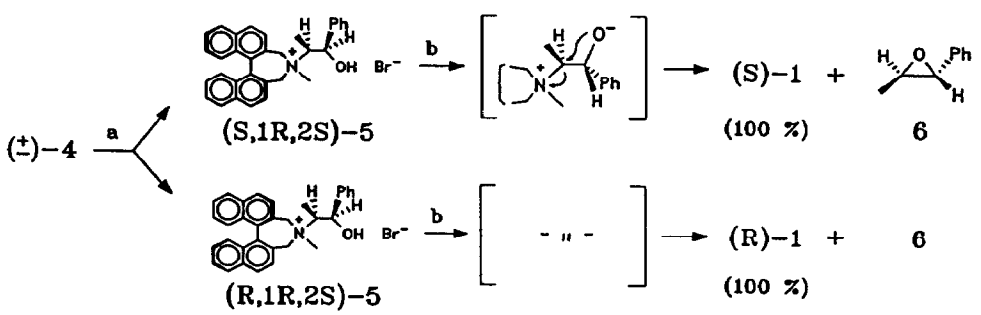
a: R=Me X= I
b: Bu^n Br
c: Pr^i I



(S) or (R)-3

a: R=Me Nu=SBu^n
b: Me N O
c: Bu^n N_3
d: Pr^i N_3

Scheme 2



a: See ref 9

b: Bu^{t}OK (1 equiv), Bu^{t}OH, 60°C, 30 min

Table 1. Preparation of Optically Active Quaternary Salts 2

educt	conditions[a]	product[b]	yield[c] (%)	$[\alpha]^{22}_D$ (c)[d]	mp (°C)
(S)-1	A	(S)-2a	99	+314 (0.42)	197-9
(R)-1	A	(R)-2a	99	-315 (0.41)	197-200
(S)-1	B	(S)-2b	94	+268 (0.51)	178-81
(S)-1	C	(S)-2c	85	+261 (0.94)	253-6 dec

[a]A, MeI (1.0 equiv), benzene, rt, overnight; B, Bu^{n}Br (2.0 equiv), benzene, reflux, 6 h; C, Pr^{i}I (5.0 equiv), benzene, reflux, 15 h. [b]See ref 18 for physical data. [c]Isolated. [d]In DMSO.

Retrosynthetic analysis suggests several alternatives for transformation of the compound 4 into 2,2'-bifunctional 1,1'-binaphthalenes. As we already pointed out elsewhere[12], racemic quaternary salts 2 react with a variety of nucleophiles (e.g. amines, azide, malonate, mercaptide, phosphide, and selenide) preferentially at the benzylic carbon affording the corresponding 2,2'-disubstituted 1,1'-binaphthalenes 3 in good chemical yields. Viability of this procedure for the preparation of the optically active[11] derivatives (S)- and (R)-3 has now been examined and some successfull examples are recorded in Table 2.

Table 2. Cleavage of Quaternary Salts 2 with Nucleophiles

educt	conditions[a]	product[b]	yield[c] (%)	$[\alpha]^{22}_D$ (c)
(R)-2a	A	(R)-3a	78	+117 (0.42)[d]
(R)-2a	B	(R)-3b	83	+ 69 (0.27)[e]
(S)-2b	C	(S)-3c	64	- 87 (0.55)[e]
(S)-2c	C	(S)-3d	94	- 94 (0.28)[e]

[a] A, Bu^nSH (2.2 equiv), Bu^tOK (2.2 equiv), EtOH, 65°C, 2 h; B, morpholine (excess), 120°C, 3 h; C, NaN_3 (1.5 equiv), DMF, 120°C, 1 h. [b] See ref 18 for physical data. [c] Isolated. [d] In benzene. [e] In $CHCl_3$.

In this way, a straightforward access to a new series of optically active 1,1'-binaphthalene bidentate ligands with two different donor groups has been provided.

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References and Notes

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8. According to a customary stereochemical analysis, axially dissymmetric bidentate ligands (C_2 symmetry) are expected to be more effective in reducing the number of possible diastereoisomeric transition states than the corresponding axially asymmetric analogues (C_1 symmetry)[13]. In practice, however, bidentate ligands with identical donor groups are often less effective than those bearing two different donor groups[3,4,14-16].
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10. The accompanying epoxide 6 has been identified by a comparison with an authentic sample, cf. ref 17.
11. Optical purity of compounds (S)-1, (R)-1, (R)-3a, and (R)-3b has been confirmed by NMR using (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)-ethanol in $CDCl_3$. The absence of configurational scrambling in azide anion cleavage of dihydroazepinium salts has been proved earlier[12].

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18. Physical Data for New Compounds:

(S)-1: mp 151-3°C, $[\alpha]^{22}_D$ +446 (c 0.47, DMSO). ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.26 (s, 3 H, CH_3), 2.94 and 3.60 (AB q, *J*=12.1 Hz, 4 H, ArCH_2N), 7.23-8.10 (m, 12 H, arom). IR (KBr) 2792 $\nu_s(CH_3)$ cm^{-1}. EI MS *m/z* (rel. inten.) 309 (M^+, 37), 294 (6), 266 (100), 252 (7).

(R)-1: mp 151.5-152.5°C, $[\alpha]^{22}_D$ -445 (c 0.46, DMSO).

(S)-2a: ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.13 (s, 6 H, 2x CH_3), 3.92 and 4.57 (AB q, *J*=13.2 Hz, 4 H, 2x ArCH_2N^+), 7.29-8.32 (m, 12 H, arom). IR (KBr) 2999 $\nu_{as}(CH_3)$, 1473 and 1466 $\delta_{as}(CH_3)$ cm^{-1}. FAB MS (thioglycerol/glycerol (3:1) matrix) *m/z* (rel. inten.) 324 (M^+-I, 100), 281 (29), 266 (12), 252 (4).

(S)-2b: ^{1}H NMR (200 MHz, DMSO-d_6) δ 0.94 (t, *J*=7.0 Hz, 3 H, CH_2-CH_3), 1.22-1.43 (m, 2 H, CH_2-CH_3), 1.63-2.03 (m, 2 H, CH_2-CH_2-CH_3), 3.08 (s, 3 H, N^+-CH_3), 3.15-3.51 (m, overlaped by signal of water from DMSO-d_6, 2 H, N^+-CH_2-CH_2), 3.87 and 4.63 (AB q, *J*=13.1 Hz, 2 H, ArCH_2N^+), 3.91 and 4.63 (AB q, *J*=13.1 Hz, 2 H, ArCH_2N^+), 7.22-8.35 (m, 12 H, arom). IR (KBr) 3003 $\nu_{as}(CH_3$ of $CH_3N^+)$, 1370 $\delta_s(CH_3$ of $Bu^n)$ cm^{-1}. FAB MS (thioglycerol/glycerol (3:1) matrix) *m/z* (rel. inten.) 366 (M^+-Br, 100), 308 (2), 281 (15), 266 (11), 252 (2).

(S)-2c: ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.35 (d, *J*=6.1 Hz, 3 H, CH-CH_3), 1.62 (d, *J*=6.1 Hz, 3 H, CH-CH_3), 2.88 (s, 3 H, N^+-CH_3), 3.49-3.67 (m, 1 H, CH_3-CH-CH_3), 3.71 and 4.78 (AB q, *J*=13.5 Hz, 2 H, ArCH_2N^+), 3.90 and 4.63 (AB q, *J*=12.5 Hz, 2 H, ArCH_2N^+), 7.20-8.40 (m, 12 H, arom). IR (KBr) 3005 $\nu_{as}(CH_3$ of $CH_3N^+)$, 1387 and 1369 $\delta_s(CH_3$ of $Pr^i)$ cm^{-1}. FAB MS (thioglycerol/glycerol (3:1) matrix) *m/z* (rel. inten.) 352 (M^+-I, 100), 308 (3), 281 (26), 266 (14), 252 (3).

(R)-3a: ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 1.01 (s, 7 H, $-CH_2$-CH_2-CH_3), 1.31 (s, 2 H, SCH_2-CH_2), 2.08 (s, 6 H, 2x CH_3), 2.93 and 3.46 (AB q, *J*=14.5 Hz, 2 H, ArCH_2N), 3.41 (s, 2 H, ArCH_2S), 7.00-8.00 (m, 12 H, arom). IR (CCl_4) 2819 and 2772 $\nu_s(CH_3$ of $(CH_3)_2N)$ cm^{-1}. FAB MS (thioglycerol/glycerol (3:1) matrix) *m/z* (rel. inten.) 414 (M^++1, 100), 356 (10), 313 (45), 279 (97), 267 (75), 252 (20).

(R)-3b: ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 2.06 (s, 6 H, 2x CH_3), 2.19 (m, *W/2*=11.5 Hz, 4 H, NCH_2CH_2O), 2.93 and 3.05 (AB q, *J*=14.2 Hz, 2 H, CH_2-benzyl), 3.23 and 3.30 (AB q, *J*=14.4 Hz, 2 H, CH_2-benzyl), 3.56 (t, *J*=4.5 Hz, 4 H, NCH_2CH_2O), 6.91-8.02 (m, 12 H, arom). IR (CCl_4) 2818 and 2771 $\nu_s(CH_3)$, 1119 $\nu_{as}(C$-O-$C)$ cm^{-1}. EI MS *m/z* (rel. inten.) 410 (M^+, 20), 365 (22), 323 (25), 279 (100), 265 (25), 252 (5).

(S)-3c: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.81 (t, *J*=6.8 Hz, 3 H, CH_2-CH_3), 1.07-1.34 (m, 4 H, CH_2-CH_2-CH_3), 1.99-2.28 (m, 2 H, N-CH_2-CH_2), 2.00 (s, 3 H, N-CH_3), 3.00 and 3.25 (AB q, *J*=14.0 Hz, 2 H, ArCH_2N), 4.08 (s, 2 H, ArCH_2N_3), 6.95-8.08 (m, 12 H, arom). IR (CCl_4) 2791 $\nu_s(CH_3$ of $CH_3N)$, 2099 $\nu_{as}(N_3)$, 1378 $\delta_s(CH_3$ of $Bu^n)$ cm^{-1}. EI MS *m/z* (rel. inten.) 407 (M^+-1, 1.6), 393 (1.1), 380 (24), 365 (13), 352 (7), 323 (5), 294 (100), 280 (99), 266 (95), 252 (23).

(S)-3d: ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 0.70 (d, *J*=6.6 Hz, 3 H, CH-CH_3), 0.75 (d, *J*=6.6 Hz, 3 H, CH-CH_3), 1.99 (s, 3 H, N-CH_3), 2.49 -2.71 (m, 1 H, CH-CH_3), 3.09 and 3.30 (AB q, *J*=14.0 Hz, 2 H, ArCH_2N), 4.09 (d, *J*=1.4 Hz, 2 H, ArCH_2N_3), 6.98-8.13 (m, 12 H, arom). IR (CCl_4) 2789 $\nu_s(CH_3$ of $CH_3N)$, 2099 $\nu_{as}(N_3)$, 1381 and 1362 $\delta_s(CH_3$ of $Pr^i)$ cm^{-1}. FAB MS (glycerol/TFA matrix) *m/z* (rel. inten.) 395 (M^++1, 100), 352 (4), 351 (4), 323 (7), 308 (7), 294 (53), 280 (26), 266 (53), 252 (41).