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New malonate macrocycle bearing two isosteviol moieties and its adduct with fullerene C_{60}

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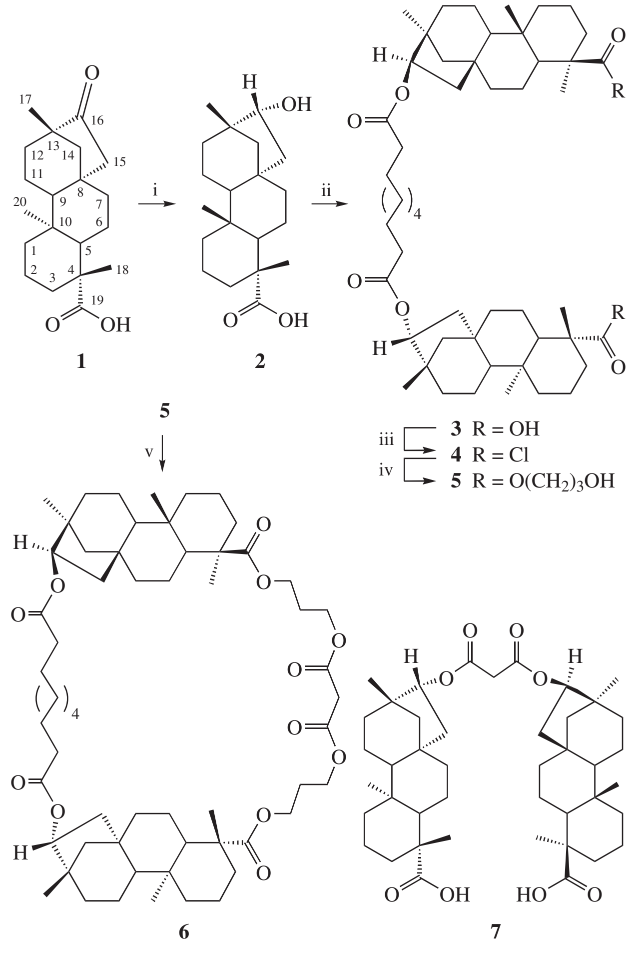
Macrocycle having two isosteviol moieties and malonate fragment has been synthesised, and its ability to inhibit the growth of *Mycobacterium tuberculosis* H37Rv *in vitro* with MIC value of 1 μg cm^{-3} has been demonstrated. The macrocycle adds fullerene C_{60} at the activated methylene group to furnish the corresponding methanofullerene conjugate.

Synthesis of macrocycles and study of their properties is topical. Macrocycles are of interest as the host molecules, capable of binding and transporting various ions or molecules[1] and of chiral recognition.[1,2] Cyclodextrins are the most well known hosts among naturally occuring macrocycles. Due to the amphiphility (the polar external surface and hydrophobic cavity), they increase solubility of biologically active compounds and food additives in water, which make them useful in pharmacology and food industry.[3] Cyclodextrins, as themselves have no biological activity, while several hundreds of other natural macrocycles do reveal such an activity.[4] It is necessary to note, that all known natural terpenoid macrocycles are not formed by covalent bonding of several terpenoid molecules by any linkers, they are terpenoids in themselves.[4] As for synthetic derivatives of natural metabolites, only a few macrocycles containing one or several steroid[5] or monoterpenoid[6] units are known by now. A few macrocycles having one diterpenoid moiety are reported.[7(*a*)–(*c*)] Recently, several macrocycles with two diterpenoid isosteviol units connected *via* linkers having anhydride, ester and hydrazide functions have been synthesized in our group.[7(*d*),(*e*)] Isosteviol **1** (*ent*-16-oxobeyeran-19-oic acid) belongs to diterpenoids of *ent*-beyeran series and is obtained by acid hydrolysis of stevioside, which is the main glycoside of *Stevia rebaudiana* Bertoni.[8(*a*)] It possesses various important properties, *e.g.* antihypertensive effect,[8(*b*)] antituberculous activity,[8(*c*)] ability to transport Fe^{III} [ref. 8(*d*)] and amino acids[8(*e*)] through liquid chloroform membrane as well as the ability to form crystalline inclusion complexes with some aromatic compounds.[8(*f*),(*g*)] One can suppose that incorporation of isosteviol **1** into macrocycles will intensify its properties, as it was in the case of diterpenoid paclitaxel (taxol).[7(*a*)–(*c*)] Therefore, the synthesis of macrocyclic derivatives of isosteviol **1** and subsequent study of their properties are important.

Here, we report the synthesis of a macrocycle having two isosteviol units connected by the ester linkers including malonate moiety. Malonate moiety is promising for the design of more complicated macrocyclic system. Herein, we accessed two hybrid molecules in which unfolded and macrocyclic compounds with two isosteviol units, coupled by malonate linker, were tethered to fullerene C_{60} by the Bingel reaction.[9] Note that pioneering macrocycles with malonate fragments, namely, 11,13-dioxo-13-crown-4 and its analogues, were obtained a long time ago,[10] however, only recently they began to be used as malonate building blocks for design of new organic compounds.[11]

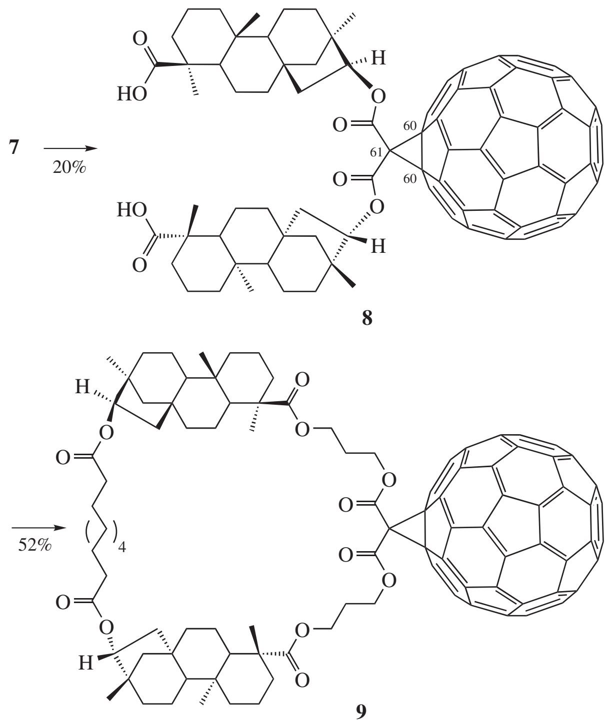
The synthesis of target macrocycle **6** is summarized in Scheme 1. Initial reduction of isosteviol **1** with $NaBH_4$ in EtOH afforded *ent*-16(*R*)-hydroxybeyeran-19-oic acid **2**[12] in a good yield. Treatment of **2** with sebacinoyl dichloride in CH_2Cl_2 in the presence of Py and DMAP furnished diester diacid **3**[8(*c*)] in 58% yield, which was then quantitatively converted with the excess of thionyl chloride into the corresponding dichloride **4**.[†] Then compound **5**[‡] was easily obtained in a good yield by the treatment of dichloride **4** with excess of 1,3-propanediol in CH_2Cl_2. The final macrocyclization of diol **5** with malonyl chloride under modified conditions brought about macrocycle **6**[§] in 61% yield.



Scheme 1 *Reagents and conditions*: i, $NaBH_4$, EtOH, room temperature (92%); ii, $ClOC(CH_2)_8COCl$, CH_2Cl_2, DMAP, Py, room temperature (58%); iii, $SOCl_2$, 40 °C (quantitative yield); iv, $HO(CH_2)_3OH$ excess, CH_2Cl_2, reflux (78%); v, $ClC(O)CH_2C(O)Cl$, CCl_4, reflux (61%).

Then we used synthetic potential of malonate linker connected to isosteviol units in **6** in the reaction with fullerene C_{60}. To the best of our knowledge, no information about the adduct of C_{60} with any terpenoid derivatives is available in literature. Therefore, first we started with the tethering of unfolded analogue of **6**, diacid **7**[8(*c*)] (Scheme 1) to fullerene C_{60} to test applicability of the Bingel conditions.[9] In fact, reaction of C_{60} with malonate **7** in the presence of DBU and CBr_4 led to the expected methanofullerene **8** in 20% yield (Scheme 2).[¶]

The complete structure elucidation of compounds **7** and **8** was carried out by a complex of correlation NMR methods[13] (see Online Supplementary Materials). ^{13}C NMR spectrum of adduct **8** contains a number of resonances in aromatic and aliphatic regions. To establish the cycloaddition pattern, one needs to assign the C^{60} and C^{61} atoms exactly (Scheme 2). Unfortunately, these carbons are in the overlapped region where several malonate carbons can also resonate. Therefore, compound **7** was first investigated in order to attribute all resonances in ^{1}H and ^{13}C NMR spectra. Proton spin systems in malonate moiety of **7** were assigned from 2D COSY spectrum and all hydrogenated carbon atoms were determined from 2D HSQC spectrum. Finally, from HMBC correlations all carbon atoms of two isosteviol skeletons in **7** were unequivocally assigned. Almost perfect correlation of calculated [GIAO B3LYP/6-31G(d)//HF/6-31G][14,15] for simpler model **7a** (see Online Supplementary Materials) *versus* experimental for **7** ^{13}C NMR chemical shift values ($R^2 = 0.998$) additionally supports the validity of above derived conclusion on the assignment (see Online Supplementary Materials). For methanofullerene **8** there are 48 peaks in ^{13}C NMR spectrum from which 22 signals were exactly ascribed by variety of 2D NMR correlation techniques to carbons of malonate fragment (see Online Supplementary Materials). Fullerene sphere of adduct **8** is characterized by signals, whose number and intensity (23 signals with the intensity of 2C, two signals with 4C and one signal corresponding to 6C) indicate the C_s symmetry of compound **8**. Thus, the sp^3-carbon of the C_{60} cage appeared at 72.82 ppm corresponding to the [6,6]-type of addend linkage.



Scheme 2 *Reagents and conditions*: C_{60}, CBr_4, DBU, *o*-dichlorobenzene, room temperature.

Furthermore, macrocycle **6** was tethered to fullerene C_{60} under the same Bingel conditions[9] as malonate **7**, affording methanofullerene **9** in a good yield (52%).[¶] The signals in ^{13}C NMR spectrum of adduct **9** were assigned by analogy with those of compound **8**.

In conclusion, firstly, we have prepared a novel malonate macrocycle **6** having two isosteviol moieties. It is necessary to note

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[†] *Dichloride* **4**. Compound **3** (0.9 g, 1.1 mmol) was dissolved in a large excess $SOCl_2$ and heated for 2 h at 40 °C. The reaction mixture was concentrated under vacuum affording **4** as viscous oil. Yield, 0.94 g (100%). IR (ν/cm^{-1}): 1732, 1795 (C=O). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 0.79–2.00 (mm, 54H, isosteviol skeleton), 0.82 (s, 6H, $C^{20'}H_3$, $C^{20}H_3$), 0.91 (s, 6H, $C^{17'}H_3$, $C^{17}H_3$), 1.32 (s, 6H, $C^{18'}H_3$, $C^{18}H_3$), 2.32 [m, 6H, 3α′,3α-H and $C^{16'}$,C^{16}-OC(O)C*H*$_2$CH$_2$], 4.75 (dd, 2H, $C^{16'}$H, C^{16}H, *J* 10.5, 4.3 Hz).

[‡] *Diol* **5**. Solution of **4** (0.46 g, 0.55 mmol) in CH_2Cl_2 (30 ml) was added dropwise to a stirred 1,3-propanediol (10 ml) under argon. The mixture was stirred at 50 °C for 1 h and the product was extracted with CH_2Cl_2. The extract was washed with water, dried and evaporated. The residue was purified by column chromatography on silica to give diol **5**. Yield, 0.40 g (78%), viscous oil. IR (ν/cm^{-1}): 1722 (C=O), 3434, 3485 (OH). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 0.70 (s, 6H, $C^{20'}H_3$, $C^{20}H_3$), 0.90 (s, 6H, $C^{17'}H_3$, $C^{17}H_3$), 1.17 (s, 6H, $C^{18'}H_3$, $C^{18}H_3$), 1.88 [m, 4H, O(O)CCH$_2$C*H*$_2$], 2.30 [t, 4H, $C^{16'}$,C^{16}-OC(O)C*H*$_2$CH$_2$, *J* 7.5 Hz], 3.69 (t, 4H, C*H*$_2$OH, *J* 6.2 Hz), 4.10 and 4.24 [m, 2H, C(O)OCH$_2$], 4.72 (dd, 2H, $C^{16'}$H, C^{16}H, *J* 10.5, 4.7 Hz). MALDI-TOF MS, *m*/*z*: 945.738 [M + Na]$^+$, 961.726 [M + K]$^+$.

[§] *Malonate macrocycle* **6**. Malonyl chloride (0.08 g, 0.6 mmol) in CCl_4 (30 ml) was added dropwise to a stirred solution of diol **5** (0.46 g, 0.5 mmol) in CCl_4 (100 ml) and the mixture was refluxed for 8 h under argon. Then the mixture was concentrated under vacuum. The residue was purified by column chromatography on silica to give macrocycle **6**. Yield, 0.31 g (61%), white powder, mp 145–148 °C (ethanol). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 0.70 (s, 6H, $C^{20'}H_3$, $C^{20}H_3$), 0.91 (s, 6H, $C^{17'}H_3$, $C^{17}H_3$), 1.16 (s, 6H, $C^{18'}H_3$, $C^{18}H_3$), 1.99 [q, 4H, O(O)CCH$_2$C*H*$_2$, *J* 6.4 Hz], 2.30 [m, 4H, OC(O)C*H*$_2$CH$_2$], 3.40 [s, 2H, O(O)CCH$_2$C(O)O], 4.04 and 4.15 [m, 2×2H, C(O)OCH$_2$], 4.25 [t, 4H, C*H*$_2$OC(O)CH$_2$OC(O)C*H*$_2$, *J* 6.2 Hz], 4.71 (dd, 2H, $C^{16'}$H, C^{16}H, *J* 10.6, 4.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.18, 18.89, 20.17, 21.67, 24.85, 25.09, 27.74, 28.98, 29.05, 34.46, 34.61, 37.93, 38.04, 39.84, 40.85, 41.37, 42.34, 43.78, 54.74, 55.58, 57.09, 60.33, 62.19, 81.38, 166.20, 173.86, 177.23. MALDI-TOF MS, *m*/*z*: 1013.740 [M + Na]$^+$, 1029.737 [M + K]$^+$.

[¶] *General procedure for the preparation of methanofullerenes* **8**, **9**. Solutions of DBU (0.125 mmol) and CBr_4 (0.125 mmol) in *o*-dichlorobenzene were added to a stirred solution of C_{60} (0.083 mmol) and malonate (**6** or **7**) (0.125 mmol) in *o*-dichlorobenzene under argon. The reaction mixture was stirred at room temperature for 24 h, then concentrated under vacuum. The residue was purified by column chromatography on silica.

For **8**: yield 20%, dark brown solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 0.87 (s, 12H, $C^{20'}H_3$, $C^{20}H_3$, $C^{17'}H_3$, $C^{17}H_3$), 1.25 (s, 6H, $C^{18'}H_3$, $C^{18}H_3$), 5.07 (br. t, 2H, $C^{16'}$H, C^{16}H, *J* 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.68, 18.64, 20.07, 21.70, 28.59, 34.63, 37.31, 38.27, 39.23, 39.65, 41.13, 43.39, 54.70, 55.13, 55.64, 55.94, 72.83, 85.13, 162.60, 185.33 (isostevioylmalonate moiety); 145.93 (2C), 145.65 (2C), 145.44 (2C), 145.32 (2C), 145.25 (2C), 145.11 (4C), 144.84 (2C), 144.80 (2C), 144.71 (2C), 144.68 (2C), 144.67 (2C), 144.64 (2C), 144.47 (2C), 143.85 (2C), 143.75 (2C), 143.06 (6C), 142.93 (4C), 142.22 (2C), 142.14 (2C), 142.13 (2C), 142.00 (2C), 141.19 (2C), 140.98 (2C), 138.24 (2C), 138.14 (2C), 72.82 (2C, C^{60}) (fullerene moiety), 42.08 (1C, $C^{61}_{sp^3}$). MALDI-TOF MS, *m*/*z*: 1427.425 [M + H]$^+$, 1450.454 [M + H + Na]$^+$, 1466.493 [M + H + K]$^+$.

For **9**: yield 52%, dark brown solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 0.74 (s, 6H, $C^{20'}H_3$, $C^{20}H_3$), 0.90 (s, 6H, $C^{17'}H_3$, $C^{17}H_3$), 1.19 (s, 6H, $C^{18'}H_3$, $C^{18}H_3$), 2.19 [m, 4H, O(O)CCH$_2$C*H*$_2$], 2.30 [m, 4H, $C^{16'}$,C^{16}-CO(O)C*H*$_2$CH$_2$, *J* 7.5 Hz], 4.15 and 4.25 [m, 2×2H, C(O)OCH$_2$], 4.60 [t, 4H, C*H*$_2$OC(O)-CH$_2$OC(O)C*H*$_2$, *J* 6.2 Hz], 4.71 (dd, 2H, $C^{16'}$H, C^{16}H, *J* 10.5, 4.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.24, 18.98, 20.21, 21.74, 24.88, 25.11, 28.00, 29.05, 34.50, 34.63, 38.09, 38.93, 40.89, 41.42, 41.41, 42.36, 43.84, 54.78, 55.62, 57.11, 60.24, 64.07, 81.36, 163.33, 173.83, 177.11 (malonate macrocycle moiety), 145.27, 145.17, 142.20, 145.11, 145.10, 144.87, 144.68, 144.65, 144.62, 144.59, 143.86, 143.06, 143.00, 142.98, 142.97, 142.19, 141.87, 140.98, 140.94, 139.00, 71.47 (fullerene moiety), 51.97 ($C^{61}_{sp^3}$). MALDI-TOF, *m*/*z*: 1710.417 [M + H]$^+$, 1733.304 [M + H + Na]$^+$, 1749.411 [M + H + K]$^+$.

that changing the length of acid dichloride applied at stage ii (Scheme 1), and that of diol applied at stage iv (Scheme 1) one can regulate the size of macrocycle **6**. Secondly, incorporation of two isosteviol fragments into macrocyle did really increase its tuberculostatic activity. Actually, isosteviol **1** inhibits the growth of *M. tuberculosis* (H37Rv *in vitro*) by 99% at minimum concentration (MIC) 50 µg cm^{-3}.[8(*c*)] The bonding of two isosteviol molecules by diester linker affording **3** reduces MIC value to 12.5 µg cm^{-3},[8(*c*)] and further macrocyclization of diacid **3**, giving **6**, leads to the subsequent decrease in MIC value down to 1 µg cm^{-3}.[††] It should be emphasized that macrocycle **6**, in contrast to antituberculous drugs currently used (Isoniazid, Pyrazinamide, Rifampin, *etc.*), has no nitrogen-containing moieties, nevertheless its antitubercular activity is higher than that of Pyrazinamide [MIC = 12.5–20 µg cm^{-3} (ref. 16)], although it is still lower than the activity of Isoniazid [MIC = 0.02–0.04 µg cm^{-3} (ref. 16)]. One can suppose, that this fact proves the existence of unknown up to now mechanism for inhibition of *M. tuberculosis*. Thirdly, pioneering hybrid molecules of isosteviol derivatives (unfolded and macrocyclic) and C$_{60}$ were obtained. Their biological activity is under investigation now.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.04.006.

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[††] *Mycobacterium tuberculosis* H37Rv were incubated at 37 °C in Middlebrook 7H9 broth where they evolved CO$_2$ measured daily in the BACTEC MGIT 960 instrument (expressed as growth index, or GI, units). The MIC value of macrocycle **6** was defined as the lowest concentration that yielded a daily change in GI less than control vials (which had received a 1:100 diluted inoculum) on the day after the control vials achieved a GI of 30. This represents a 99% inhibition of the inoculum.