Synthesis of planar chiral ferrocene alcohols as potential dendrimer cores

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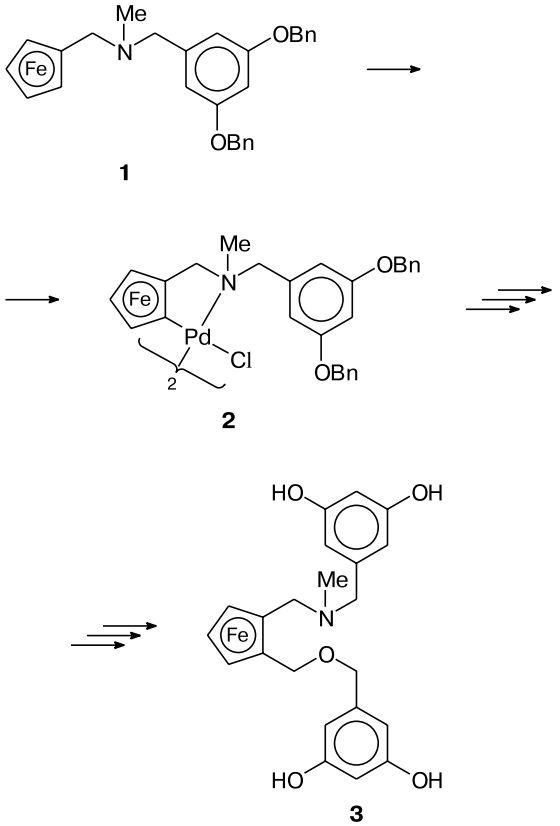
Planar chiral compounds, 1-hydroxymethyl-2-methylferrocene and new 3-(2-hydroxymethylferrocenyl)propanol, were synthesized to be used as dendrimer cores. The ethers of these compounds, namely, 1-(benzyloxymethyl)-2-methylferrocene and 2-(benzyloxymethyl)-1-(benzyloxypropyl)ferrocene, can be regarded as zero-generation Freche type dendrimers.

Key words: ferrocenes, planar chirality, Freche type dendrimers, palladacycles.

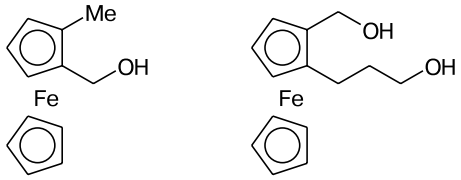
In the previous study,[1] we described the synthesis of ferrocenic amine **1** (Scheme 1), which was meant for the preparation of the optically active core of dendrimer **3** containing a planar chiral 1,2-disubstituted ferrocene.

Scheme 1



The cyclopalladation of amine **1**, which already contains a Freche dendrone fragment, was planned as the key stage of this synthesis. However, we could not obtain the desired cyclopalladation product **2** in a sufficiently pure state. The reaction gave mixtures containing apparently both cyclopalladation products of the ferrocene and aryl rings and L_2PdCl_4 type complexes, and further work along this line was considered inappropriate.

In this work we propose a different route to dendrimers based on 1,2-disubstituted planar chiral ferrocenes with one (**4**) or two (**5**) hydroxy groups, which can be converted into ethers.



The reactions of these compounds with the bromides of Freche dendrones of different generations[2] in the presence of sodium hydride should result in dendrimers with one or two branches and with a planar-chiral ferrocene as the core. To evaluate this possibility and to determine the stability of the resulting ethers, we carried out the model reaction between ferrocenylmethanol and 2-fluorobenzyl chloride (Scheme 2).

Ether **6** was formed in a high yield (82%) and was fairly stable. A 3 : 1 THF—DMF mixture proved to be the solvent of choice.

The favorable outcome of the test reaction allowed us to proceed to the synthesis of target compounds **4** and **5**. The palladium dimer **7**, whose synthesis is well developed

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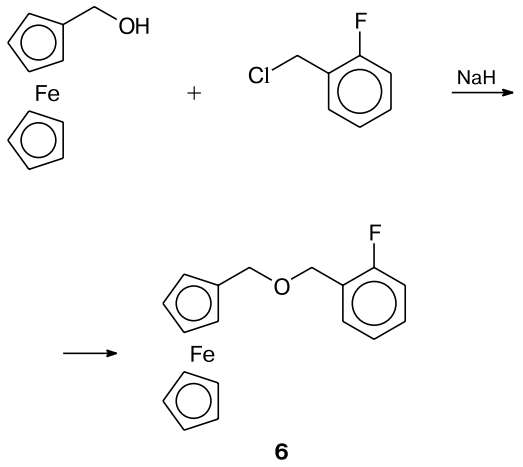
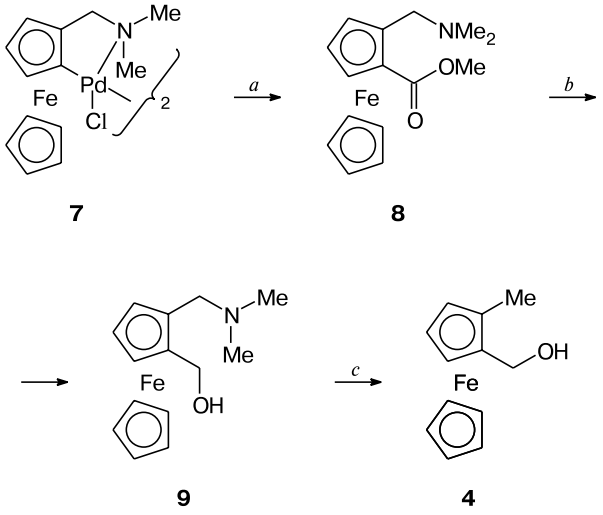
Scheme 2



6

for both racemic and scalemic forms,[3] served as the key compound in the synthesis. Alcohol **4** has been known previously;[4] however, in this study we prepared it by a different method (Scheme 3).

Scheme 3



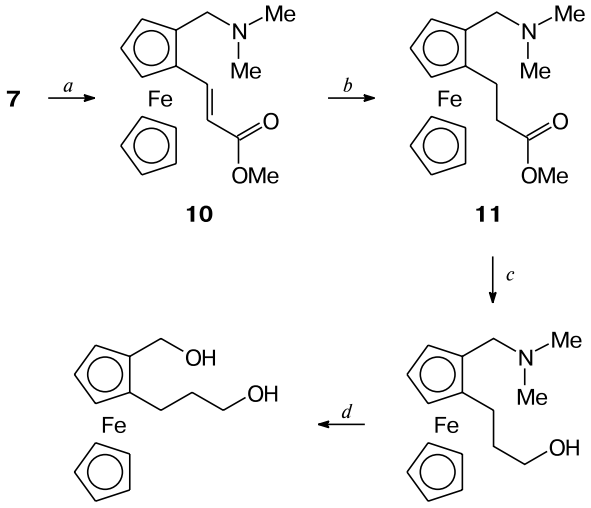
7 **8** **9** **4**

Reagents and conditions: *a*. CO, MeOH, C_6H_6; *b*. $LiAlH_4$, THF; *c*. 1) MeI, 2) $NaBH_4$, MeCN, 80 °C.

It should be emphasized that, according to our synthetic route, compound **4** is formed upon the transformation of the dimethylaminomethyl group into methyl, while in the method developed previously,[4] palladium was replaced by a methyl group. Thus, when working with optically active material, both enantiomers **4** and then two enantiomeric series of dendrimers can be obtained from the same precursor **7**.

Unlike alcohol **4**, diol **5** has not been prepared previously. We synthesized it from the same dimer **7**. The reaction of **7** with methyl acrylate followed by the reduction of, first, the double bond and, second, the ester group gave amino alcohol **12** and, after hydrolysis of the intermediate ammonium salt, diol **5** (Scheme 4).

Scheme 4

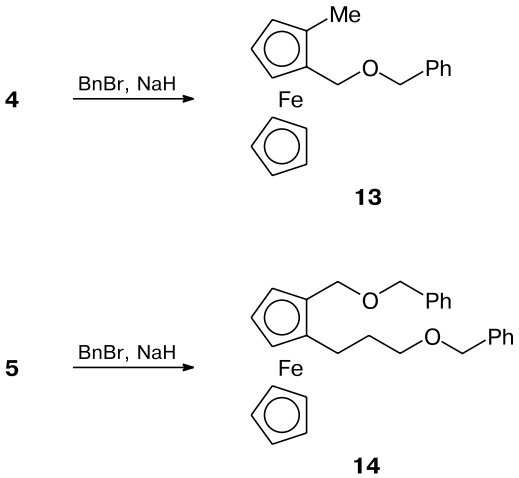


10 **11** **5** **12**

Reagents: *a*. CH_2=CHCOOMe, Et_3N, C_6H_5Me; *b*. H_2, 5% Pd/C, MeOH; *c*. $LiAlH_4$, THF; *d*. 1) MeI, 2) NaOH, H_2O.

The double bond in compound **10** was reduced in two ways: by catalytic hydrogenation at room temperature at a moderate hydrogen pressure and by catalytic reduction with heating using ammonium formate as the source of hydrogen.[5] Both methods furnish the desired product **11** in a high yield; however, the possibility of addition of two H atoms in the autoclave-free version seems fairly attractive.

Scheme 5



13 **14**

In this work both planar-chiral alcohols **4** and **5** were obtained as racemates. In attempted synthesis of dendrimers based on them, they were made to react with benzyl bromide in the presence of NaH (Scheme 5). This gave ethers **13** and **14**, which are zero-generation dendrimers. This result suggests that higher-generation dendrimers, including optically active ones, could be prepared in the future based on ferrocene alcohols **4** and **5**.

Experimental

^{1}H NMR spectra were recorded on a Bruker AMX-400-ST instrument.

Dimer **7**[3] and ferrocenylmethanol[6] were synthesized by known procedures. The solvents were preliminarily dehydrated by standard procedures.

(2-Fluorobenzyloxy)methylferrocene (6). Sodium hydride (0.18 g, 4.5 mmol) as a 60% dispersion in mineral oil was added to a solution of ferrocenylmethanol (0.70 g, 3.2 mmol) and 2-fluorobenzyl chloride (0.54 mL, 4.5 mmol) in THF (30 mL) and DMF (5 mL). The mixture was stirred for ~24 h, carefully diluted with water, extracted with ether, dried with Na_2SO_4, concentrated, and chromatographed on SiO_2 (hexane : AcOEt = (100 : 0)—(90 : 10)) to give 0.85 g (82%) of ether **6**, yellow oil. Found (%): C, 66.69; H, 5.29. $C_{18}H_{17}FFeO$. Calculated (%): C, 66.95; H, 5.21. ^{1}H NMR ($CDCl_3$), δ: 4.19 (s, 5 H, C_5H_5); 4.21, 4.31 (both m, 2 H each, C_5H_4); 4.34, 4.58 (both s, 2 H each, 2 CH_2); 7.04, 7.12, 7.27, 7.42 (all m, 1 H each, C_6H_4).

2-Methylferrocenylmethanol (4) (see Ref. 4). Carbon monoxide was passed for 3 h through a stirred solution of palladium dimer **7** (3.44 g, 9 mmol) in a benzene—MeOH mixture (4 : 1) (60 mL), and the mixture was filtered and concentrated. The residue was dissolved in AcOEt, washed with water and a $NaHCO_3$ solution, dried with Na_2SO_4, and concentrated to give ester **8** (2.16 g, 7.2 mmol, 80%) as an orange oil. The product was dissolved in THF (30 mL) and added dropwise to a suspension of $LiAlH_4$ (0.22 g, 5.8 mmol) in THF (30 mL) stirred at 0 °C. The cooling was removed, the mixture was stirred at room temperature for 4 h and cooled with ice. Water (20 mL) and then 15 *N* aqueous NaOH (20 mL) were added, the organic layer was separated, the aqueous layer was extracted with ether, and the combined organic fractions were washed with water, dried with Na_2SO_4, and concentrated to give amino alcohol **9** (1.8 g, 6.8 mmol, 92%) as a yellow oil. At 0 °C, MeI (1 mL) was added dropwise to its solution in acetone (5 mL), the mixture was stirred for 30 min, ether (50 mL) was added, and the precipitate was filtered off, washed with ether, dried, and dissolved in MeCN (30 mL). Sodium tetrafluoroborate (1 g, 13.5 mmol) was added, the mixture was refluxed for 4 h, diluted with water, and extracted with ether, and the extract was washed with water, dried with Na_2SO_4, and concentrated. The residue was chromatographed on SiO_2 (hexane : AcOEt = 100 : 1→50 : 50→0 : 100) to give compound **4** (1 g, 66%) as a yellow powder, m.p. 44—46 °C. Found (%): C, 63.11; H, 6.42; Fe, 23.92. $C_{12}H_{14}FeO$. Calculated (%): C, 62.64; H, 6.13; Fe, 24.27. ^{1}H NMR ($CDCl_3$), δ: 1.62 (br.s, 1 H, OH); 2.07 (s, 3 H, CH_3); 4.09 (m, 1 H, C_5H_3); 4.14 (s, 5 H, C_5H_5); 4.19, 4.21 (both m, 1 H each, C_5H_3); 4.44 (dd, 2 H, CH_2, J_1 = 1.18 Hz, J_2 = 2.60 Hz).

Methyl 3-(2-dimethylaminomethylferrocenyl)acrylate (10). A solution of palladium dimer **7** (10 g, 26 mmol), methyl acrylate (2.8 mL, 31 mmol), and triethylamine (5.4 mL, 39 mmol) in toluene (100 mL) was refluxed for 6 h and filtered. The filtrate was washed with water and a solution of $NaHCO_3$, dried with Na_2SO_4, concentrated, chromatographed on SiO_2 (hexane : AcOEt = (100 : 0)—(50 : 50), then hexane : triethylamine = (80 : 20)—(50 : 50)), and concentrated to give 5 g (59%) of ester **10** as a dark-cherry oil. Found (%): C, 62.84; H, 6.22; Fe, 16.63. $C_{17}H_{21}FeNO_2$. Calculated (%): C, 62.40; H, 6.47; Fe, 17.07. ^{1}H NMR ($CDCl_3$), δ: 2.16 (s, 6 H, NMe_2); 3.26, 3.52 (dd, 1 H each, CH_2N, J_1 = 1.29 Hz, J_2 = 7.56 Hz); 3.76 (s, 3 H, Me); 4.08 (s, 5 H, C_5H_5); 4.38, 4.42, 4.55 (all m, 1 H each, C_5H_3); 6.10 and 7.69 (both d, 1 H each, =CH, J = 15.6 Hz).

Methyl 3-(2-dimethylaminomethylferrocenyl)propionate (11).
A. A mixture of ester **10** (5 g, 15.3 mmol) and 5% Pd/C (1 g) in MeOH (50 mL) was hydrogenated in an autoclave for 6 h (10 atm, 20 °C), filtered, concentrated, and chromatographed on SiO_2 (toluene : AcOEt = (100 : 0)—(50 : 50), then toluene : triethylamine = (100 : 0)—(80 : 20)) to give compound **11** (4.7 g, 93%) as an orange oil.

B. To a solution of ester **10** (2.11 g, 6.5 mmol) and ammonium formate (1.6 g, 25.4 mmol) in MeOH (50 mL), was added 5% Pd/C (0.4 g). The mixture was refluxed with stirring for 6 h, filtered, concentrated, and chromatographed on SiO_2 (hexane : triethylamine = (100 : 0)—(80 : 20)) to give 1.6 g (75%) of compound **11**. Found (%): C, 62.50; H, 7.06; N, 4.21; Fe, 16.95. $C_{17}H_{23}FeNO_2$. Calculated (%): C, 62.02; H, 7.04; N, 4.25; Fe, 16.96. ^{1}H NMR ($CDCl_3$), δ: 2.14 (s, 6 H, NMe_2); 2.50—2.75 (m, 4 H, 2 CH_2); 3.10, 3.52 (dd, 1 H each, CH_2N, J_1 = 1.34 Hz, J_2 = 9.32 Hz); 3.69 (s, 3 H, Me); 4.02 (m, 7 H, C_5H_5 + C_5H_3); 4.13 (m, 1 H, C_5H_3).

3-(2-Dimethylaminomethylferrocenyl)propanol (12). A solution of ester **11** (4.7 g, 14.3 mmol) in THF (30 mL) was added dropwise with stirring at 0 °C to a suspension of $LiAlH_4$ (0.46 g, 12.2 mmol) in THF (30 mL), cooling was removed, and the mixture was stirred at room temperature for 4 h and cooled with ice. Water (25 mL) and 15 *N* aqueous NaOH (25 mL) were successively added dropwise, the organic layer was separated, the aqueous layer was extracted with ether, and the combined organic fractions were washed with water, dried with Na_2SO_4, and concentrated to give compound **12** (4.26 g, 90%) as a yellow oil. Found (%): C, 63.96; H, 7.64; N, 4.43; Fe, 18.59. $C_{16}H_{23}FeNO$. Calculated (%): C, 63.80; H, 7.70; N, 4.65; Fe, 18.54. ^{1}H NMR ($CDCl_3$), δ: 1.40 (m, 1 H, CH); 1.50—2.00 (m + br.s, 2 H, CH + OH); 2.19 (s, 6 H, NMe_2); 2.59 (m, 2 H, 2 CH); 2.73 (dd, 1 H, CH_2N, J_1 = 1.26 Hz, J_2 = 31.44 Hz); 3.05, 3.34 (both m, 1 H each, 2 CH); 3.78 (dd, 1 H, CH_2N, J_1 = 1.26 Hz, J_2 = 31.44 Hz); 4.00—4.10 (s + m, 8 H, C_5H_5 + C_5H_3).

3-(2-Hydroxymethylferrocenyl)propanol (5). Methyl iodide (4 mL) was added dropwise with stirring at 0 °C to a solution of alcohol **12** (4.26 g, 14.1 mmol) in acetone (10 mL), the mixture was stirred for 30 min, ether (100 mL) was added, and the precipitate was filtered off, washed with ether, dried, and dissolved in 4% NaOH (50 mL). The solution was refluxed for 6 h, extracted with ether, dried with Na_2SO_4, concentrated, and chromatographed on SiO_2 (hexane : AcOEt = 100 : 1→50 : 50→0 : 100) to give compound **5** (2.7 g, 70%) as a yellow oil. Found (%): C, 62.53; H, 6.89; Fe, 19.07. $C_{14}H_{18}FeO_2 \cdot 0.2C_6H_{14}$. Calculated (%): C, 62.66; H, 7.20; Fe, 19.17. ^{1}H NMR ($CDCl_3$), δ: 1.58 (m, 1 H, CH); 1.67—1.90, 2.33—2.90 (m + br.s, 2 H each, CH + OH); 3.38—3.62 (m, 2 H,

CH_2); 4.04—4.20 (s + m, 8 H, C_5H_5 + C_5H_3); 4.26, 4.50 (dd, 1 H each, $FcCH_2O$, J_1 = 1.20 Hz, J_2 = 7.32 Hz).

1-(Benzyloxymethyl)-2-methylferrocene (13). Sodium hydride (0.1 g, 2.5 mmol) in mineral oil (60%) was added to a solution of alcohol **1** (0.23 g, 1 mmol) and benzyl bromide (0.17 g, 1 mmol) in anhydrous THF (6 mL) and anhydrous DMF (2 mL), the mixture was stirred for 24 h, more alcohol **1** (0.05 g) and NaH (0.03 g) were added, and the mixture was stirred for an additional 2 h, carefully diluted with water, and extracted with ether. The extract was dried with Na_2SO_4, concentrated, chromatographed on SiO_2 (hexane : AcOEt = (100 : 0)—(90 : 10)), and concentrated to give ether **13** (0.26 g, 81%) as a yellow oil. Found (%): C, 71.30; H, 6.23; Fe, 17.26. $C_{19}H_{20}FeO$. Calculated (%): C, 71.27; H, 6.30; Fe, 17.44. ^{1}H NMR ($CDCl_3$), δ: 2.01 (s, 3 H, CH_3); 4.02 (s + m, 6 H, C_5H_5 + C_5H_3); 4.11, 4.16 (both m, 1 H each, C_5H_3); 4.26 (dd, 1 H, CH_2, J_1 = 1.11 Hz, J_2 = 6.66 Hz); 4.47 (dd, 1 H, CH_2, J_1 = 1.17 Hz, J_2 = 2.11 Hz); 4.48 (dd, 1 H, CH_2, J_1 = 1.11 Hz, J_2 = 6.66 Hz); 4.54 (dd, 1 H, CH_2, J_1 = 1.17 Hz, J_2 = 2.11 Hz); 7.25—7.39 (m, 5 H, Ph).

2-(Benzyloxymethyl)-1-(3-benzyloxypropyl)ferrocene (14). Sodium hydride (0.20 g, 5 mmol) in mineral oil (60%) was added to a solution of diol **5** (0.27 g, 1 mmol) and benzyl bromide (0.34 g, 2 mmol) in THF (9 mL) and DMF (3 mL). The mixture was stirred for 24 h, more diol **5** (0.05 g) and NaH (0.05 g) were added, and the mixture was stirred for 2 h, carefully diluted with water, extracted with ether, dried with Na_2SO_4, concentrated, chromatographed on SiO_2 (hexane : AcOEt = (100 : 0)—(90 : 10)), and concentrated to give diether **14** (0.28 g, 62%) as a yellow oil. Found (%): C, 74.23; H, 6.54; Fe, 11.49. $C_{28}H_{30}FeO_2$. Calculated (%): C, 74.01; H, 6.65; Fe, 12.29. ^{1}H NMR ($CDCl_3$), δ: 1.73—1.98 (m, 2 H, CH_2); 2.46 (t, 2 H, CH_2, J = 0.78 Hz); 3.51 (t, 2 H, CH_2, J = 0.65 Hz); 4.05 (s + m, 6 H, C_5H_5 + C_5H_3); 4.12 (m, 1 H, C_5H_3); 4.17—4.27 (m, 2 H, C_5H_3 + $FcCH_3$); 4.43—4.60 (m, 5 H, 2 $PhCH_2O$ + $FcCH_3$); 7.24—7.42 (m, 10 H, Ph).

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References

1. N. S. Khrushcheva and V. I. Sokolov, *Izv. Akad. Nauk. Ser. Khim.*, 2004, 794 [*Russ. Chem. Bull.*, *Int. Ed.*, 2004, **53**, 830].
2. C. J. Hawker and J. M. J. Frechet, *J. Am. Chem. Soc.*, 1990, **112**, 7638.
3. V. I. Sokolov, L. L. Troitskaya, and O. A. Reutov, *J. Organomet. Chem.*, 1979, **182**, 537.
4. V. I. Sokolov, L. L. Troitskaya, L. A. Bulygina, P. V. Petrovskii, *Metallorgan. Khim.*, 1989, **2**, 356 [*Organomet. Chem. USSR*, 1989, **2** (Engl. Transl.)].
5. S. Ram and R. E. Ehrenkaufer, *Synthesis*, 1988, 91.
6. C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, 1957, **22**, 906.

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