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Synthesis of [60]fullerene–quercetin dyads

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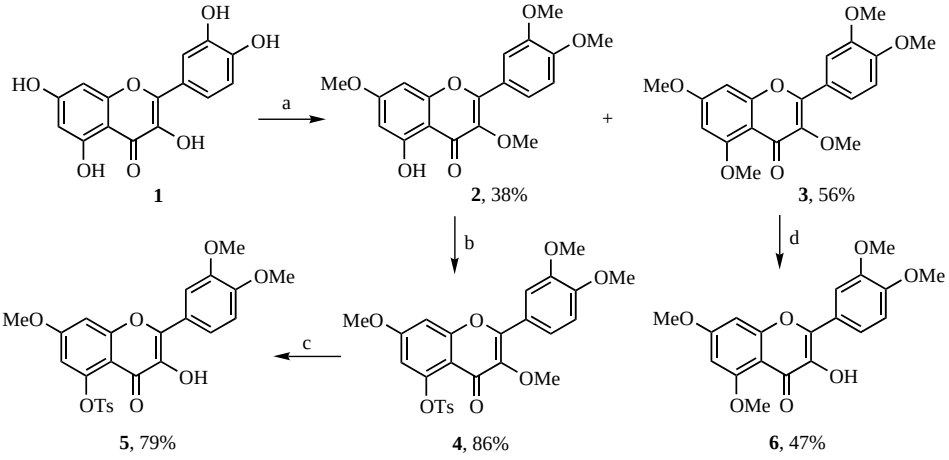
Abstract—Starting from quercetin, a natural flavonol with high antioxidant activity, three novel [60]fullerene–flavone derivatives were synthesized via cyclopropanation of C_{60}.

Among the various potential applications of the fullerene derivatives, their use in medicinal chemistry is probably the most promising one. It has been shown that they exhibit several types of biological activities, both in vitro and in vivo, that can be exploited for medicinal purposes.[1,2] The ability of C_{60} and its derivatives to scavenge a large number of radicals per molecule[3,4] makes them potentially useful drugs in the prevention or treatment of pathologies in which oxidative damage is involved, namely cardiovascular[5,6] and neurodegenerative diseases.[7,8]

Flavonoids, a widely distributed class of phytochemicals, also possess important medicinal properties: they act as antioxidants[9,10] and anticarcinogens,[11,12] and they express beneficial effects in inflammatory and immunomodulatory systems.[13,14]

Currently we are developing a project concerning the synthesis of new radical scavengers with potential application in medicine. Knowing the aptitude of fullerenes and flavonoids to trap radicals, we have been preparing fullerene–flavonoid dyads aiming to obtain compounds that may behave as radical sponges. Recently we reported[15] the synthesis of novel fullerene–chalcone and fullerene–flavone dyads, obtained by 1,3-dipolar cycloaddition reactions of azomethine ylides to C_{60}. Synthetic chalcones and flavones were then used. Now we report the synthesis of new fullerene–flavone dyads but starting with quercetin, a natural flavonol with high antioxidant activity. The new compounds were obtained by cyclopropanation[16] of C_{60} with the appropriate malonate derivatives. The antioxidant activity of quercetin (3,3′,4′,5,7-pentahydroxyflavone) is higher than other pentahydroxyflavonoids (catequin, for



Scheme 1. (a) CH_3I (30 mmol), K_2CO_3 (22.5 mmol), CH_3CN/CH_3OH (2:1) 60°C, 10 h. (b) *p*-TsCl (4 equiv.), K_2CO_3 (8 equiv.), CH_3CN, 60°C, 1 h. (c) $AlBr_3$ (3.1 equiv.), CH_3CN, 0°C, 1 h. (d) $AlBr_3$ (1.1 equiv.), CH_3CN, 0°C, 1 h.

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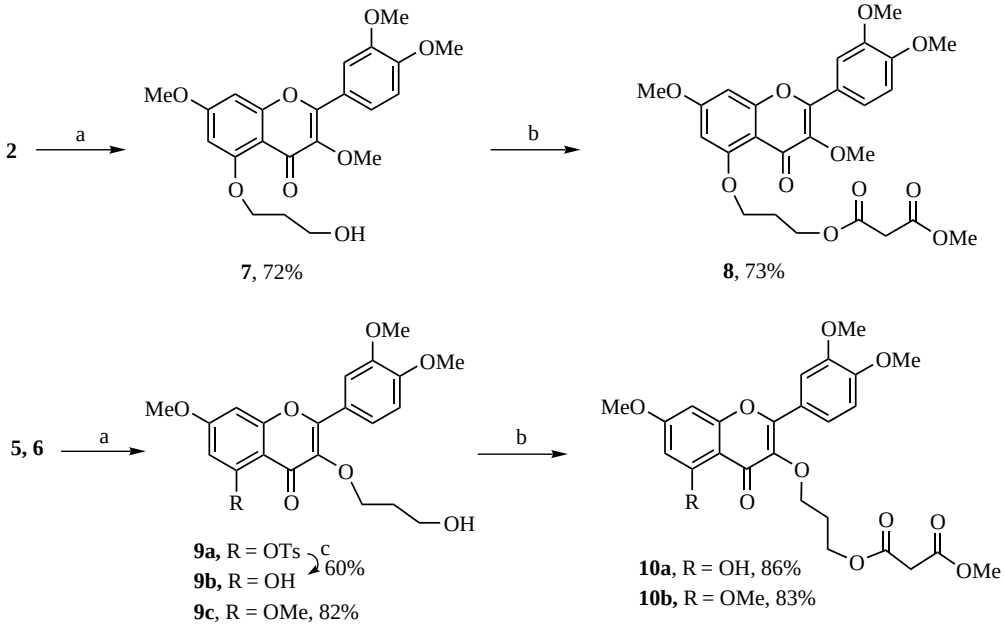
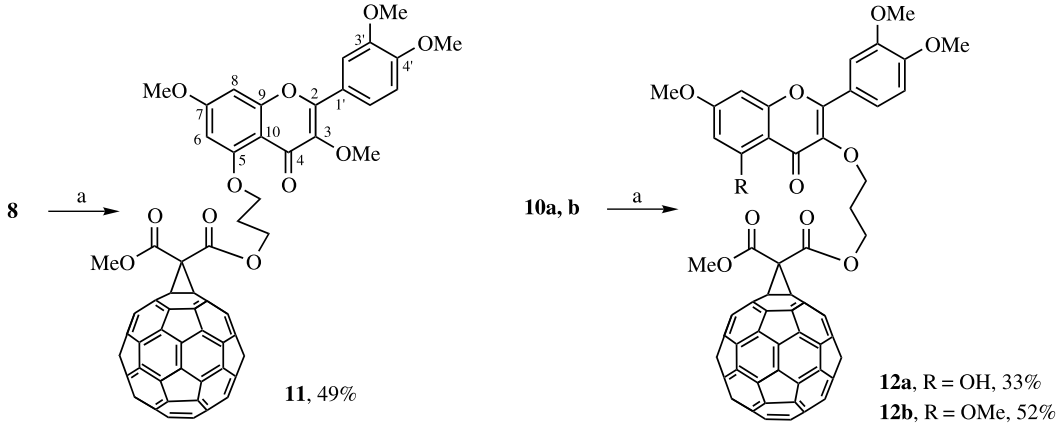
instance). This is due to the presence of a 2,3-double bond and to the 4-oxo function in ring C which allows electron delocalization across the molecule and increases the stability of the aryloxyl radical after hydrogen donation.[10] The presence of a 3′,4′-dihydroxyphenyl system and a 3-hydroxyl group also contributes to the high antioxidant activity of this compound.[10]

The synthetic steps for the formation of different C_{60}-quercetin derivative dyads are indicated in Schemes 1–3. It involved the alkylation of one hydroxyl group of the quercetin with 3-iodo-1-propanol, conversion of the resulting alcohol into a malonate derivative and, finally, coupling the malonate to C_{60} via a cyclopropanation reaction (Bingel reaction).[16] Since quercetin has five hydroxyl groups, to prevent the formation of mixtures of isomers, it is important to protect selectively four hydroxyl groups. As indicated in Scheme 1, by a *O*-methylation/demethylation process,[17] we succeeded to prepare quercetin derivatives with 5-OH (compound **2**) and 3-OH (compounds **5** and **6**) free groups.

Methylation of quercetin with methyl iodide afforded a mixture of compounds **2** and **3**. These compounds were separated by flash chromatography using mixtures of CH_2Cl_2/acetone (9:1 to 7:3) as eluent and were crystallized from ethanol. Demethylation of compound **3** gave the 3-OH derivative **6** and an additional amount of **2** (26%). Compound **2** was used in the reaction with 3-iodo-1-propanol (Scheme 2) and also in the preparation of derivative **5** (Scheme 1): tosylation followed by demethylation led exclusively to **5**. All these compounds were purified by flash chromatography using dichloromethane/acetone 9:1 as eluent and were crystallized from ethanol. Alkylation of **2** and **6** with 3-iodo-1-propanol afforded directly the propanol derivatives **7**



Scheme 2. (a) 3-Iodo-1-propanol (2 equiv.), K_2CO_3 (4 equiv.), dimethylformamide, 60°C, 3 h. (b) Methyl malonyl chloride (4.3 equiv.), triethylamine (2 equiv.), CH_2Cl_2, 0°C to rt, 3 h. (c) K_2CO_3 (2 equiv.), methanol, reflux, 0.5 h.



Scheme 3. (a) C_{60} (2.5 equiv.), I_2 (1.1 equiv.), DBU (3.5 equiv.), toluene, rt, 1 h.

and **9c** in good yields (Scheme 2). In a similar process, **5** yielded the corresponding tosylated propanol derivative **9a** which after treatment with K_2CO_3 in refluxing methanol afforded **9b** in 60% (two steps). These compounds were converted into the corresponding malonates **8** and **10** by esterification with methyl malonyl chloride (Scheme 2).

Compounds **7** and **9** were purified by flash chromatography using dichloromethane/acetone 4:1 as eluent and were crystallized from ethanol; compounds **8** and **10** were also purified by flash chromatography but using dichloromethane/acetone 95:5 as eluent.

Cyclopropanation reactions of C_{60} with malonates **8** or **10** afforded the final dyads **11** or **12** in moderate yields (Scheme 3). Compounds **11** and **12** were separated from the unreacted C_{60} by flash column chromatography using toluene to toluene/ethyl acetate 7:3 as eluent. The first fraction was the unchanged C_{60} and the next one was the monoadduct **11** or **12**. Products with higher polarity, probably bis-adducts, were discharged. The fullerene derivatives were fully characterized by mass and ^{1}H and ^{13}C NMR spectra.[18–20] In the ^{13}C NMR spectra the signals appearing at ca. 52 and 71.5 ppm correspond, respectively, to the methano bridge and to the C_{60}-sp^3 carbons. These assignments were corroborated by DEPT (135°) experiments. The signals of all carbons from the malonyl moiety were unequivocally assigned by HETCOR (or HSQC) and HMBC experiments. When we compare the NMR spectra of a series of derivatives (**7**, **8** and **11**, for instance) there are no significant variations in the signals corresponding to the quercetin moiety.

The extension of this work to the synthesis of novel fullerene derivatives having other natural antioxidant moieties and the evaluation of the properties of the final products is currently under way.

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References

1. Da Ros, T.; Prato, M. *Chem. Commun.* **1999**, 663–669.
2. Jensen, W.; Wilson, S. R.; Schuster, D. I. *Bioorg. Med. Chem.* **1996**, *4*, 767–779.
3. Morton, J. R.; Negri, F.; Preston, K. F. *Acc. Chem. Res.* **1998**, *31*, 63–69.
4. Bensasson, R. V.; Brettreich, M.; Frederiksen, J.; Göttinger, H.; Hirsch, A.; Land, E. J.; Leach, S.; McGarvey, D. J.; Schönberger, H. *Free Rad. Biol. Med.* **2000**, *29*, 26–33.
5. Wang, I. C.; Tai, L. A.; Lee, D. D.; Kanakamma, P. P.; Shen, C. K.-F.; Luh, T.-Y.; Cheng, C. H.; Hwang, K. C. *J. Med. Chem.* **1999**, *42*, 4614–4620.
6. Hsu, H. C.; Chiang, P. Y.; Chen, W. J.; Lee, Y. T. *J. Cardiovascular Pharmacol.* **2000**, *36*, 423–427.
7. Dugan, L. L.; Turetsky, D. M.; Du, C.; Lobner, D.; Wheeler, M.; Almli, C. R.; Shen, C. K.-F.; Luh, T.-Y.; Choi, D. W.; Lin, T. S. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 9434–9439.
8. Dugan, L. L.; Lovett, E. G.; Quick, K. L.; Lotharius, J.; Lin, T. T.; O'Malley, K. L. *Parkinsonism Related Disorders* **2001**, *7*, 243–246.
9. Pietta, P.-G. *J. Nat. Prod.* **2000**, *63*, 1035–1042.
10. Rice-Evans, C. A.; Miller, N. J.; Paganga, G. *Free Rad. Biol. Med.* **1996**, *20*, 933–956.
11. Beudot, C.; De Méo, M. P.; Dauzone, D.; Elias, R.; Laget, M.; Guiraud, M.; Balausard, G.; Dúmenil, G. *Mutation Res.* **1998**, *417*, 141–153.
12. Akama, T.; Ishida, H.; Shida, Y.; Kimura, U.; Gomi, K.; Saito, H.; Fuse, E.; Kobayashi, S.; Yoda, N.; Kasai, M. *J. Med. Chem.* **1997**, *40*, 1894–1900.
13. Bors, W.; Heller, W.; Michel, C.; Stettmaier, K. Flavonoids and Polyphenols: Chemistry and Biology, In Handbook of Antioxidants, Cadenas, E.; Packer, L., Eds.; Marcel Dekker: New York, 1996; p. 409
14. *Flavonoids in Health and Diseases*; Rice-Evans, C. A.; Packer, L., Eds; Marcel Dekker: New York, 1998.
15. De la Torre, M. D. L.; Marcorin, G. L.; Pirri, G.; Tomé, A. C.; Silva, A. M. S.; Cavaleiro, J. A. S. *Tetrahedron Lett.* **2002**, *43*, 1689–1691.
16. Bingel, C. *Chem. Ber.* **1993**, *126*, 1957.
17. Horie, T.; Kitou, T.; Kawamura, Y.; Yamashita, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1033–1041.
18. Selected data for compound **11**: ^{1}H NMR [300.13 MHz, $CDCl_3$, δ (ppm), J (Hz)]: 7.66–7.63 (m, 2H, H-2′, H-6′), 6.98 (d, $J=8.4$, 1H, H-5′), 6.45 (d, $J=2.2$, 1H, H-8), 6.25 (d, $J=2.2$, 1H, H-6), 4.96 (t, $J=5.7$, 2H), 4.19 (t, $J=5.7$, 2H), 4.80 (s, 3H, CO_2CH_3), 3.97, 3.96, 3.86, 3.80 (4 s, 4×3H, 4×OCH_3), 2.48 (qui, $J=5.7$, 2H); ^{13}C NMR [75.47 MHz, $CDCl_3$, δ (ppm)]: 173.6 (C-4), 163.8 (CO_2CH_3), 163.7 (C-7), 163.4 (CO_2R), 160.0 (C-5), 158.8 (C-9), 152.9 (C-2), 150.8 (C-4′), 148.6 (C-3′), 145.4, 145.2, 145.1, 145.0, 144.8, 144.7, 144.6, 144.5, 144.3, 144.2, 143.8, 143.0, 142.9, 142.8, 142.5, 142.1, 142.0, 141.8, 141.6, 141.2, 140.8, 140.7 (C-3), 139.5, 138.3, 129.2, 128.2, 125.3, 123.3 (C-1′), 121.6 (C-6′), 111.1 (C-2′), 110.7 (C-5′), 109.8 (C-10), 96.8 (C-6), 92.8 (C-8), 71.5 (C_{60}-sp^3), 64.9 ($OCH_2CH_2CH_2OCO$), 63.9 ($OCH_2CH_2CH_2OCO$), 59.9 (3-OCH_3), 56.0 (7-OCH_3), 55.8 (3′-OCH_3 and 4′-OCH_3), 54.1 (CO_2CH_3), 52.0 (methano bridge), 28.0 ($OCH_2CH_2CH_2OCO$); HRMS (FAB) m/z calculated for $C_{86}H_{27}O_{11}$ $(M+H)^+$: 1235.1553, found: 1235.1599.
19. Selected data for compound **12a**: ^{1}H NMR [300.13 MHz, $CDCl_3$, δ (ppm), J (Hz)]: 12.60 (s, 1H, 5-OH), 7.73 (dd, $J=8.5$ and 1.9, 1H, H-6′), 7.60 (d, $J=1.9$, 1H, H-2′), 7.01 (d, $J=8.5$, 1H, H-5′), 6.43 (d, $J=2.1$, 1H, H-8), 6.34 (d, $J=2.1$, 1H, H-6), 4.65 (t, $J=6.2$, 2H), 4.15 (t, $J=6.2$, 2H), 4.07 (s, 3H, CO_2CH_3), 4.04, 3.96, 3.86 (3 s, 3×3H, 3×OCH_3), 2.27 (qui, $J=6.2$, 2H); ^{13}C NMR [75.47 MHz, $CDCl_3$, δ (ppm): 178.5 (C-4), 165.5 (CO_2CH_3), 165.5 (C-7), 164.0 (COR), 162.0 (C-5), 158.0 (C-9), 156.7 (C-2), 151.4 (C-4′), 148.7 (C-3′), 145.3, 145.2, 145.1, 145.0, 144.9, 144.8, 144.7, 144.5, 143.9, 143.8, 143.0, 142.9,

142.8, 142.2, 142.1, 141.9, 141.7, 140.9, 139.3, 138.6, 138.0, 137.9 (C-3), 129.0, 128.2, 125.3, 122.8 (C-6′), 122.5 (C-1′), 111.2 (C-2′), 110.8 (C-5′), 106.1 (C-10), 98.0 (C-6), 92.3 (C-8), 71.5 (C_{60}-sp^3), 69.3 ($OCH_2CH_2CH_2OCO$), 64.3 ($OCH_2CH_2CH_2OCO$), 56.1 (7-OCH_3), 56.0, 55.8 (3′-OCH_3 and 4′-OCH_3), 54.1 (CO_2CH_3), 52.3 (methano bridge), 29.5 ($OCH_2CH_2CH_2OCO$); HRMS (FAB) m/z calculated for $C_{85}H_{25}O_{11}$ $(M+H)^+$: 1221.1397, found: 1221.1399.

20. Selected data for compound **12b**: ^{1}H NMR [300.13 MHz, $CDCl_3$, δ (ppm), J (Hz)]: 7.71 (dd, $J=8.5$ and 1.9, 1H, H-6′), 7.64 (d, $J=1.9$, 1H, H-2′), 7.00 (d, $J=8.5$, 1H, H-5′), 6.50 (d, $J=2.1$, 1H, H-8), 6.35 (d, $J=2.1$, 1H, H-6), 4.65 (t, $J=6.2$, 2H), 4.17 (t, $J=6.2$, 2H), 4.04 (s, 3H, CO_2CH_3), 3.97, 3.95, 3.90 (3 s, 4×3H, 4×OCH_3), 2.28 (qui, $J=6.2$, 2H); ^{13}C NMR [75.47 MHz, $CDCl_3$, δ (ppm)]: 173.8 (C-4), 164.1 (CO_2CH_3), 164.0 (C-7), 163.4 (CO_2R), 160.1 (C-5), 158.8 (C-9), 152.8 (C-2), 150.8 (C-4′), 148.6 (C-3′), 145.3, 145.2, 145.1, 145.0, 144.9, 144.8, 144.7, 144.6, 144.5, 143.9, 143.8, 143.0, 142.9, 142.8, 142.2, 142.1, 141.9, 141.7, 140.9, 140.2 (C-3), 139.3, 138.5, 138.0, 137.9, 129.0, 128.2, 125.3, 123.2 (C-1′), 122.0 (C-6′), 110.8 (C-5′), 111.2 (C-2′), 109.4 (C-10), 95.9 (C-6), 92.1 (C-8), 71.5 (C_{60}-sp^3), 69.0 ($OCH_2CH_2CH_2OCO$), 64.7 ($OCH_2CH_2CH_2OCO$), 55.8 (7-OCH_3), 56.4, 55.1 (3′-OCH_3, 4′-OCH_3 and 5-OCH_3), 54.1 (CO_2CH_3), 52.3 (methano bridge), 29.7 (OCH_2CH_2-CH_2OCO); HRMS (FAB) m/z calculated for $C_{86}H_{27}O_{11}$ $(M+H)^+$: 1235.1553, found: 1235.1542.