JOC*Note*

Chemoselective Functionalization of 3,3′-Substituted BINOL Derivatives

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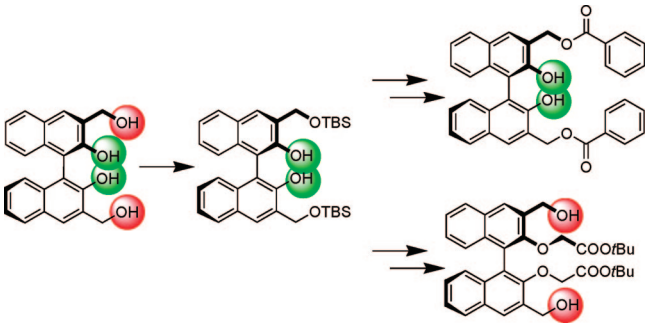

An efficient chemoselective differentiation of vicinal phenolic and benzylic alcohols on optically active binaphthyl skeletons has been achieved via TBS protection of the less sterically hindered, external 3,3′ benzylic positions. Further manipulation of functionalities either in the 2,2′ or 3,3′ positions is then easily achieved in high yields via the use of BOC protecting groups, functioning orthogonally to TBS.

Binaphthyl derivatives are a versatile class of compounds which have found applications in many different areas of chemistry.[1] Being characterized by a C_2 symmetrical aromatic skeleton, possessing a robust configurational stability in a broad range of conditions, BINOL (1,1′-binaphthyl-2,2′-diol)-based synthons have become attractive molecular modules for applications in fields as diverse as asymmetric catalysis,[2] chiral supramolecular recognition,[3] crystal engineering,[4] electrooptic materials,[5] and molecular electronics.[6] The basic BINOL moiety

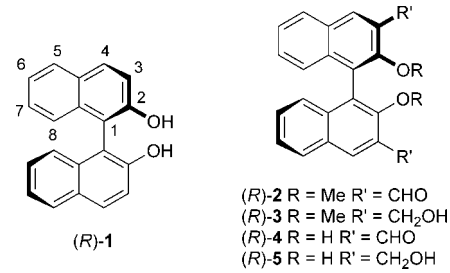

FIGURE 1. The structure of BINOL, and of the key precursors used in this study.

(compound **1** in Figure 1) can be conveniently functionalized in various positions; the most frequent ones are the 4,4′ and 6,6′ positions, and access to the 3,3′ positions is also well documented.[1,3–7] The possibility of a certain variation of the "bite" angle, defined by the two naphthyl rings, provides an ideal chiral environment for the transfer of the stereoinformation in the applications mentioned above. In recent examples, BINOL-based macrocycles, used as enantioselective fluorescent sensors for the detection of chiral guests, have been obtained by means of an efficient reductive amination protocol, starting from dialdehyde **2** or **4** (Figure 1),[8] thus introducing conformationally flexible methylene carbon atoms (modulating the distortion derived by the incorporation in a cyclic structure of the axially chiral units) in the 3,3′ positions. As part of a project dealing with chiral nanostructures, we have previously reported the rapid construction of D_2 and D_3 symmetrical BINOL-containing macrocycles by means of esterification developed on the 3,3′ benzylic alcohol functionalities, starting from compound **3**, avoiding reductive amination protocols and thus the incorporation of amines as basic, hydrogen-bonding sites in the cyclic framework.[9]

The simplest and most efficient multigram-scale synthetic methodology able to introduce 3,3′-functionalization on optically active **1** was found in our hands to be by direct formylation on 2,2′-OMe derivatives, to yield (*R*)-**2**, following the procedure

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(10) (a) Stock, H. T.; Kellogg, R. M. *J. Org. Chem.* **1996**, *61*, 3093–3105. (b) Athough 3,3′-formylation of MOM-protected BINOL has also been reported by these authors, its purification was more problematic than in the case of compound (*R*)-**2**. Deprotection protocols for MOM protecting groups, however, usually require harsh acidic conditions that can be unsuitable for acid-sensitive substrates such as benzoyl or benzyl esters.

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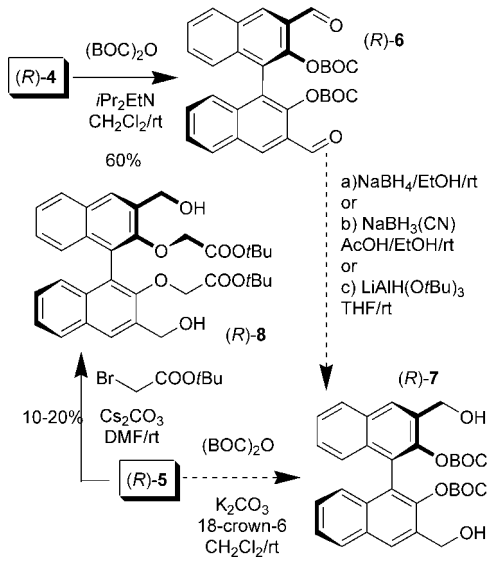
SCHEME 1. Initial Attempts at the Synthesis of Elaborated Synthons 7 and 8

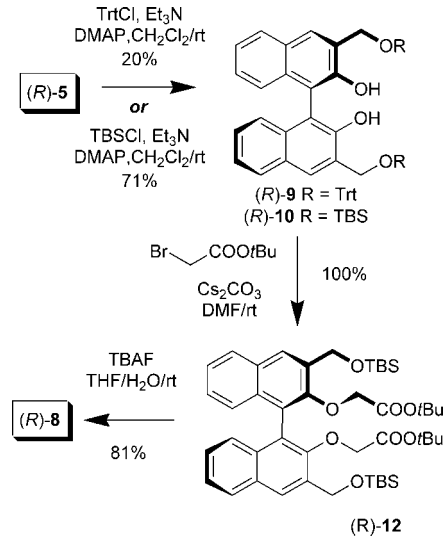


reported by Kellog and co-workers.[10] Although the orthogonality between methyl ether protected phenols and benzoyl or benzyl ester functionalities has been the subject of controversial literature reports,[11] the selective deprotection in the 2,2′ positions proved impossible under a variety of conditions without degradation of benzoyl esters in the 3,3′ positions in the macrocyclic structures mentioned above.[9] As a development of this work, we were therefore interested in developing access to BINOL derivatives in which the 2,2′ and 3,3′ positions, both as OH functionalities, could be differentiated and orthogonally protected, in order to efficiently introduce the functionalities of choice in either position.

In this Note, we report an efficient synthetic protocol for the differentiation of vicinal OH groups in the 2,2′ and 3,3′ positions of the binaphthyl skeleton, based on the orthogonal protection of the functionalities with TBS and BOC protecting groups, and its use in the reliable preparation of internally (on the 2,2′) or externally (in the 3,3′) functionalized derivatives. Our initial attempt toward the direct functionalization/differentiation of OH groups in the vicinal 2,2′ and 3,3′ positions is summarized in Scheme 1.

Although BOC protection of dialdehyde (*R*)-**4** worked smoothly, to yield (*R*)-**6**, its subsequent reduction, attempted by using hydride sources of differing activity ($NaBH_4$, $LiAlH(OtBu)_3$, $NaBH_3CN$/AcOH), as reported for salicylaldehyde[12] or analogous dendritic[13] derivatives, always gave complex mixtures of products as indicated by TLC analyses; the vicinal nucleophilic alcoxides, once formed, seem to interact quickly with the protecting groups in the 2,2′ positions giving scrambling of functionalities and thus mixtures of compounds difficult to isolate and purify.[12] Attempts aimed at the direct functionalization of the less basic phenolic functionalities, by means of the introduction of BOC protecting groups under phase-transfer catalysis to yield (*R*)-**7**, following procedures developed previously for analogous substrates,[14] were also unsuccessful.

SCHEME 2. Efficient Synthesis of Compound (*R*)-8



The selective alkylation of the phenolic hydroxyl groups with *tert*-butyl bromoacetate, under mild base treatment, gave the desired product in low and variable yields, probably as a consequence of the activation under these basic conditions of naphthoquinone−methide intermediates[15] which can react further with nucleophiles or polymerize in the reaction mixture.[16] The expected substitution occurring internally on the less basic phenolic functionalities, to yield (*R*)-**8** was unambiguously determined by means of 2D HMBC NMR experiments, showing correlation between the ^{13}C resonance of the carbons linked to the phenolic oxygens and the methylene protons of the $-CH_2COOtBu$ fragments inserted in the molecule.

We therefore turned our attention to the possibility of an orthogonal protection, and therefore differentiation, of the OH functionalities in either position (Scheme 2). Although a literature survey revealed only a few reports on the regioselective protection of hydroxyalkyl phenols,[17] a promising report described the use of silyl protecting groups:[18] more specifically, salicyl alcohol derivatives were differentially and chemoselectively protected on the benzylic functionality with use of the TBS protecting group, and on the phenolic functionality with use of the more sterically hindered Trt protecting group.

The application of the reported reaction protocol with Trt-Cl on the tetrafunctional derivative (*R*)-**5** gave in our case external, benzylic protection to yield (*R*)-**9** as the major product in poor yield. It was necessary to use an excess of Trt-Cl (up to 4 equiv) to achieve moderate conversion to the product (*R*)-**9**, which demonstrated to us the unviability of this route.

(11) See, for example: Nagaoka, N.; Schmid, G.; Iio, H.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 899–902. In this case, standard deprotection with BCl_3 cleaves both OMe protecting groups and acetate esters on polyphenolyic aromatic substrates.

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(16) In control experiments run under the same mildly basic conditions, alkylation of BINOL (*R*)-**1** proceeds quantitatively. Alkylation of dialdehyde (*R*)-**4**, instead, gives decomposition products.

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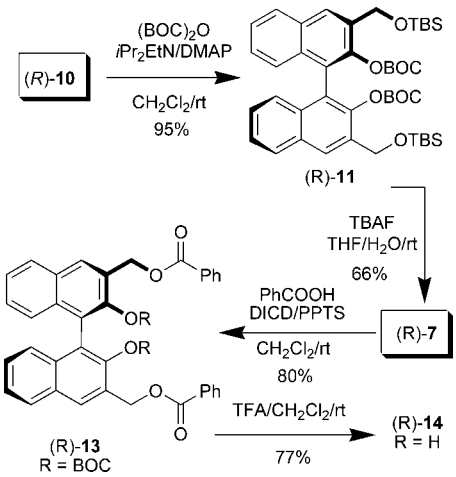
(18) Sefkow, M.; Kaatz, H. *Tetrahedron Lett.* **1999**, *40*, 6561–6562.

SCHEME 3. Efficient Synthesis of Compound (*R*)-7 and Its Further Elaboration[a]



[a] DICD = diisopropylcarbodiimide. DPTS = 4-dimethylaminopyridinium *p*-toluenesulfonate.

The use of 2 equiv of TBS-Cl under the reported conditions, instead, yielded compound (*R*)-**10**, after purification by column chromatography, in 70% yield. Evidence for external functionalization for both **9** and **10**, on the more reactive and less sterically hindered benzylic functionalities in the 3,3′ positions, can be summarized by the presence of symmetrical NMR spectra, of resonances attributed to the free phenolic functionalities at ca. 6 ppm, exchanging upon addition of D_2O, and by comparison of the chemical shift (in the ^1H NMR spectra) for the benzylic CH_2 groups between **10**, **11**, and the precursor **5**, showing small but significant changes (ca. 0.2 and 0.4 ppm for **9** and **10**, respectively, in opposite directions). With this result in hand, subsequent functionalization of (*R*)-**10** with *tert*-butylbromoacetate, using conditions identical with those reported in Scheme 1, gave difunctionalized compound (*R*)-**12** in quantitative yield. The subsequent deprotection with TBAF in the presence of H_2O gave target compound (*R*)-**8** in 81% yield (Scheme 2), identical by all means with the sample previously obtained (Scheme 1) and characterized by 2D NMR spectroscopy.

To be able to selectively manipulate the OH groups in the 3,3′ positions, a protecting group possessing reliable orthogonal properties with respect to TBS[19] was introduced in the 2,2′ positions (Scheme 3). Reaction of (*R*)-**10** with BOC anhydride gave compound (*R*)-**11** in excellent yields, which could be externally chemoselectively deprotected under classical conditions (TBAF/THF in the presence of stoichiometric amounts of H_2O to quench the native alkoxide).

To test our initial synthetic motivation, functionalization via ester formation with benzoic acid (DICD/DPTS)[20] yielded (*R*)-**13**, after purification by column chromatography, and deprotection of the internal BOC groups in standard conditons afforded compound (*R*)-**14**, with free phenolic fucntionalities and external aromatic esters, in good overall yields.

The chiroptical properties of all compounds synthesized were characterized with use of UV and CD spectroscopy. A maximum absorption in the UV/vis spectra was found to occur at ca. 230 nm (the ^1B spectral region of the 2-naphthol chromophore) in all compounds, but in the case of the benzoylated derivatives

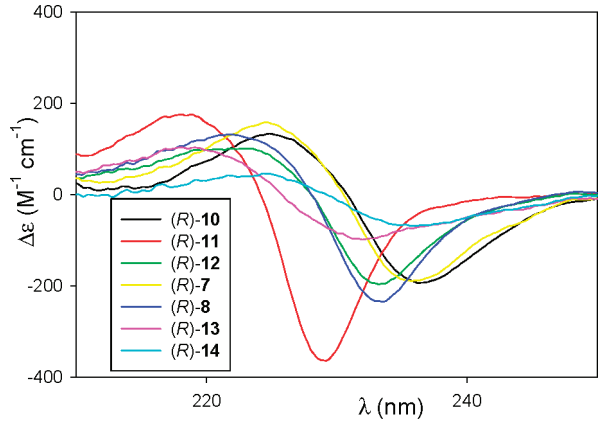


FIGURE 2. CD Spectra in EtOH ($c = 2-4 \times 10^{-6}$ M).

13 and **14** a strong absorption band was also found at around 280 nm (see the Supporting Information). In their CD spectra (Figure 2), however, the only evident transition was found to be the exciton couplet associated with the former absorption band. Previous authors have shown a clear qualitative correlation between chiroptical response of BINOL derivatives (in terms of $\Delta\epsilon_{max}$ of the low-energy branch of the couplet) and the"bite" or torsional angle defined by the naphthyl molecular modules.[21] Within families of 2,2′-substituted compounds in this study, clear differences can be found, suggesting variable conformations in solution. In the case of the 2,2′ BOC protected derivatives (**7**, **11**, and **13**) these differences are substantial ($\Delta\epsilon_{max}$= −190, −364, and −99, respectively), clearly indicating buttressing effects, provoking a larger or smaller bite angle induced by the differing steric sizes of the substituents introduced in the 3,3′ positions.

In conclusion, we have developed an efficient route for the differentiation and functionalization of binaphthyl derivatives bearing vicinal OH functionalities (in the 2,2′ and 3,3′ positions of the aromatic skeleton). The key step involves the chemoselective protection of the more nucleophilic and less sterically hindered external OH functionalities, and the subsequent protection of the internal functionalities with BOC as orthogonal groups. These findings are currently under exploitation for the tailoring of chemical properties of suitable molecular modules in the construction of nanoscale, shape-persistent self-aggregating macrocycles.

Experimental Section

Typical Procedures: Synthesis of Key Compounds. Compound (*R*)-10. Et_3N (149 mg, 1.47 mmol) was added to a solution of compound (*R*)-**5** (255 mg, 0.74 mmol) and DMAP (9 mg, 0.072 mmol) in dry CH_2Cl_2 (20 mL) under nitrogen. After 10 min $ClSiMe_2t$-Bu (223 mg, 1.47 mmol) was added and mixture was stirred for 20 h at room temperature under nitrogen. The reaction was then quenched with H_2O/ice. The solution was extracted with CH_2Cl_2 (3 × 20 mL) and dried (Na_2SO_4). The product was isolated as a colorless oil (302 mg, 71%) by flash chromatography (hexane/ethyl acetate 99/1). $[\alpha]^{rt}_D$ +59 (*c* 0.002, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (m, 2H, CH binaphthyl), 7.85 (m, 2H, CH binaphthyl), 7.34 (t, 2H, J = 6 Hz, CH binaphthyl), 7.24 (t, 2H, J = 6 Hz, CH binaphthyl), 7.14 (d, 2H, J = 5 Hz, CH binaphthyl),

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(20) Moore, J. S.; Stupp, S. I. *Macromolecules* **1990**, *23*, 65–70.
(21) (a) Rosini, C.; Superchi, S.; Peerlings, H. W. I.; Meijer, E. W. *Eur. J. Org. Chem.* **2000**, *6*, 1–71. (b) Proni, G.; Spada, G. P.; Lustenberger, P.; Welti, R.; Diederich, F. *J. Org. Chem.* **2000**, *65*, 5522–5527. (c) Blakemore, P. R.; Kilner, C.; Milicevic, S. D. *J. Org. Chem.* **2006**, *71*, 8212–8218.

6.81 (s, 2H, −OH binaphthol), 5.13 (d, 2H, $J = 14$ Hz, $-CH_2O-$), 5.09 (d, 2H, $J = 14$ Hz, $-CH_2O-$), 0.97 (s, 18H, $-SiMe_2C(CH_3)_3$), 0.19 (s, 12H, $-Si(CH_3)_2t$-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ =151.3 (Cq), 133.1 (Cq), 128.6 (Cq), 128.2 (Cq), 127.9 (CH), 126.6 (CH), 126.3 (CH), 124.5 (CH), 123.5 (CH), 113.8 (Cq), 63.6 (CH_2), 25.8 (CH_3), 18.2 (Cq), −5.4 (CH_3); MS(ESI) *m*/*z* (%) 597 [M + Na]$^+$ (85), 613 [M + K]$^+$ (45), 465 [M − (OSiMe$_2t$-Bu) + Na]$^+$ (100), 481 [M − (OSiMe$_2t$-Bu) + K]$^+$ (15). Anal. Calcd for $C_{34}H_{46}O_4Si_2$: C 71.0, H 8.1. Found: C 71.4, H 7.8.

Compound (*R*)-11. Compound (*R*)-**10** (350 mg, 0.61 mmol) and *N*,*N*-diisopropylethylamine (47.2 mg, 0.37 mmol) were added to a solution of DMAP (7.4 mg, 0.061 mmol) in dry THF (5 mL). After 5 min $(BOC)_2O$ (425 mg, 1.9 mmol) was added. After 20 h of stirring at rt, the reaction was quenched with H_2O (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). Product was isolated (449.5 mg, 95%) by flash chromatography (hexane/ethyl acetate 95/5). $[\alpha]^{rt}_D$ −69 (*c* 0.002, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (m, 2H, CH binaphthyl), 7.90 (m, 2H, CH binaphthyl), 7.42 (m, 4H, $J = 6$ Hz, CH binaphthyl), 7.24 (t, 2H, $J = 6$ Hz, CH binaphthyl), 5.00 (d, 2H, $J = 15$ Hz, $-CH_2O-$), 4.89 (d, 2H, $J = 15$ Hz, $-CH_2O-$), 1.04 (s, 18H $-OCOOC(CH_3)_3$), 1.01 (s, 18H, $-SiMe_2C(CH_3)_3$), 0.18 (s, 6H, $-Si(CH_3)_2t$-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3 (C═O), 144.5 (Cq), 133.2 (Cq), 132.1 (Cq), 131.7 (Cq), 127.6 (CH), 126.7 (CH), 126.3 (CH), 125.7 (CH), 125.5 (CH), 123.7 (Cq), 82.7 (Cq), 77.1 (Cq), 60.2 (CH_2), 26.8 (CH_3), 25.9 (CH_3), −5.4 (CH_3);. MS(ESI) *m*/*z* 797 [M + Na]$^+$ (100). Anal. Calcd for $C_{44}H_{62}O_8Si_2$: C 68.2, H 8.1. Found: C 68.5, H 7.9.

Compound (*R*)-12. Compound (*R*)-**10** (150 mg, 0.263 mmol) and after 10 min $BrCH_2COOt$-Bu (205 mg, 1 mmol) were added to a solution of Cs_2CO_3 (514 mg, 1.6 mmol) in dry DMF (4 mL). After 20 h H_2O (20 mL) was added and the solution was extracted with Et_2O (3 × 30 mL) and dried with Na_2SO_4. The product was isolated as colorless oil (213 mg, 100%) by flash chromatography (hexane/ethyl acetate 97/3). $[\alpha]^{rt}_D$ −40 (*c* 0.002, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (m, 2H, CH binaphthyl), 7.90 (m, 2H, CH binaphthyl), 7.40 (dd, 2H, $J = 6$ Hz, CH binaphthyl), 7.22 (t, 2H, $J = 6$ Hz, CH binaphthyl), 7.11 (d, 2H, $J = 5$ Hz, binaphthyl), 5.11 (m, 4H, $-CH_2O-$), 3.96 (d, 2H, $J = 16$ Hz, OCH_2CO-), 3.82 (d, 2H, $J = 16$ Hz, OCH_2CO-), 1.26 (s, 18H, $-COOC(CH_3)_3$), 1.05 (s, 18H, $-SiMe_2C(CH_3)_3$, 0.21 (s, 6H, $-Si(CH_3)_2t$-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6 (C═O), 152.9 (Cq), 135.0 (Cq), 133.0 (Cq), 130.7 (Cq), 128.0 (CH), 126.5 (CH), 126.0 (CH), 125.3 (CH), 124.7 (CH), 122.5 (Cq), 81.2 (Cq), 77.1 (Cq), 69.8 (CH_2), 61.0 (CH_2), 27.7 ($C(CH_3)_3$), 26.0 ($C(CH_3)_3$), −5.3 ($-Si(CH_3)_2t$-Bu); MS(ESI) *m*/*z* (%) 825 [M + Na]$^+$ (100). Anal. Calcd for $C_{46}H_{66}O_8Si_2$: C 68.8, H 8.3. Found: C 69.1, H 8.0.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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