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Double benzyne–furan cycloaddition and the assembly of 1,1′-binaphthyl and 1,1′-dinaphthyl ether systems

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Abstract—1,1′-Binaphthyl and 1,1′-dinaphthyl ether systems have been prepared via double benzyne–furan cycloadditions, and a dibenzofuran derivative was formed as a major product in the lithiation of two di-(chloroaryl) ethers.

The palmarumycins,[1] diepoxins,[2] preussomerins[3] and spiroxins [4] are structurally remarkable classes of natural products isolated from various fungal cultures. They are all graced with a spiro-ketal entity formally derived from 1,8-naphthalenediol and 1,4-naphthoquinone, but at rich and varied oxidation levels. These unusual natural products are exemplified by palmarumycin CP_1 **1**, diepoxin σ **2**, preussomerin G **3** and spiroxin C **4** (Fig. 1). All four classes of fungal metabolites are undoubtedly closely interrelated biosynthetically and may well be derived from a 1,8-naphthalenediol spiro-ketal with late introduction of the unusual oxygenation patterns. They collectively show diverse biological effects including antifungal, antibacterial and antitumour activities.[1] Since our original publication on the palmarumycins,[5] other routes for the total synthesis of several palmarumycins, diepoxins, preussomerins and spiroxins have been published by our group and others.[4c,6]

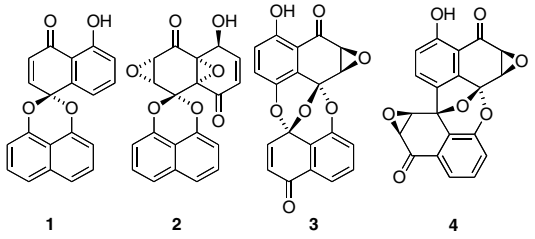

Figure 1.

In connection with further work on spirocyclic naphthalene natural products, we now report our recent investigations on the synthesis of 1,1′-binaphthyl **5** and dinaphthyl ethers **6** (Fig. 2). Initially we sought to access **5** and **6**, both key intermediates, via double benzyne–furan Diels–Alder reactions. The key step in both routes involves the generation of either a simple benzyne, which was trapped by 2,2′-bifuryl **7** or the elaboration of a double benzyne capable of undergoing reaction with 2-methoxyfuran **15** twice.

The binaphthyl system **5** was prepared using 2,2′-bifuryl **7** and 2-chloro-1,4-dimethoxybenzene **8**. Chloride **8** was allowed to react with *sec*-butyllithium in THF at −100 °C[7,8] for 15 min, and the resultant *ortho*-lithiated product allowed to warm up to room temperature in the

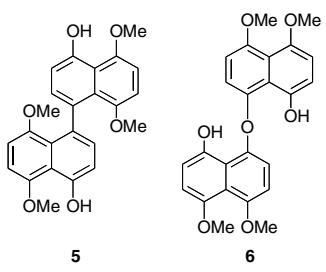

Figure 2.

Keywords: 1,1′-Binaphthyl; 1,1′-Dinaphthyl ether; Benzyne; Cycloaddition; Dibenzofuran.
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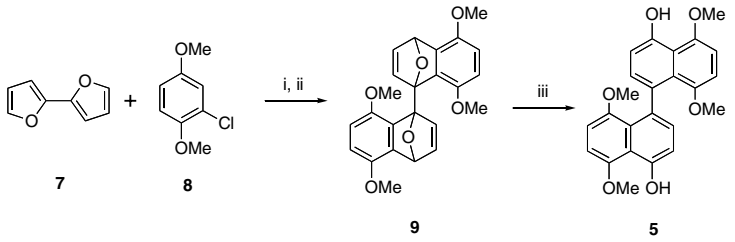
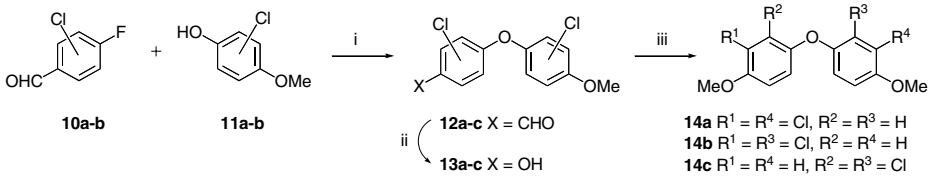


Scheme 1. Reagents and conditions: (i) *s*-BuLi, **8**, −100 °C; (ii) **7**, −100–25 °C, 38%; (iii) TFA, CH_2Cl_2, 25 °C, 83%.

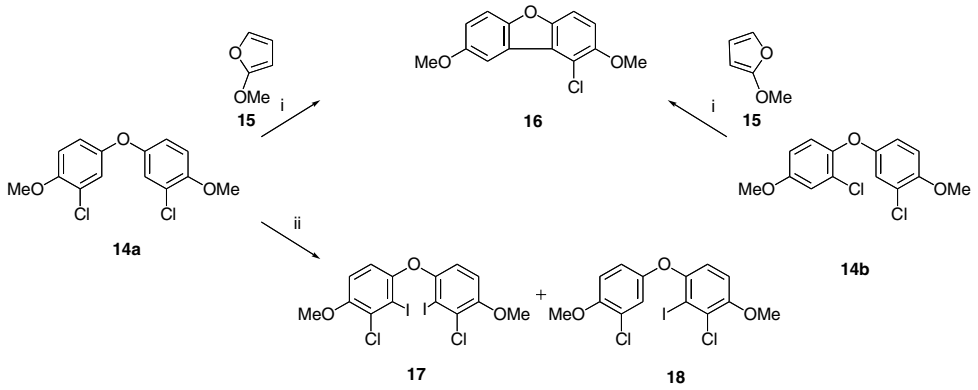
presence of the 2,2′-bifuryl **7**. This produced the double Diels–Alder cycloadduct **9** in 38% yield. Diether **9** was aromatized by reaction with trifluoroacetic acid in dichloromethane to provide the desired binaphthyl system **5** (Scheme 1).[9]

This double benzyne cycloaddition strategy was extended to the three dichloro-diaryl ethers **14a**–**c**. We considered that double *ortho*-lithiation should provide a dibenzyne, or its synthetic equivalent. In situ trapping with 2-methoxyfuran **15** was expected to provide the dinaphthyl ether **6** on aromatization. Initial attempts to synthesize the compounds **14a**–**c** by Ullmann-coupling[10,11] proceeded in poor yields. However, nucleophilic aromatic substitution of fluorobenzaldehydes **10a**–**b** by reaction with the methoxyphenols **11a**–**b** mediated by the Barton base, $(Me_2N)_2C{=}N^tBu$, followed by Baeyer–Villiger oxidation and methylation[12] of the resultant phenols **13a**–**c** gave the desired benzyne precursors **14a**–**c**[13] (58%, 63% and 56% overall yields, respectively) (Scheme 2). When chlorides **14a** and **b** were allowed to react with an excess of *sec*-butyllithium (2 equiv) and 2-methoxyfuran **15**, no dinaphthyl ether **6** was observed. Instead the dibenzofuran **16**[14] was isolated as the only product (72–82%) (Scheme 3). Barluenga has reported similar observations on the formation of benzo-fused heterocyclic derivatives from benzyne precursors.[15]

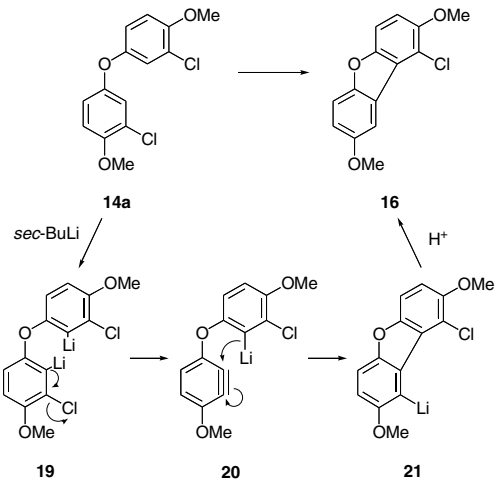
Formation of the dibenzofuran ring system **16** probably proceeds via the intermediates **19** and **20** in which the benzyne is trapped intramolecularly by the aryllithium to form **21** (Scheme 4). This process is undoubtedly very fast and takes place at very low temperatures.[7] Thus 2-methoxyfuran **15** is unable to react with the double benzyne to form the dinaphthyl system **6**. In support of the proposed mechanism **14a** was allowed to react with *sec*-butyllithium (2 equiv) in the presence of iodine (4 equiv) at −100 °C to give the expected iodo compounds **17** and **18** in 16% and 53% yields, respectively, (Scheme 3). This result is consistent with the fact that *ortho*-lithiation has taken place prior to the heterocyclization reaction. The structure of dibenzofuran **16** (CCDC 231192) was confirmed by ring iodination and



Scheme 2. Reagents and conditions: (i) $(Me_2N)_2C{=}N^tBu$, MeCN, 70 °C, 1 h 15 min, 68–74%; (ii) *m*-CPBA, CH_2Cl_2, 25 °C, 24 h, 70–74% (iii) $(MeO)_2SO_2$, K_2CO_3, Me_2CO, 25 °C, 3 h, (80–86%).



Scheme 3. Reagents and conditions: (i) *s*-BuLi (2 equiv), −100–25 °C, 20 min, 82% (from **14a**) or 72% (from **14b**); (ii) *s*-BuLi (2 equiv), I_2 (4 equiv), −100–25 °C, 20 min, 16% (**17**) and 53% (**18**).



Scheme 4.

an X-ray crystallographic structure determination (Fig. 3).

In contrast to chlorides **14a** and **14b**, the reaction of chloride **14c** with 2-methoxyfuran **15**, under the same conditions, gave a mixture of the mono-cycloadducts, **23** and **24**, and the desired 1,1′-dinaphthyl ethers **6** and **22**[16] after facile aromatization during purification in 7%, 5%, 9% and 12% yields, respectively, (Scheme 5). It should be noted that **14c** is clearly not capable of forming the dibenzofuran **16** via intramolecular carbanion attack onto a benzyne. The structure of dinaphthyl ether **22** (CCDC 231193) was confirmed by X-ray crystallography (Fig. 4).

In summary we have described the application of double furan-benzyne cycloaddition reactions to produce binaphthyls **5** and dinaphthyl ethers **6** and **22**. This work has also led to the identification of a procedure for the

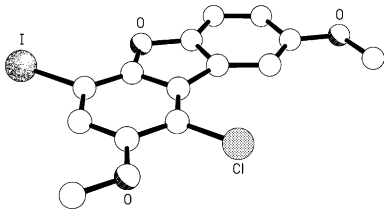


Figure 3.

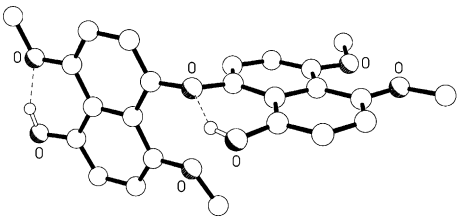


Figure 4.

synthesis of dibenzofuran **16**, which is relevant to other classes of natural products.[17]

Acknowledgements

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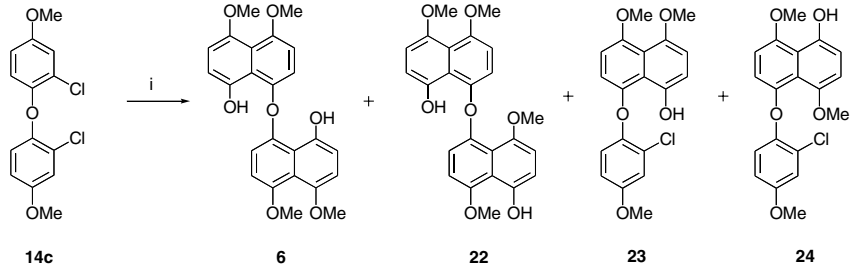

Scheme 5. Reagents and conditions: (i) *s*-BuLi (4 equiv), **15** −100–25 °C, 20 min, 9% (**6**), 12% (**22**), 7% (**23**) and 5% (**24**).

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9. Spectroscopic data: Compound **5**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.81 (s, 6H), 3.84 (s, 6H), 5.98 (s, 2H), 6.65–6.70 (m, 4H), 7.05–7.20 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 79.8, 80.5, 110.8, 114.8, 139.2, 142.2, 143.6, 144.1, 144.3, 147.3, 147.4, 148.5; MS (CI) m/z 407 $(M+H)^+$, 424 $(M+NH_4)^+$; HRMS m/z calcd for $C_{24}H_{23}O_6$: $(M+H)^+$, 407.1495; found: 407.1495.
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13. Spectroscopic data: dichloride **14a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.90 (s, 6H), 6.83–6.96 (m, 4H), 7.00–7.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 57.0, 113.2, 118.1, 121.3, 123.5, 151.4, 151.7; MS (CI) m/z 316 $(M+NH_4)^+$, 298 $(M)^+$, 283, 52; HRMS m/z calcd for $C_{14}H_{12}Cl_2O_3$: $(M)^+$, 298.0164; found: 298.0170. Anal. Calcd for $C_{14}H_{12}Cl_2O_3$: C, 56.21; H, 4.04. Found: C, 56.36; H, 4.25. Dichloride **14b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.82 (s, 3H), 3.89 (s, 3H), 6.76–6.91 (m, 3H), 6.92–7.05 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 56.2, 57.0, 113.2, 114.2, 116.2, 116.3, 119.5, 122.6, 123.4, 127.1, 146.0, 151.2, 152.0, 156.9; MS (CI) m/z 316 $(M+NH_4)^+$, 298 $(M)^+$, 283, 52; HRMS m/z calcd for $C_{14}H_{12}Cl_2O_3$: $(M)^+$, 298.0164; found: 298.0169. Anal. Calcd for $C_{14}H_{12}Cl_2O_3$: C, 56.21; H, 4.04. Found: C, 56.14; H, 3.95. Dichloride **14c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.82 (s, 6H), 6.68–6.88 (m, 4H), 6.91–7.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 56.2, 113.9, 116.2, 120.3, 125.7, 146.9, 156.3; MS (CI) m/z 316 $(M+NH_4)^+$, 298 $(M)^+$, 283, 52; HRMS m/z calcd for $C_{14}H_{16}Cl_2NO_3$: $(M+NH_4)^+$, 316.0507; found: 316.0502. Anal. Calcd for $C_{14}H_{12}Cl_2O_3$: C, 56.21; H, 4.04. Found: C, 56.31; H, 3.94.
14. Spectroscopic data: dibenzofuran **16**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.95 (s, 3H), 3.99 (s, 3H), 7.03–7.14 (m, 2H), 7.35–7.48 (m, 2H), 7.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 56.4, 57.8, 103.9, 106.3, 110.1, 112.2 (2C), 112.6, 116.5, 124.0, 124.4, 151.4, 152.0, 156.0; MS (CI) m/z 280 $(M+NH_4)^+$, 262 $(M)^+$, 247, 229, 52; HRMS m/z calcd for $C_{14}H_{15}ClNO_3$: $(M+NH_4)$, 280.0740; found 280.0744. Anal. Calcd for $C_{14}H_{11}ClO_3$: C, 64.01; H, 4.22. Found: C, 64.01; H, 4.27.
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16. Spectroscopic data: ether **6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.89–4.01 (m, 12H), 6.70 (d, $J = 8.5$ Hz, 2H), 6.86 (d, $J = 8.5$ Hz, 2H), 6.91–7.01 (m, 4H), 8.36 (s, 2H); MS (CI) m/z 440 $(M+NH_4)^+$, 423 $(M+H)^+$, 203; HRMS m/z calcd for $C_{24}H_{23}O_5$: $(M+H)^+$, 423.1443; found: 423.1433. Ether **22**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.47 (s, 3H), 3.87 (s, 3H), 3.93 (s, 3H), 4.10 (s, 3H), 6.24 (d, $J = 8.5$ Hz, 1H), 6.55 (d, $J = 8.5$ Hz, 1H), 6.76 (d, $J = 8.5$ Hz, 1H), 6.90–6.98 (m, 4H), 7.12 (d, $J = 8.5$ Hz, 1H), 9.26 (s, 1H), 9.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 56.4, 56.9, 57.6, 58.5, 104.7, 106.8, 108.3, 109.3, 111.1, 111.2, 111.3, 111.5, 116.3, 118.0, 119.9, 121.0, 143.8, 148.3, 148.6, 149.1, 150.0, 151.4, 152.2, 154.1; MS (CI) m/z 440 $(M+NH_4)^+$, 423 $(M+H)^+$, 203; HRMS m/z calcd for $C_{24}H_{23}O_5$: $(M+H)^+$, 423.1443; found: 423.1437.
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