



Reactions of 4,4'-difluoro-biphenyl-3,3'-dicarboxylic acid dimethyl ester with amino alcohols. A convenient route to biphenyl tetra-alcohols

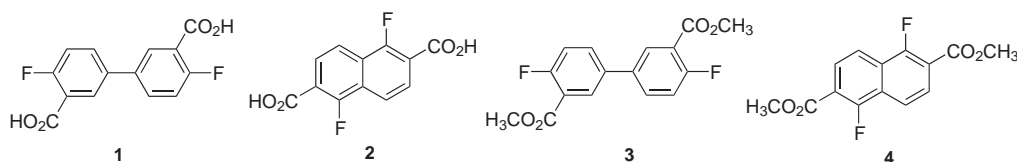
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Abstract—An efficient method for the preparation of biphenyl tetraols **10–15** and **18** is described. These poly-functional products should prove valuable as scaffolds for combinatorial library construction and as core structural units for dendrimer synthesis. © 2001 Published by Elsevier Science Ltd.

Over the past decade, poly-functional molecules with flexible or rigid core structures have attracted increasing attention from synthetic chemists due to their potential as candidates for the studies of dendrimer synthesis and combinatorial library construction. For example, rigid tetrafunctional xanthene and cubane substrates are used as scaffolds in the construction of combinatorial libraries for screening biologically active small organic molecules,¹ while the flexible tetraol amine units serve as the building blocks for the synthesis of dendrimers of relatively high molecular weight in the search for new functional materials.²



Recently we have developed a convenient procedure to prepare tri- and tetra-functional biphenyl and naphthalene compounds, such as **1** and **2**, by utilization of the excellent ability of fluorine to direct *ortho*-metallation.³ By using this method, a large number of monomeric and oligomeric naphtho- and biaryl-fused 1,8-diaza-14-crown-4 macrocycles have been synthesized.⁴ The outstanding reactivity of fluorine in the course of formation of the macrocycles under very mild reaction

conditions relies on the activation of the amide carbonyl groups *ortho* to the fluorine atoms in the ring systems of starting substrates.⁵ In fact, the unactivated fluorine remained unaffected under the reaction conditions, leaving the potentially reactive fluoro substituents for further modifications of the macrocyclic molecules.

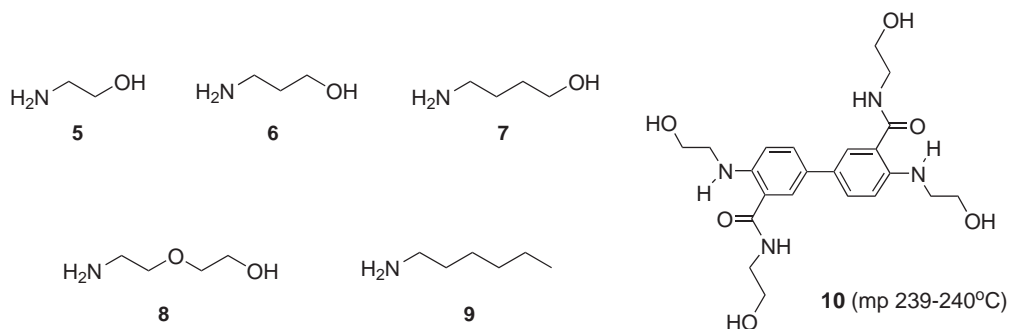
Herein we disclose reactions of biphenyl ester **3** with amino alcohols and hexylamine **5–9** to give highly branched biphenyl alcohol products **10–14**. Compound **3** was readily prepared from commercially available 4,4'-difluorobiphenyl. The bis-carboxylations of the

difluorobiphenyl with excess *sec*-BuLi/TMEDA followed by addition of CO₂ gave diacid **1** in quantitative yield and conversion of **1** to **3** was carried out by treatment with SOCl₂ and methanol, respectively. Flash chromatography of the resulting residue on silica gel gave **3** in high yield as a crystalline solid (mp 159–161°C, chemical ionisation HRMS, *m/z* calcd for M+1 C₁₆H₁₂F₂O₄: 306.0704, C 62.70, H 3.95, found: 306.0704, C 62.67, H 4.01).

The reaction of **3** with 2-aminoethanol **5** was performed by heating **3** in excess **5** at reflux temperature for 2 h. After excess **5** was removed at reduced pressure, a yellow solid was thus obtained. Washing the solid with

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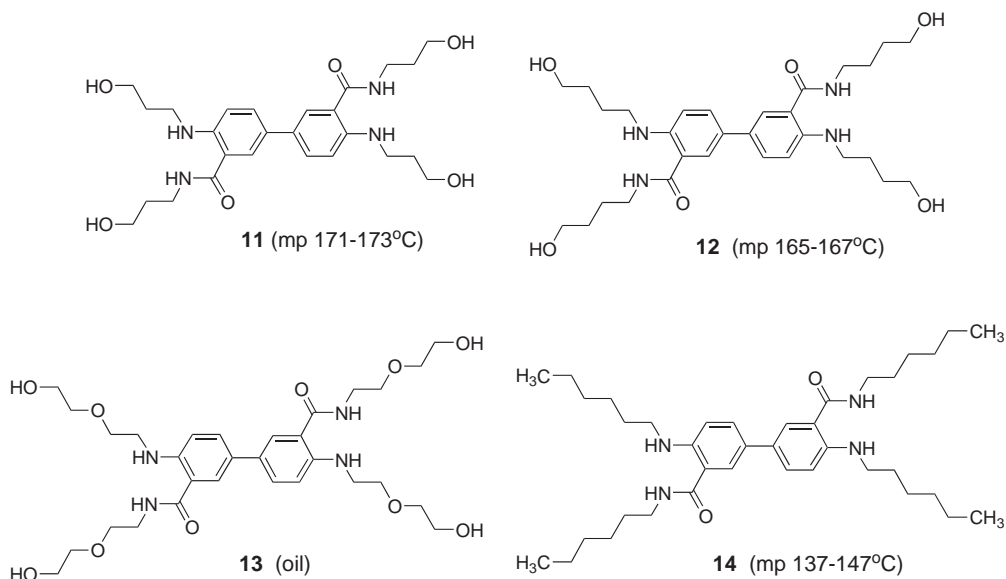


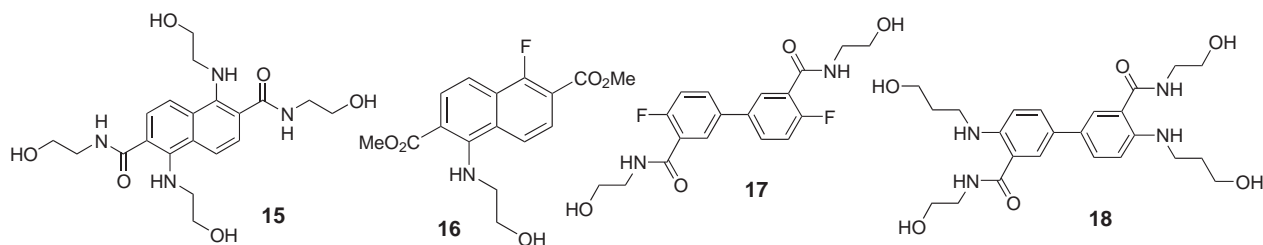
CH_2Cl_2 , HCl, and water, respectively, and drying afforded pure tetraol product **10** in 87% yield (mp 239–240°C);⁶ none of the other possible products could be detected. Compound **10** was found to be insoluble in methylene chloride, benzene, and methanol, but seemed slightly soluble in acetone. An assignment of its structure rests mainly on ^1H and ^{13}C NMR as well as IR spectroscopy, electronic ionisation mass spectrum, and elemental analysis. The ^1H NMR spectrum obtained from $\text{DMSO}-d_6$ indicated the presence of eight active protons, exchanging with D_2O at δ 4.72 (4H), 7.80 (2H), and 8.39 (2H). ^{13}C NMR spectrum showed 11 resonance peaks, suggesting the symmetry of the molecular structure. The lowest energy conformation of **10** (not shown) was obtained by calculations using an MM2 program. It was found that the distances between the amide carbonyl oxygen and amino protons were in the ranges of 1.85–1.95 Å, suggesting that strong hydrogen bonding should exist among these groups in the molecule. The amide oxygen atoms were directed toward the amino group *ortho* to the amide groups due to the hydrogen bonding interaction, leaving an envelope-like conformation with only the oxygen being out of the six-membered ring plane. As a result, the hydroxyethyl side chains on the amide group were pushed away from the one attached to the aniline nitrogen atoms, and overall, the most stable conformation of **10** adopted a conformation of propellant shape.

For amines **6–9**, reactions of **3** provided branched alcohol products **11–14**⁷ in 81, 98, 44, and 73% yields, respectively, using the same procedure. In addition, methyl ester **4** of the corresponding naphthalene substrate also reacted with 2-aminoethanol **5** in the same way to give naphthalene tetraol **15** in 66% yield. Calculations of **15** by MM2 also showed strong intramolecular hydrogen bonding interaction between the carbonyl oxygen and amino hydrogen in the most stable conformer. A very interesting feature of the naphthalene analog **15** relative to **4** existed in that the two fused benzene rings in the naphthalene molecule twisted slightly with each other and the resulting deformed ring system resembled a propeller.

More interestingly, utilization of milder reaction conditions (refluxing in CH_2Cl_2 solution for 24 h) for **4** afforded only mono-substituted product **16** in 11% yield along with recovered starting material. It is worth noting that only one of the two fluorines was selectively reacted with the amino nucleophile. This reaction would be useful for the preparation of unsymmetrically tetrafunctional products if optimized.

As discussed above, **10–14** homogeneously contain the same amino alcohol subunit as the side chain in the molecules. Extension of this methodology to selectively prepare heterogeneous tetraol biphenyls with mixed





functionality was achieved by using sequential introduction of different amino alcohols. For example, 2-aminoethanol derivative **17** (prepared by treatment of **1** with SOCl_2 and **5**, respectively) reacted with excess 3-aminopropanol **6** to give **18**⁸ in 73% yield. The ^{13}C NMR spectrum clearly demonstrated the existence of twelve carbon resonance signals. In this case, no amine exchange reaction was observed.

The interesting reactivity of **3** inspired us to consider a potential application to combinatorial synthesis. Presumably these reactions might be useful in constructing combinatorial libraries with diversities of structures for new drug discovery. As a result, treatment of **3** with a mixture of an equal amount of the four amino alcohols **5–8** under the same reaction conditions gave a product mixture that showed a very complicated but understandable ^1H NMR spectrum corresponding to a diversity of products. Theoretically, the product mixture consists of 136 compounds.

Acknowledgements

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- ^1H NMR ($\text{DMSO}-d_6$): δ 3.17 (t, $J=5.3$ Hz, 4H), 3.30 (q, $J=5.9$ Hz, 4H), 3.50 (t, $J=6.2$ Hz, 4H), 3.59 (t, $J=5.5$ Hz, 4H), 4.72 (br, 4H), 6.72 (d, $J=8.8$ Hz, 2H), 7.60 (dd, $J=1.5$ and 8.5 Hz, 2H), 7.80 (m, 4H), 8.39 (t, $J=5.4$ Hz, 2H). ^1H NMR ($\text{DMSO}-d_6+\text{D}_2\text{O}$): δ 3.14 (t, $J=5.6$ Hz, 4H), 3.29 (t, $J=5.8$ and 6.1 Hz, 4H), 3.50 (t, $J=6.1$ Hz, 4H), 3.57 (t, $J=5.6$ Hz, 4H), 6.72 (d, $J=9.0$ Hz, 2H), 7.55 (dd, $J=2.2$ and 8.8 Hz, 2H), 7.71 (d, $J=2.2$ Hz, 2H). ^{13}C NMR ($\text{DMSO}-d_6$): 42.00, 45.11, 59.65, 59.89, 111.57, 115.70, 125.63, 126.34, 129.82, 147.93, 169.43. IR (KBr) 3649, 3475, 3388, 3075, 2908, 2835, 1647, 1618, 1582 cm^{-1} . EIMS m/z (relative intensity) 446 (M^+ , 40%). Anal. calcd for $\text{C}_{22}\text{H}_{30}\text{N}_4\text{O}_6$: C, 58.01; H, 6.86. Found: C, 58.37; H, 6.79.
- 11**: ^1H NMR ($\text{DMSO}-d_6$): δ 1.69 (m, 8H), 3.16 (t, $J=6.8$ Hz, 4H), 3.27 (t, $J=7.1$ Hz, 4H), 3.34 (s, 2H), 3.46 (m, $J=5.3$, 5.6 Hz, 8H), 4.48 (br s, 2H), 4.54 (br s, 2H), 6.73 (d, $J=8.8$ Hz, 2H), 7.57 (d, $J=8.8$ Hz, 2H), 7.72 (m, 4H), 8.44 (t, $J=5.3$ Hz, 2H). ^{13}C NMR ($\text{DMSO}-d_6$): δ 32.14, 32.54, 36.28, 36.40, 58.38, 58.50, 58.67, 58.79, 111.54, 115.48, 125.52, 126.32, 129.82, 147.97, 169.41. IR (KBr) 3470, 3341, 3281, 2883, 2923, 1651, 1616, 1581, 1552 cm^{-1} . MS (CI): no M^++1 peak was seen. Anal. calcd for $\text{C}_{26}\text{H}_{38}\text{N}_4\text{O}_6$: C, 62.13; H, 7.62. Found: C, 62.05; H, 7.63.
- 12**: ^1H NMR (DMSO): δ 1.45 (m, 16H), 3.12 (m, 4H), 3.23 (m, 4H), 3.42 (m, 10H), 4.43 (t, $J=5.1$ Hz, 2H), 4.48 (t, $J=5.2$ Hz, 2H), 6.69 (d, $J=8.8$ Hz, 2H), 7.54 (dd, $J=1.7$, 8.5 Hz, 2H), 7.90 (t, $J=5.4$ Hz, 2H), 7.96 (d, $J=1.7$, 2H), 8.81 (t, $J=5.4$ Hz, 2H). ^{13}C NMR (DMSO): δ 25.53, 25.99, 30.07, 30.23, 30.26, 42.36, 60.62, 60.67, 111.58, 115.33, 125.63, 126.33, 129.81, 148.05, 169.31. IR (KBr) 3410, 3630, 2942, 1635, 1560, 1522 cm^{-1} . Anal. calcd for $\text{C}_{30}\text{H}_{46}\text{N}_4\text{O}_6$: C, 64.49; H, 8.30. Found: C, 64.37; H, 8.23.
- 13**: ^1H NMR (CDCl_3): δ 3.30 (m, 4H), 3.51 (m, 4H), 3.56 (m, 8H), 3.68 (m, 8H), 4.09 (br s, 2H), 6.68 (d, $J=8.8$ Hz, 2H), 7.42 (dd, $J=1.5$, 8.6 Hz, 2H), 7.73 (s, 2H), 7.83 (br s, 4H). ^{13}C NMR (CDCl_3): δ 39.35, 42.69, 61.21, 61.56, 68.95, 69.84, 72.09, 72.35, 112.25, 115.97, 125.52, 127.58, 130.24, 148.24, 170.04. IR (neat): 3300, 2900, 2850, 1700, 1660 cm^{-1} .
- 14**: ^1H NMR (CDCl_3): δ 0.89 (m, 12H), 1.31 (m, 20H), 1.59 (m, 4H), 1.66 (m, 4H), 3.13 (m, 4H), 3.38 (m, 4H), 6.22 (t, $J=5.4$ Hz, 2H), 6.70 (d, $J=9.1$ Hz, 2H), 7.36 (br s, 2H), 7.42 (m, 4H); ^{13}C NMR (CDCl_3): δ 13.89, 13.93, 22.46, 26.59, 26.82, 29.06, 29.54, 31.38, 31.50, 39.68, 43.14, 111.88, 115.64, 124.89, 127.16, 130.43, 148.18, 169.76, one

missing. IR (KBr) 3420, 3364, 2956, 2850, 1644, 1626, 1595, 1529, 812 cm^{-1} . MS (CI): 607 ($\text{M}^+ + 1$, 14). Anal. calcd for $\text{C}_{38}\text{H}_{62}\text{N}_4\text{O}_2 \cdot 1/2\text{H}_2\text{O}$; C, 74.16; H, 10.24. Found: C, 74.17; H, 10.01.

8. **18**: ^1H NMR ($\text{DMSO}-d_6$): δ 1.71 (m, 4H), 3.17 (m, 4H), 3.30 (m, 4H), 3.50 (m, 8H), 4.56 (t, $J=4.8$ Hz, 2H), 4.76 (t,

$J=5.6$ Hz, 2H), 6.72 (d, $J=8.8$ Hz, 1H), 7.58 (dd, $J=2.2$, 8.8 Hz, 2H), 7.78 (t, $J=5.1$ Hz, 2H), 7.85 (s, 2H), 8.50 (t, $J=5.3$ Hz, 2H). δ 4.56, 4.76, 7.78, 8.50 were exchangeable with D_2O . ^{13}C NMR ($\text{DMSO}-d_6$): δ 32.13, 34.40, 41.95, 58.54, 59.90, 111.56, 115.24, 125.71, 126.28, 129.92, 147.97, 161.24, 169.50.