Synthesis of Regioisomeric Functionalized Benzodifurans and Angelicins

by **Elías Quezada**[a][b], **Giovanna Delogu***[a], **Dolores Viña**[c], **Lourdes Santana**[b], **Gianni Podda**[a], **Maria Joao Matos**[a][b], and **Carmen Picciau**[a][b]

[a]) Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Cagliari, I-09124 Cagliari (phone: +390706758675; fax: +390706758553; e-mail: delogug@unica.it)

[b]) Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Santiago de Compostela, SP-15782 Santiago de Compostela

[c]) Departamento de Farmacología, Facultad de Farmacia, Universidad de Santiago de Compostela, SP-15782 Santiago de Compostela

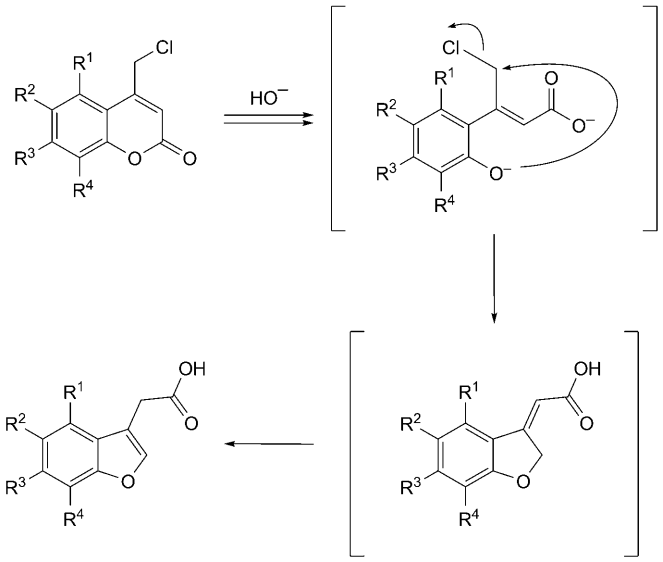
Arenofurans have important biological and pharmacological activities. Compared to benzofurans, the reports on the synthesis of benzodifurans are rather limited. Here, we report the synthesis of a linear and an angular 3,3′-bis(carboxymethyl)substituted benzodifuran and 4′-carboxymethyl-substituted angelicins from phloroglucinol, using 4-halomethyl-substituted dipyrones as key intermediates in the synthetic route. This strategy shows that the stability of a pyrone ring depends on the type of substituent at C(4) and the conditions used.

Introduction. – Arenofurans have important biological and pharmacological activities [1–4] and potential applications as fluorescent dyes and probes, and as photosensitizers [5][6]. Among arenofurans, benzofurans have been the subject of the most extensive studies, and numerous synthetic methods have been developed for them [1][2][7–9]. Compared to benzofurans, the reports on the synthesis of benzodifurans are rather limited [3][7][10]. The most important route for the synthesis of various arene ring-fused furan derivatives is the intramolecular formation of a furan moiety starting from properly substituted arenes *via* dehydrative cyclization either of *o*-alkoxycarbonyl compounds or α-aryloxycarbonyl compounds. Continuing our research on a convenient contraction reaction of the coumarin pyrone ring, we now describe a facile synthesis of a linear and an angular 3,3′-bis(carboxymethyl)-substituted benzodifuran and functionalized angelicins from phloroglucinol involving an alkali-mediated rearrangement of 4-(halomethyl)-coumarins *via* α,β-unsaturated acids (*Scheme 1*) [11].

Results and Discussion. – From phloroglucinol (**1**) and ethyl 4-chloro-3-oxobutanoate, angular and linear dipyrons **2** and **3**, respectively, precursors for the synthesis of angular and linear benzodifurans, as well as coumarin **4**, were obtained, following a synthetic route previously described by us (*Scheme 2*) [12].

Under strong alkaline conditions, the pyrone ring of **3**, condensed with the furan ring, undergoes hydrolysis and generates one furanoacetic fragment. Simultaneously, the pyrone ring with the 4-(chloromethyl) group undergoes a contraction reaction forming the other furanoacetic fragment of the final benzodifuran skeleton of

Scheme 1



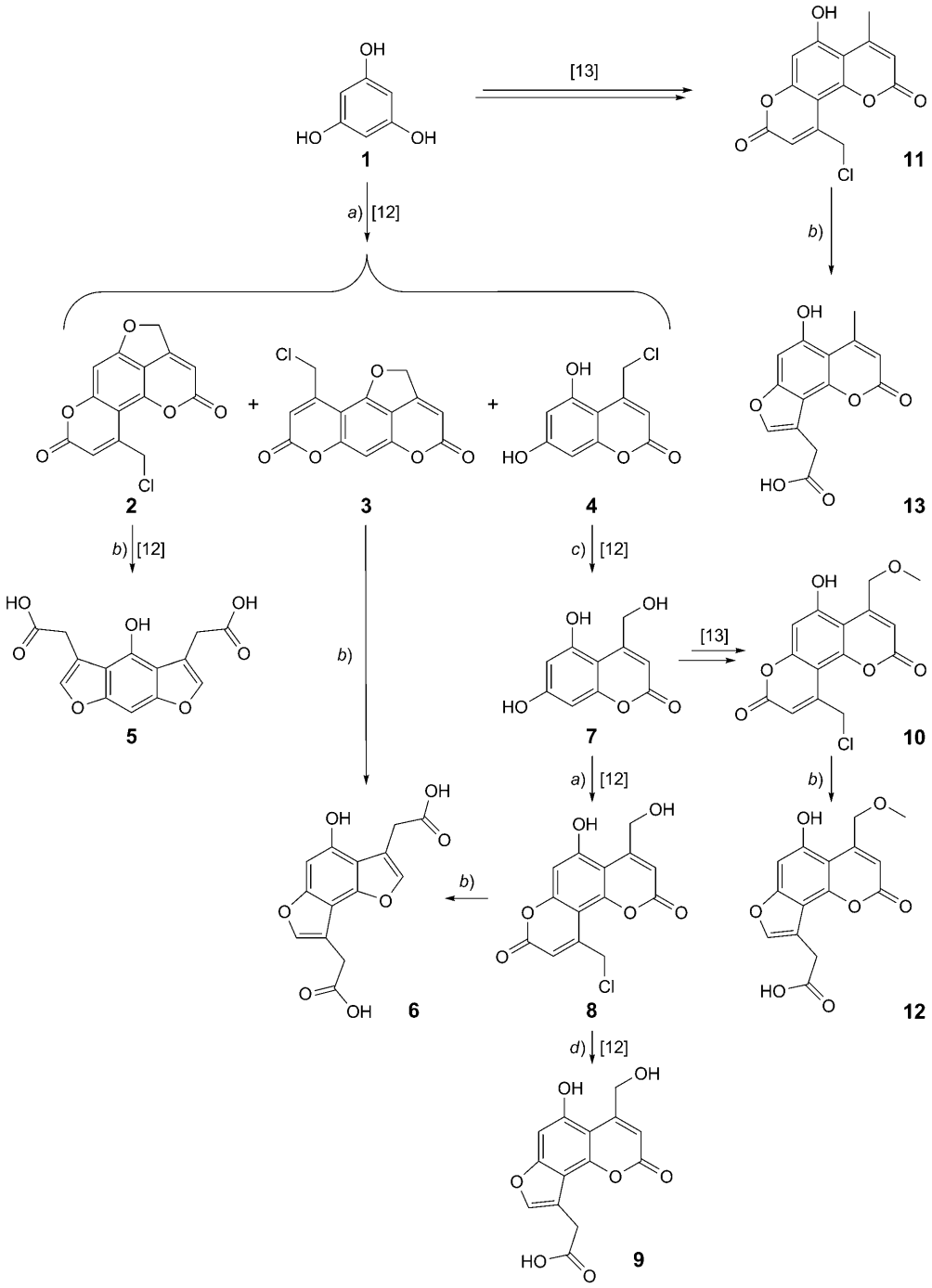
compound **6**, as it had been observed in the formation of compound **5** from **2** [12]. In others words, the synthetic strategy allows to obtain linear or angular benzodifurans, starting either from the angular or linear benzodipyrone, respectively. The synthesis of this type of benzodifurans is also possible starting from 4-bis(chloromethyl)-substituted dipyrones for contraction of both pyrone rings [11].

The spectroscopic data of the compound **6** are very similar to those obtained for benzodifuran **5** [12]. In both cases, the ^{1}H-NMR spectrum shows two very intense *singlet*s that integrate for two H-atoms each between 3.7 and 3.8 ppm, corresponding to the two CH_2 groups. Two signals for aromatic H-atoms appear at 7.67 and 7.69 ppm that correspond to the furan ring H-atoms. Finally, a broad *singlet* that integrates for two H-atoms appears at 12.31 ppm, corresponding to the two acid groups. The ^{13}C-NMR data confirm the existence of the two CH_2 groups with two signals very close to 30 ppm, and the appearance of two signals very close to 172 ppm, that correspond to the two acid groups.

Therefore, NOE experiments were necessary for the unequivocal assignment of both isomers. When **6** was irradiated at the frequency of the OH signal, an intense NOE of 10.9% was observed for a *singlet* in the aromatic zone, assigning that this OH group correlates to one H-atom in *o*-position, *i.e.*, H–C(5), whereas irradiation of the OH group of **5** did not provide a NOE for the H-atom of the benzene ring.

When **4** [12] was treated with H_2O, the Cl-atom was replaced by a OH group to give (hydroxymethyl)coumarin **7**. The treatment of this compound with ethyl 4-chloro-3-oxobutanoate under *Pechmann* conditions led to the dipyrone **8**. For this dipyrone, contraction either of one or both pyrone rings can be performed. Treatment of **8** with 3M NaOH, at room temperature, causes the contraction of both pyrone rings, which

Scheme 2



a) Ethyl 4-chloro-3-oxobutanoate, 12M H_2SO_4, r.t., 12 h. *b*) 3M NaOH, r.t., 30 min, 3M HCl. *c*) H_2O, reflux, 48 h; *d*) 0.1M NaOH, 0°, 30 min.

gives the angular benzodifuran **6** in a yield of 70%. As compound **3** was obtained in a very low yield from phloroglucinol, the above described way could be considered a very suitable alternative to access compound **6**. When soft conditions – 0.1M NaOH at 0° – are used, the angular furocoumarin **9** [12] is obtained from dipyrone **8**, because the pyrone ring bearing the 4-hydroxymethyl group remains stable under these reaction conditions.

This stability of the pyrone ring is more evident when the substituent at the 4-position is not a good leaving group. In fact, when the benzodipyrones **10** and **11** [13] (*Scheme 2*) react in the presence of 3M NaOH at room temperature, the furocoumarins **12** and **13** are obtained as major compounds, in 86 and 62% yield, respectively. The used synthetic route determinates that the presence of a stable group, such as 4-(methoxymethyl) or Me, in one of the rings guarantees the stability of those rings under basic conditions, while the stability in the presence of the 4-(hydroxymethyl) group depends on the used conditions. The application of the contraction reaction of a benzopyrone ring to a benzofuran allows to obtain a wide number of 4′-(carboxymethyl)-substituted furocoumarins, which are difficult to obtain otherwise in an efficient, direct, and versatile way.

Experimental Part

General. Silica gel (SiO_2; 35–60 mesh) was used for flash chromatography (FC). Anal. TLC: on plates precoated with silica gel (*Merck 60* F_{254}, 0.25 mm). M.p.: *Reichert Kofler* thermophan or in capillary tubes with a *Büchi 510* apparatus; uncorrected. IR Spectra: *Perkin-Elmer 1640FT* spectrometer (KBr in cm^{-1}). ^{13}C- and ^1H-NMR spectra: *ca.* 10% in (D_6)DMSO; at r.t. in 5 mm outsider diameter tubes; Me_4Si as internal standard, chemical shifts δ are expressed in ppm, *J* in Hz. One-dimensional ^{13}C-NMR: *Bruker AMX 500* spectrometer, at 125.77 MHz, typically with a 30° pulse flip angle, a pulse repetition time of 1.8 s and a spectral width of 31250 with 32 K data points. EI-MS: *Hewlett-Packard 5988A* spectrometer (70 eV). Elemental analyses: *Perkin-Elmer 240B* microanalyser; within ±0.4% of calc. values in all cases.

*10-(Chloromethyl)-5-hydroxy-4-(hydroxymethyl)-2*H,*8*H-*pyrano[2,3-*f*]*chromene-2,8-dione* (**8**). A mixture of **7** (5,7-dihydroxy-4-(hydroxymethyl)-2*H*-chromen-2-one; 200 mg, 0.96 mmol), 12M H_2SO_4 (20 ml), and ethyl 4-chloro-3-oxobutanoate (0.649 ml, 790 mg, 4.803 mmol) was stirred at r.t. overnight, and then quenched with ice (100 ml). The resulting solid was filtered off, washed with cold H_2O until pH 7.0, and purified by FC (SiO_2, hexane/AcOEt, 4:1) to afford pure **8** as a white solid. Yield: 85%. M.p. 250° (dec). IR (KBr): 3468, 2940, 1680, 1620, 1598, 836. ^1H-NMR ((D_6)DMSO): 4.60 (br., CH_2OH); 4.83 (*s*, CH_2OH); 5.13 (*s*, CH_2Cl); 6.49 (*s*, H–C(3), H–C(9)); 6.64 (*s*, H–C(6)); 12.01 (br., OH). ^{13}C-NMR ((D_6)DMSO): 44.88 (CH_2Cl); 61.48 (CH_2OH); 98.81 (C(6)); 99.41 (C(10a)); 104.58 (C(4a)); 106.64 (C(3)); 112.13 (C(9); 149.95 (C(10); 152.22 (C(4)); 156.35 (C(5)); 158.34 (C(2)); 158.73 (C(8)); 159.40 (C(10b)); 159.43 (C(6a)). EI-MS: 308 (11, M^+), 270 (3), 209 (4), 185 (5), 129 (4), 54 (100). Anal. calc. for $C_{14}H_9ClO_6$ (308.67): C 54.48, H 2.94; found: C 54.55, H 3.00.

General Procedure for Contraction of 4-Substituted Pyrone Rings. A mixture of **3** (596 mg, 2.05 mmol) in 3M NaOH (10 ml), was stirred at r.t. for 3 h. Once the reaction had been completed, the mixture was acidified with 3M HCl until pH 6.0, and a dark brown solid precipitated, which was filtered and washed with H_2O until neutral pH. The solid was purified by FC (SiO_2, CH_2Cl_2/MeOH, 9:1). 362 mg (yield: 61%) of pure **6** were obtained as a light brown solid. Compounds **6**, **12**, and **13** were also obtained from **8**, **10**, and **11** resp., by the same procedure.

*2,2′-(4-Hydroxybenzo[1,2-*b*:3,4-*b′*]difuran-3,8-diyl)diacetic Acid* (**6**). Yield from **3**: 61%, from **8**: 70%. M.p. 150° (dec). IR (KBr): 3520, 1746, 1620, 1599, 830. ^1H-NMR ((D_6)DMSO): 3.74, 3.77 (2*s*, 2 CH_2); 6.73 (*s*, H–C(5)); 7.67, 7.69 (2*s*, H–C(2), H–C(7)); 9.99 (br., OH); 12.31 (br., 2 COOH). ^{13}C-NMR ((D_6)DMSO): 29.75, 29.78 (2 CH_2); 91.97; 106.38; 112.82; 112.00; 114.31; 140.96; 141.02;

148.20; 149.96; 154.23; 171.85, 172.23 (2 CO). EI-MS: 290 (0.5, M^+), 261 (12), 247 (58), 231 (12), 203 (100), 201 (15). Anal. calc. for $C_{14}H_{10}O_7$ (290.23): C 57.94, H 3.47; found: C 57.99, H 3.52.

*[5-Hydroxy-4-(methoxymethyl)-2-oxo-2*H*-furo[2,3-*h*]chromen-9-yl]acetic Acid* (**12**). Yield 86%. M.p. 277° (dec). IR (KBr): 3520, 2920, 2810, 1710, 1599, 1422, 1100, 1095, 822. ^{1}H-NMR ((D$_6$)DMSO): 3.32 (*s*, Me); 3.85 (*s*, CH_2CO); 4.71 (*s*, CH_2O); 6.30 (*s*, H–C(3)); 6.80 (*s*, H–C(6)); 7.58 (*s*, H–C(8)); 10.16 (*s*, 2 OH). ^{13}C-NMR ((D$_6$)DMSO): 31.03 (CH_2CO); 58.89 (Me); 70.48 (CH_2O); 93.79 (C(6)); 108.89 (C(3)); 110.81; 112.63; 116.70; 144.36 (C(8)); 147.40; 150.62; 151.16; 156.92 (C(2)); 157.03 (C(6a)); 173.03 (CH_2CO). EI-MS: 304 (100, M^+), 275 (29), 261 (9), 214 (21). Anal. calc. for $C_{15}H_{12}O_7$ (304.25): C 59.22, H 3.98; found: C 59.10, H 4.02.

*(5-Hydroxy-4-methyl-2-oxo-2*H*-furo[2,3-*h*]chromen-9-yl)acetic Acid* (**13**). Yield 62%. M.p. 314° (dec). IR (KBr): 3550, 2949, 2840, 1790, 1657, 1599, 1432, 1108, 1088, 832. ^{1}H-NMR ((D$_6$)DMSO): 2.44 (*s*, Me); 3.72 (*s*, CH_2CO); 6.04 (*s*, H–C(3)); 6.81 (*s*, H–C(6)); 7.66 (*s*, H–C(8)); 10.67 (br., COOH); 12.33 (br., OH). ^{13}C-NMR ((D$_6$)DMSO): 24.34 (Me); 29.82 (CH_2); 94.57 (C(6)); 105.57; 108.93; 111.43; 113.79 (C(3)); 142.66 (C(8)); 149.46; 155.11; 156.00; 157.24 (C(2); 159.29 (C(6a)); 172.10 (COOH). EI-MS: 274 (100, M^+), 230 (89), 228 (66), 202 (5). Anal. calc. for $C_{14}H_{10}O_6$ (274.23): C 61.32, H 3.68; found C 61.65, H 3.97.

The authors acknowledge the Xunta de Galicia (PGIDIT05BTF 20302PR-2), Ministerio de Sanidad y Consumo (PI061457) for their financial support and Progetto Ricerca Scientifica 2006-Università di Cagliari. We thank *Ramon Gesto* for his technical assistance.

REFERENCES

[1] P. Cagniant, D. Cagniant, *Adv. Heterocycl. Chem.* **1975**, *18*, 337; B. A. Keay, P. W. Dibble, in 'Comprehensive Heterocyclic Chemistry II', Eds. A. R. Katritzky, C. W. Rees, E. F. V. Scriben, Pergamon, UK, 1996, Vol. 4, pp. 395–436.

[2] G. A. Kraus, N. Zhang, J. G. Verkade, M. Nagarajan, P. B. Kisanga, *Org. Lett.* **2000**, *2*, 2409.

[3] R. Royer, E. Bisagni, C. Hudry, A. Cheutin, M.-L. Desvoye, *Bull. Soc. Chim. Fr.* **1963**, 1003; H. Hagiwara, K. Sato, T. Suzuki, M. Ando, *Heterocycles* **1999**, *51*, 497; H. Hagiwara, K. Sato, D. Nishino, T. Hoshi, T. Suzuki, M. Ando, *J. Chem. Soc., Perkin Trans. 1* **2001**, 2946.

[4] J. J. Chambers, D. M. Kurrasch-Orbaugh, M. A. Parker, D. E. Nichols, *J. Med. Chem.* **2001**, *44*, 1003; K. S. K. Murthy, B. Rajitha, M. K. Rao, T. R. Komuraiah, S. M. Reddy, *Heterocycl. Commun.* **2002**, *8*, 179.

[5] M. Abdul-Aziz, J. V. Auping, M. A. Meador, *J. Org. Chem.* **1995**, *60*, 1303.

[6] P. K. Frederiksen, M. Jørgensen, P. R. Ogilby, *J. Am. Chem. Soc.* **2001**, *123*, 1215; T. D. Poulsen, P. K. Frederiksen, M. Jørgensen, K. V. Mikkelsen, P. R. Ogilby, *J. Phys. Chem. A* **2001**, *105*, 11488.

[7] L. Rene, J. P. Buisson, R. Royer, D. Averbeck, *Eur. J. Med. Chem.* **1978**, *13*, 435; K. C. Nicolaou, S. A. Snyder, A. Bigot, J. A. Pfefferkorn, *Angew. Chem., Int. Ed.* **2000**, *39*, 1093; H. M. Meshram, K. C. Sekhar, Y. S. S. Ganesh, J. S. Yadav, *Synlett* **2000**, 1273.

[8] K. K. Park, H. Seo, J.-G. Kim, I.-H. Suh, *Tetrahedron Lett.* **2000**, *41*, 1393; K. K. Park, I. K. Han, J. W. Park, *J. Org. Chem.* **2001**, *66*, 6800.

[9] X. Xie, B. Chen, J. Lu, J. Han, X. She, X. Pan, *Tetrahedron Lett.* **2004**, *45*, 6235; M. del Carmen Cruz, J. Tamariz, *Tetrahedron Lett.* **2004**, *45*, 2377.

[10] V. F. Traven, D. V. Kravtchenko, T. A. Chibisova, *Mendeleev Commun.* **1995**, 21; A. R. Katritzky, L. Serdyuk, L. Xie, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1059; M. Jørgensen, F. C. Krebs, K. Bechgaard, *J. Org. Chem.* **2000**, *65*, 8783; I. Yavari, M. Anary-Abbasinejad, A. Alizadeh, *Tetrahedron Lett.* **2002**, *43*, 4503.

[11] V. I. Dulenko, V. M. Golyak, V. I. Gubar, N. N. Alekseev, *Chem. Heterocycl. Comp.* **1979**, *15*, 815; L. Crombie, R. C. F. Jones, C. J. Palmer, *J. Chem. Soc., Perkin Trans. 1* **1987**, 333; Y. Fall, L. Santana, M. Teijeira, E. Uriarte, *Heterocycles* **1995**, *41*, 647; A. M. Piloto, S. P. G. Costa, M. S. T. Gonçalves, *Tetrahedron Lett.* **2005**, *46*, 4757; A. M. Piloto, A. S. C. Fonseca, S. P. G. Costa, M. S. T. Gonçalves, *Tetrahedron* **2006**, *62*, 9258.

[12] G. Delogu, C. Picciau, E. Quezada, L. Santana, E. Uriarte, *Synlett* **2007**, 1951.
[13] E. Quezada, G. Delogu, D. Viña, L. Santana, C. Picciau, G. Podda, E. Uriarte, *Magn. Reson. Chem.* **2008**, *46*, 701.

Received November 24, 2008