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Selective mono-functionalisation at the 6-position of (*R*)-(+)-2,2′-diethoxy-1,1′-binaphtalene

Jean-Bernard Regnouf de Vains*

GEVSM, UMR 7565 CNRS-UHP, Faculté de Pharmacie, 5 rue Albert Lebrun, F-54001 Nancy Cedex, France

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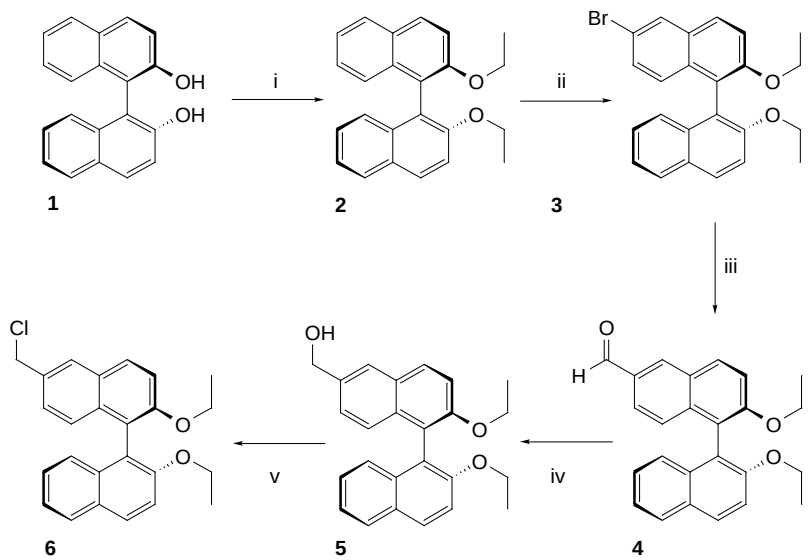
Abstract—New (*R*)-(+)-1,1′-binaphtalene derivatives displaying one bromo-, carbaldehyde, hydroxymethyl- or chloromethyl-substituent at the 6-position have been prepared and characterised.

1,1′-Binaphtyl derivatives have gained a strong interest[1] in supramolecular[2] and macromolecular chemistry,[3] notably in the design of chiral ligands and new polymeric chiral catalysts. For this purpose, symmetrical synthetic pathways have been developed in order to introduce, notably at the 3,3′- and 6′6′-positions of this aromatic species, some adapted reactive groups allowing the building of various macrocycles and polymers.

A small, but growing, effort has been made concerning the introduction of a single attachment group, which should allow the 1,1′-binaphtyl derivatives to be grafted as chiral pendant arms on various molecular supports. In this sense, the relatively rare reports dedicated to this approach deal with a controlled introduction of functional groups at the 3-position of unprotected or *O*,*O*-diprotected 1,1′-bi-2-naphtol **1**. Thus, *ortho*-directed lithiation of bis-*O*-protected **1** allowed the selective introduction of one electrophile in the 3-position, such as for example the reactive bromo-, formyl- or carboxy-groups, precursors for the Suzuki couplings, or imine, amine, alcohol, alkyl halide, alkene, alkane, ester and amide derivatives formation.[4]



Scheme 1. *Reagents and conditions*: (i) Ref. 10; (ii) Br_2, CH_2Cl_2, −10°C, 40%; (iii) a. BuLi, Et_2O, 0–20°C, b. DMF, 52%; (iv) $NaBH_4$, MeOH, rt, 99%; (v) $SOCl_2$, CH_2Cl_2, reflux, 80%.

* Fax: (33)3 83 17 90 57; e-mail: jean-bernard.regnouf@pharma.u-nancy.fr

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We were surprised to find that the 6-position did not gain more attention. In fact, no specific work dedicated to the controlled introduction of one active group in this position has been reported until now. Nevertheless, Cram et al[2a] described the efficient mono-functionalisation at this position on a binaphthyl-containing chiral macrocycle in view of attaching it to a polymer. The single active group was introduced by lithiation of the 6,6′-dibromo-analogue followed by treatment with ethylene oxide to give a mixture of 6-hydroxyethyl derivative, unsubstituted and di-substituted analogues which were separated by chromatography. On the other hand, racemic 6-bromo-1,1′-bi-2-naphtol was also prepared by coupling of 6-bromo-2-naphtol and 2-naphtol in the presence of $FeCl_3$,[5] or observed in the coupling reactions of 2-naphtol and 1,6-dibromo-2-naphtol,[6] but no further development has been proposed on pure enantiomers.

In this sense, we thus describe here (Scheme 1) the synthesis of four new chiral 2,2′-diethoxy-1,1′-binaphtalenes incorporating at the 6-position an halogen group (**3**), a carbaldehyde function (**4**), an hydroxymethyl group (**5**) and a chloromethyl group (**6**), which should display attractive reactivities for the preparation of various aryl derivatives, in Wittig couplings, in amine, ester or ether syntheses and in alkylation processes, respectively.

Our synthetic approach, described here with *R*-(+)-1,1′-binaphtol **1**, follows parts of the non-racemising strategy developed by Deussen et al for the 6,6′-disubstituted analogues.[7]

Thus, **1** was preliminary prepared following the simple and efficient resolution method of Cai et al.[8] involving the formation of an inclusion complex with *N*-benzylcinchonidinium chloride; 99.5% enantiomeric excess was then obtained for both isomers, as assessed by HPLC analysis.[9]

Compound **1** was then protected by ethylation of the two hydroxyl groups following the non-racemising conditions of Kellogg et al.[10] The resulting diether **2** was carefully treated in CH_2Cl_2 at −10°C with one equivalent of bromine dissolved in CH_2Cl_2, under a stream of argon to remove HBr. The reaction mixture, which contained traces of the 6,6′-dibromo-analogue,[7] unreacted **2** and **3** was chromatographed (SiO_2, hexane:CH_2Cl_2 80:20) to give **3** with a yield of 40%. The bromide **3** was then lithiated by reaction with BuLi in dry Et_2O at rt and the resulting salt was quenched with dry DMF to give the mono-aldehyde **4** with a yield of 52% after chromatography. We noted that the lithiation does not occur in Et_2O if low temperatures are maintained, resulting in the recovering of almost all the bromide **3** after addition of DMF.

Compound **4** was then reduced in the corresponding alcohol **5** with $NaBH_4$ in MeOH with a yield of 99%. In order to avoid strong acidic conditions, which may result in racemisation,[10] we introduced the halide group by rapid treatment of **5** with $SOCl_2$ in dry CH_2Cl_2. This afforded the chloromethyl analogue **6** as a vitreous solid with a yield of 80% after chromatography (SiO_2, CH_2Cl_2).

All compounds gave satisfactory analyses,[11] and this synthetic approach was also applied with success on the *S*-(−) enantiomer.

Further investigations dedicated to the building of more elaborate chiral structures with compounds **3–6** and (*S*)-enantiomers are under development.

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11. General aspects: Melting points (°C, uncorrected) were determined on an Electrothermal 9200 in Capillary apparatus. ^1H and ^{13}C NMR spectra were recorded on a

Bruker DRX 400 (chemical shifts in ppm). Mass spectra (electronic ionisation – ei) were recorded on a Nermag R-1010C apparatus at the Service Commun de Spectrométrie de Masse Organique, Nancy. Optical rotatory measurements were performed on a Perkin–Elmer 141 polarimeter at room temperature (29°C). Elemental analyses were performed at the Service de Microanalyse, Nancy. Merck TLC plates were used for chromatography analysis (SiO_2, ref 1.05554; Al_2O_3, ref 1.05581). All commercially available products were used without further purification unless otherwise specified. **Bromide 3**: A solution of Br_2 (0.97 M, 1.5 ml, 1.45 mmol) in CH_2Cl_2 was added under argon to a solution of (*R*)-(+)-2,2′-diethoxy-1,1′ binaphthalene (0.5 g, 1.45 mmol) in CH_2Cl_2 (30 ml) at −78°C. Argon was bubbled to remove HBr over 4 h. The solution was treated with 10% $NaHSO_3$, then basified with K_2CO_3. The organic phase was washed with water, dried over Na_2SO_4, then chromatographed (SiO_2, hexane:CH_2Cl_2 80:20) to give pure **3** (0.245 g, 40%). Mp: 71–72°C. $[\alpha]_D^{29}=+43$ (*c* 0.214, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): 1.088 (t, $J=7$ Hz, 3H, OCH_2CH_3); 1.097 (t, $J=7$ Hz, 3H, OCH_2CH_3); 4.00–4.15 (m, 4H, $2OCH_2CH_3$); 7.051 (d, $J=9$ Hz, 1H); 7.125 (d, $J=8.5$ Hz, 1H); 7.22–7.31 (m, 2H); 7.351 (td, $J_1=7$ Hz, $J_2=1.1$ Hz, 1H); 7.446 (d, $J=9$ Hz, 1H); 7.46 (d, $J=9$ Hz, 1H); 7.83 (s, $J=9$ Hz, 1H); 7.89 (d, $J=9$ Hz, 1H); 7.97 (d, $J=9$ Hz, 1H); 8.04 (d, $J=1.84$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz): 15.355, 15.421 ($2OCH_2CH_3$); 65.54, 65.56 ($2OCH_2CH_3$); 117.63, 120.24, 121.27, 129.62, 130.70, 133.12, 134.43, 154.69, 155.02 (C(1), C(2), C(6), C(9), C(10), C(1′), C(2′), C(9′), C(10′)); 116.03, 117.12, 123.94, 125.64, 126.65, 127.85, 128.32, 128.61, 129.72, 129.79, 130.14 (C(3), C(4), C(5), C(7), C(8), C(3′), C(4′), C(5′), C(6′), C(7′), C(8′)). MS: (e.i.) 422–420 [$M^{+\bullet}$]. Anal. calcd for $C_{24}BrH_{21}0_2$ (423.35): C, 68.42; H, 5.02; found: C, 68.35; H, 5.11. **Aldehyde 4**: A solution of *n*BuLi (1.6 M in hexane, 2.18 ml, 3.5 mmol) was added to a solution of **3** (0.37 g, 0.874 mmol) in dry Et_2O (30 ml) at −78°C under argon. The mixture was stirred at rt for 1 h then cooled to −20°C prior to dry DMF (1 ml, 13 mmol) being added. Stirring was continued at rt for 1 h, then THF (5 ml) was added. The solution was acidified with 1 M HCl and the organic solvent was evaporated. The mixture was extracted with CH_2Cl_2 and the organic phase was evaporated to dryness. Chromatography (SiO_2, CH_2Cl_2) afforded pure **4** (0.17 g, 0.46 mmol, 52%). Mp: 69–70°C. $[\alpha]_D^{29}=+29$ (*c* 0.209, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): 1.078 (t, $J=7$ Hz, 3H, OCH_2CH_3); 1.123 (t, $J=7$ Hz, 3H, OCH_2CH_3); 4.00–4.20 (m, 4H, $2OCH_2CH_3$); 7.115 (d, $J=8.5$ Hz, 1H); 7.20–7.30 (m, 2H); 7.351 (td, $J_1=8$ Hz, $J_2=1.1$ Hz, 1H); 7.454 (d, $J=9$ Hz, 1H); 7.53 (d, $J=9$ Hz, 1H); 7.70 (dd, $J_1=9$ Hz, $J_2=1.5$ Hz, 1H); 7.898 (d, $J=8.2$ Hz, 1H); 7.99 (d, $J=9$ Hz, 1H); 8.129 (d, $J=9$ Hz, 1H); 8.379 (d, $J=1.1$ Hz, 1H); 10.12 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 400 MHz): 15.22, 15.38 ($2OCH_2CH_3$); 65.25, 65.46 ($2OCH_2CH_3$); 119.86, 121.25, 129.62, 132.49, 134.30, 137.99, 138.21, 154.66, 157.49 (C(1), C(2), C(6), C(9), C(10), C(1′), C(2′), C(9′), C(10′)); 115.87, 116.32, 123.44, 123.96, 125.45, 126.71, 126.94, 128.40, 129.95, 131.49, 135.36 (C(3), C(4), C(5), C(7), C(8), C(3′), C(4′), C(5′), C(6′), C(7′), C(8′)); 192.55 (CHO). MS: (e.i.) 370 [$M^{+\bullet}$]. Anal. calcd for $C_{25}H_{22}O_3$ (370.45): C, 81.06; H, 5.98; found: C, 80.79; H, 6.07. **Alcohol 5**: A solution of **4** (0.17 g, 0.46 mmol) and $NaBH_4$ (0.08 g, 2.1 mmol) in MeOH (15 ml) was stirred at rt for 3 h. The mixture was acidified with 1 M HCl and evaporated to dryness. The residue was chromatographed (SiO_2, CH_2Cl_2:MeOH 4%) to give the pure alcohol **5** (0.17 g, 99%). Mp: 51–52°C. $[\alpha]_D^{29}=+40$ (*c* 0.209, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): 1.079 (t, $J=7$ Hz, 3H, OCH_2CH_3); 1.080 (t, $J=7$ Hz, 3H, OCH_2CH_3); 4.00–4.13 (m, 4H, $2OCH_2CH_3$); 4.81 (s, 2H, CH_2OH); 7.10–7.25 (m, 4H); 7.33 (td, $J_1=7$ Hz, $J_2=1.1$ Hz, 1H); 7.44 (d, $J=9$ Hz, 1H); 7.45 (d, $J=9$ Hz, 1H); 7.85 (s, 1H); 7.88 (d, $J=8$ Hz, 1H); 7.95 (d, $J=9$ Hz, 1H); 7.96 (d, $J=9$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz): 15.39 ($2OCH_2CH_3$); 65.61 ($2OCH_2CH_3$); 66.00 (CH_2OH); 119.47, 120.95, 121.09, 129.65, 134.16, 134.55, 136.16, 149.19, 154.70 (C(1), C(2), C(6), C(9), C(10), C(1′), C(2′), C(9′), C(10′)); 116.26, 116.34, 123.86, 125.81, 125.98, 126.15, 126.45, 126.51, 128.23, 129.46, 129.55 (C(3), C(4), C(5), C(7), C(8), C(3′), C(4′), C(5′), C(6′), C(7′), C(8′)). MS: (e.i.) 372 [$M^{+\bullet}$]. Anal. calcd for $C_{25}H_{24}0_3$ (372.46): C, 80.62; H, 6.50; found: C, 80.38; H, 6.52. **Chloride 6**: A solution of **5** (0.17 g, 0.46 mmol) in $SOCl_2$ (3 ml) was refluxed for 1 h. The solvent was evaporated to dryness and the residue chromatographed (SiO_2, CH_2Cl_2) to give the pure chloride **6** (0.145 g, 0.37 mmol, 80%). Mp: 80.0–81.0°C. $[\alpha]_D^{29}=+28$ (*c* 0.209, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): 1.093 (t, $J=7$ Hz, 3H, OCH_2CH_3); 1.097 (t, $J=7$ Hz, 3H, OCH_2CH_3); 4.12–4.20 (m, 4H, $2OCH_2CH_3$); 4.75 (s, 2H, CH_2Cl); 7.10–7.27 (m, 4H); 7.345 (td, $J_1=7$ Hz, $J_2=1.3$ Hz, 1H); 7.45 (d, $J=9$ Hz, 1H); 7.46 (d, $J=9$ Hz, 1H); 7.85–8.00 (m, 4H). ^{13}C NMR ($CDCl_3$, 400 MHz): 15.37, 15.42 ($2OCH_2CH_3$); 47.29 (CH_2Cl); 65.52, 65.57 ($2OCH_2CH_3$); 120.66, 121.07, 129.23, 132.61, 134.38, 134.50, 154.71, 155.33 (C(1), C(2), C(6), C(9), C(10), C(1′), C(2′), C(9′), C(10′)); 116.14, 116.56, 123.89, 125.78, 126.57, 126.77, 126.94, 128.08, 128.27, 129.61, 129.65 (C(3), C(4), C(5), C(7), C(8), C(3′), C(4′), C(5′), C(6′), C(7′), C(8′)). MS: (e.i.) 390–392 [$M^{+\bullet}$]; 355 [$M-Cl]^{+\bullet}$. Anal. calcd for $C_{25}H_{23}ClO_2$ (390.91): C, 76.81; H, 5.93; found: C, 76.56; H, 6.00.