JOC*Article*

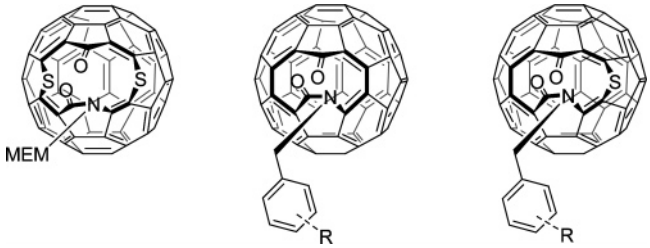
Open-Cage Fullerene Derivatives Having 11-, 12-, and 13-Membered-Ring Orifices: Chemical Transformations of the Organic Addends on the Rim of the Orifice

Manolis M. Roubelakis, Georgios C. Vougioukalakis, and Michael Orfanopoulos*

Department of Chemistry, University of Crete, Iraklion, Voutes 71003, Crete, Greece

orfanop@chemistry.uoc.gr

Received April 16, 2007



A novel open-cage [60]fullerene derivative, having two sulfur atoms on the rim of its 13-membered-ring orifice, has been isolated and characterized. Extensive studies on the *N*-MEM group reactivity of this as well as other previously reported open-cage [60]fullerene derivatives led to several new open-cage [60]-fullerene adducts.

Introduction

Endohedral fullerenes are currently being prepared by utilizing the evaporation of graphite−metal composites, high-temperature and high-pressure conditions, ion implantation, or high-energy plasma insertion into pure fullerenes.[1−4] The disadvantages of the above-mentioned methods are the low yields of the so formed endohedral complexes, as well as the difficult and tedious separation processes from the empty fullerene molecules.[5]

The proposal of the "molecular surgery approach",[6] soon after the isolation of the first open-cage fullerene derivative,[7] came up as an alternative route to the production of endohedral fullerenes. This innovative premise led several research groups to the development of a number of techniques for transforming the fullerenes' σ-framework, resulting open-cage derivatives.[8−12] According to this technique, a series of organic reactions creates an effective aperture on the surface of the fullerenes, allowing one small atom, molecule, or ion, such as He, H_2, or Li^+, to

(1) Shinohara, H. *Rep. Prog. Phys.* **2000**, *63*, 843−892.
(2) Nagase, S.; Kobayashi, K.; Akasaka, T. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2131−2142.
(3) (a) Mauser, H.; Van Eikema Hommes, N. J. R.; Clark, T.; Hirsch, A.; Pietzak, B.; Weidinger, A.; Dunsch, L. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2835−2838. (b) Pietzak, B.; Waiblinger, M.; Murphy, T. A.; Weidinger, A.; Höhne, M.; Dietel, E.; Hirsch, A. *Chem. Phys. Lett.* **1997**, *279*, 259−263.
(4) Stevenson, S.; Rice, G.; Glass, T.; Harich, K.; Cromer, F.; Jordan, M. R.; Craft, J.; Hadju, E.; Bible, R.; Olmstead, M. M.; Maitra, K.; Fisher, A. J.; Balch, A. L.; Dorn, H. C. *Nature* **1999**, *401*, 55−57.
(5) Rubin, Y. *Top. Curr. Chem.* **1999**, *199*, 67−91 and references therein.
(6) (a) Rubin, Y. *Chem.—Eur. J.* **1997**, *3*, 1009−1016. (b) Rubin, Y.; Jarrosson, T.; Wang, G.-W.; Bartberger, M. D.; Houk, K. N.; Schick, G.; Saunders, M.; Cross, R. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1543−1546.
(7) Hummelen, J. C.; Prato, M.; Wudl, F. *J. Am. Chem. Soc.* **1995**, *117*, 7003−7004.
(8) Schick, G.; Jarrosson, T.; Rubin, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 2360−2363.
(9) (a) Murata, Y.; Murata, M.; Komatsu, K. *Chem.—Eur. J.* **2003**, *9*, 1600−1609. (b) Murata, Y.; Murata, M.; Komatsu, K. *J. Am. Chem. Soc.* **2003**, *125*, 7152−7153. (c) Carravetta, M.; Murata, Y.; Murata, M.; Heinmaa, I.; Stern, R.; Tontcheva, A.; Samoson, A.; Rubin, Y.; Komatsu, K.; Levitt, M. H. *J. Am. Chem. Soc.* **2004**, *126*, 4092−4093. (d) Stanisky, C. M.; Cross, R. J.; Saunders, M.; Murata, M.; Murata, Y.; Komatsu, K. *J. Am. Chem. Soc.* **2005**, *127*, 299−302. (e) Komatsu, K.; Murata, M.; Murata, Y. *Science* **2005**, *307*, 238−240. (f) Vougioukalakis, G. C.; Prassides, K.; Orfanopoulos, M. *Org. Lett.* **2004**, *6*, 1245−1247.
(10) (a) Inoue, H.; Yamaguchi, H.; Iwamatsu, S.-i.; Uozaki, T.; Suzuki, T.; Akasaka, T.; Nagase, S.; Murata, S. *Tetrahedron Lett.* **2001**, *42*, 895−897. (b) Murata, Y.; Komatsu, K. *Chem. Lett.* **2001**, *30*, 896−897. (c) Murata, Y.; Murata, M.; Komatsu, K. *J. Org. Chem.* **2001**, *66*, 8187−8191.
(11) (a) Iwamatsu, S.-i.; Ono, F.; Murata, S. *Chem. Commun.* **2003**, 1268−1269. (b) Iwamatsu, S.-i.; Ono, F.; Murata, S. *Chem. Lett.* **2003**, *32*, 614−615. (c) Iwamatsu, S.-i.; Kuwayama, T.; Kobayashi, K.; Nagase, S.; Murata, S. *Synthesis* **2004**, 2962−2964. (d) Vougioukalakis, G. C.; Prassides, K.; Campanera, J. M.; Heggie, M. I.; Orfanopoulos, M. *J. Org. Chem.* **2004**, *69*, 4524−4526. (e) Chen, Z.-X.; Wang, G.-W. *J. Org. Chem.* **2005**, *70*, 2380−2383.
(12) (a) Iwamatsu, S.-i.; Uozaki, T.; Kobayashi, K.; Re, S.; Nagase, S.; Murata, S. *J. Am. Chem. Soc.* **2004**, *126*, 2668−2669. (b) Iwamatsu, S.-i.; Murata, S. *Tetrahedron Lett.* **2004**, *45*, 6391−6394.

10.1021/jo070796l CCC: $37.00
Published on Web 07/27/2007

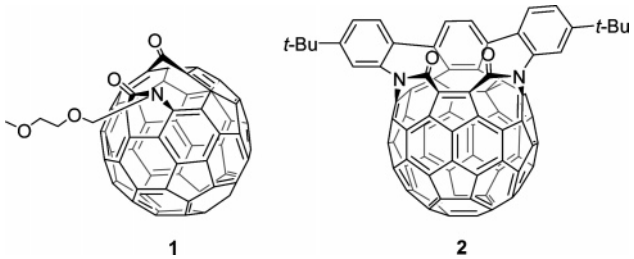


FIGURE 1. Open-cage fullerene structures reported earlier.

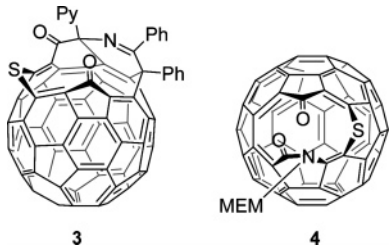


FIGURE 2. Open-cage fullerene derivatives bearing a sulfur heteroatom along the rim of their orifice.

pass through the hole and to be placed inside the cavity of these hollow structures. Restoration of the disrupted cage gives back the pristine fullerene with the desired species encapsulated.

Thus, open-cage fullerene derivatives have attracted much attention as key intermediates to endohedral complexes. Furthermore, due to the fact that they can trap and release a molecule reversibly,[13] these compounds could be used for molecular storage.

The first open-cage fullerene derivative (*N*-MEM-ketolactam **1**, Figure 1) was reported in 1995 by Wudl and co-workers.[7] However, even small atoms, such as He, could not pass through this small-sized orifice, at the temperature of 200 °C.[5] The first successful attempt in introducing an atom or molecule inside the fullerene cavity by the "molecular surgery approach" was reported in 2001 by Rubin and co-workers.[6b] Open-cage bislactam derivative **2** (Figure 1), with an elliptic 14-membered-ring orifice, was prepared, and both a He atom and a H_2 molecule were inserted in the cage with yields of 1.5 and 5%, respectively.

Later on, Komatsu and co-workers synthesized open-cage fullerene derivative **3** (Figure 2) bearing a 13-membered-ring orifice.[9a] The circular-like shape of the aperture in **3** allowed, for the first time, 100% encapsulation of molecular hydrogen at an applied H_2 pressure of 800 atm at 200 °C.[9b] Furthermore, it was shown that, upon laser irradiation, generation of $H_2@C_{60}$ is possible in the gas phase by self-restoration of $H_2@$**3**. More recently, they achieved the complete closure of the orifice of $H_2@$**3** by means of conventional chemistry, accomplishing the first preparation of the endohedral complex $H_2@C_{60}$ from empty C_{60} by organic synthesis.[9e] That work demonstrates that the molecular surgery approach might be an efficient methodology for the preparation of other kinds of endohedral fullerenes.

Recently, we demonstrated the versatility of Komatsu's method[9a] in enlarging the aperture of an open-cage fullerene, by inserting a sulfur atom along its rim. Thereby, *N*-MEM-ketolactam **1** was converted into compound **4** (Figure 2).[9f]

(13) (a) Iwamatsu, S.-i.; Murata, S. *Synlett* **2005**, 2117−2129 and references therein. (b) Chuang, S.-C.; Murata, Y.; Murata, M.; Mori, S.; Maeda, S.; Tanabe, F.; Komatsu, K. *Chem. Commun.* **2007**, 1278−1280.

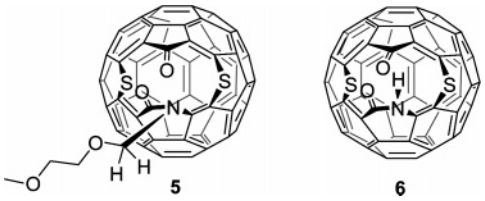


FIGURE 3. Doubly sulfur-inserted products **5** and **6**.

Herein, we report for the first time the isolation and characterization of the novel open-cage fullerene derivative **5**, shown in Figure 3, bearing two sulfur atoms on the rim of its orifice. Several transformations of the *N*-MEM protective group from adducts **1**, **4**, and **5** are also reported.

Results and Discussion

Synthesis, Isolation, Characterization, and Chemical Transformations of 5: Thermal treatment of **1** at 180 °C together with S_8 in 1,2-dichlorobenzene (ODCB) as the solvent for 40 min, in the presence of tetrakis(dimethylamino)ethylene (TDAE), afforded **4** and **5** in yields of 72 and 11%, respectively (based on the amount of the isolated adducts). Compound **4** has been previously reported and fully characterized in a preliminary communication.[9f] The molecular ion peak of **5** was observed at *m*/*z* 920 in its MALDI-TOF mass spectrum. On the basis of NMR and MALDI-TOF mass data, we suggest that two sulfur atoms have been incorporated into the fullerene skeleton of **5** as shown in Figure 3: one sulfur atom is inserted into the central C−C single bond of each butadiene unit of the starting material **1**. The ^{1}H NMR spectrum of adduct **5** is almost identical to that of the precursor **1**, apart from a slight upfield shift of the two double peaks that correspond to the protons adjacent to the carbon next to the nitrogen. The ketone ^{13}C NMR absorption is shifted from δ 198.5 ppm in the starting material **1** to δ 183.8 ppm in the adduct **5**, while the lactam ^{13}C chemical shift change is insignificant (the lactam carbon resonances are at 163.6 and 163.1 ppm in **1** and **5**, respectively). The lactam carbonyl absorption in the IR spectrum of **5** is shifted to 1680 cm^{-1}, from 1693 cm^{-1} in the starting material **1**, while the ketone carbonyl is practically unaffected since it moves from 1727 to 1724 cm^{-1}. The UV−vis spectrum of the new adduct in chloroform is similar to the starting material *N*-MEM-ketolactam, showing absorption maxima at 251 and 320 nm, whereas the corresponding absorptions of **1** are at 260 and 328 nm, respectively.

Treatment of adduct **5** with 1000 equiv of trifluoroacetic acid (vide infra) in chlorobenzene at 100 °C for 40 min afforded adduct **6** (Figure 3), without organic addends on the rim of the orifice, in 78% isolated yield. The solubility of this fully deprotected compound is extremely low even in ODCB. The molecular ion peak of **6** was clearly observed at *m*/*z* 831 in its MALDI-TOF mass spectrum. The ^{1}H NMR spectrum of adduct **6** (ODCB-d_4) showed only a D_2O exchangeable singlet at δ 9.48 ppm.

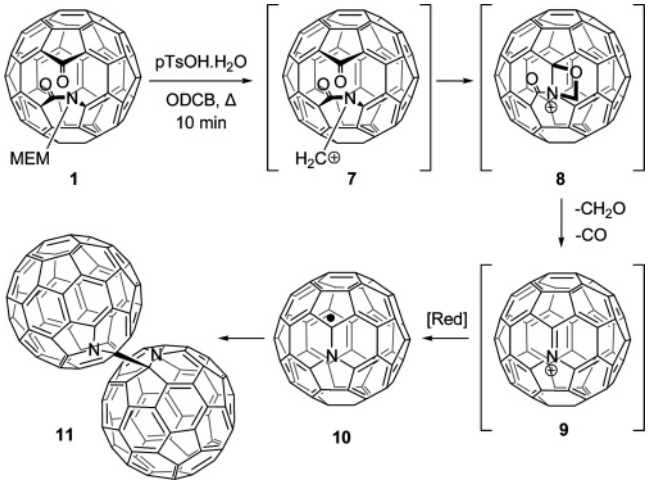
We next tried to improve the yield for **5** by increasing the sulfur as well as the TDAE equivalents used in the previous reaction. As shown in Table 1, the **4** to **5** ratio, determined by HPLC analysis, remained unaffected even in the presence of 100 equiv of elemental sulfur at a reaction time of 2 h. We also used adduct **4** as starting material in the place of *N*-MEM-ketolactam **1**. Again, the change in the yield of **5** was insignificant. These results indicate that the ratio of derivatives **4**/**5** is independent of the concentration of both sulfur and TDAE.

TABLE 1. Reaction of Open-Cage Compounds 1 and 4 with Elemental Sulfur

starting material	sulfur equiv	TDAE equiv	reaction time (min)	ratio **4**/**5**
1	2	2	40	6.5/1[a]
1	4	4	120	~6.5/1[b]
1	8	8	120	~6.5/1[b]
1	50	4	60	~6.5/1[b]
1	100	4	120	~6.5/1[b]
4	4	4	40	~6.5/1[b]

[a] Based on the amount of the isolated product. [b] Based on peak area % of HPLC observed at the end of the reaction.

SCHEME 1. Mechanism for the Formation of the $(C_{59}N)_2$ Dimer 11 from *N*-MEM-ketolactam 1 Proposed by Wudl and Co-workers



In order to confirm the necessity for the TDAE presence in the formation of the open-cage fullerene derivatives **4** and **5**, we tried to perform the reaction without adding any TDAE. After 4 h of heating *N*-MEM-ketolactam with 4 equiv of sulfur in ODCB at 180 °C, no products were detected. However, when TDAE was added, formation of adducts **4** and **5** was observed immediately.

Chemical Transformations of the Organic Addends of Derivatives 1 and 4. A Comparative Study: In an earlier work, Wudl and co-workers have shown that, upon refluxing ketolactam **1** with *p*-toluenesulfonic acid monohydrate in ODCB for 10 min, azafullerene dimer $(C_{59}N)_2$ is formed (**11**, Scheme 1).[14] That mechanism includes the initial formation of carbocation **7** which, subsequently, rearranges to the four-membered 1,3-oxazetidinium ring compound **8**, which in turn loses formaldehyde and carbon monoxide to yield the azafulleronium ion **9**. Intermediate **9** can be reduced to the azafullerenyl radical **10**, which dimerizes to yield the azafullerene dimer **11**.

In our efforts to synthesize the respective thioaza[60]fullerene dimer **12** from the S-ketolactam derivative **4**, through the corresponding carbocation **13** (Figure 4), we utilized the above-mentioned method for compound **4**.[9f] However, instead of the thioaza[60]fullerene **12**, we isolated adduct **14** (Figure 4) after the removal of the MEM protective group from the fullerene core. We anticipated that milder deprotection conditions could possibly lead to the formation of the thioazafullerene dimer **12**. Such mild conditions were recently reported by Iwamatsu and co-workers.[12b] They succeeded in the preparation of a new open-cage fullerene derivative **15a** (Figure 5), with a 19-membered ring orifice, by sequential cage scission reactions of *N*-MEM-ketolactam **1** with *o*-phenylenediamine, and next, they managed a gradual deprotection of the MEM protecting group by treatment with trifluoroacetic acid in toluene at ambient temperature. These mild conditions for the removal of the MEM group afforded derivatives **15b** and **15c** (Figure 5).

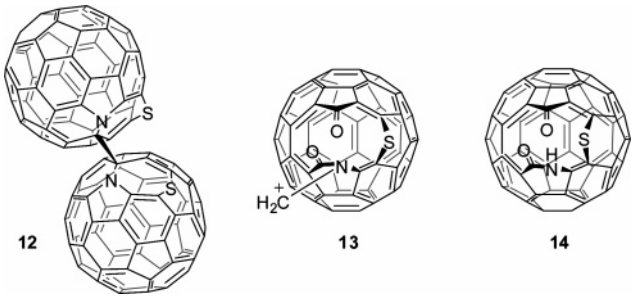


FIGURE 4. The structures of thioaza[60]fullerene dimer **12**, carbocation **13**, and fully deprotected derivative **14**.

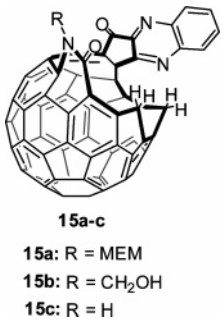


FIGURE 5. Open-cage fullerene derivatives with a 19-membered ring orifice.

Thus, following Iwamatsu's experimental procedure, open-cage fullerene derivative **4** was treated with a large excess of trifluoroacetic acid (600 equiv) in both toluene and chlorobenzene solutions at ambient temperature. According to TLC and HPLC analysis, **4** remained intact even after 3 days of stirring in each solvent. Thereupon, we increased the reaction temperature to 60 °C. After 1 day of stirring, for the reaction in toluene, a new spot appeared on TLC with an R_f value larger than that of S-ketolactam **4**. Both reactions were left at 60 °C for 2 more days.

HPLC analysis for the reaction in toluene showed two new peaks with retention times longer than that for **4**. Some starting material was still present in the solution. The integration of the three peaks, as determined by HPLC analysis, was 43% for the *N*-MEM-S-ketolactam **4**, 30% for the first adduct, and 27% for the second adduct. After column chromatographic purification, we isolated and characterized the two products. The first one, with retention time close to that of S-ketolactam **4**, was identified by ^{1}H NMR spectroscopy to be the already known adduct **14**.[9f] According to the related work of Iwamatsu,[12b] we initially thought that the second adduct would have been the open-cage derivative **16** (Figure 6). Nevertheless, on the basis of ^{1}H NMR, ^{13}C NMR, HMQC, ^{1}H−^{1}H COSY, and ^{13}C DEPT experiments as well as MS (MALDI), FT-IR, and UV−vis spectroscopy, we concluded that this new derivative is a mixture of the two isomers **17a** and **17b** (66/34 ratio based on ^{1}H NMR), shown in Figure 6. We propose that these new adducts are produced

(14) Hummelen, J. C.; Knight, B.; Pavlovich, J.; González, R.; Wudl, F. *Science* **1995**, *269*, 1554−1556.

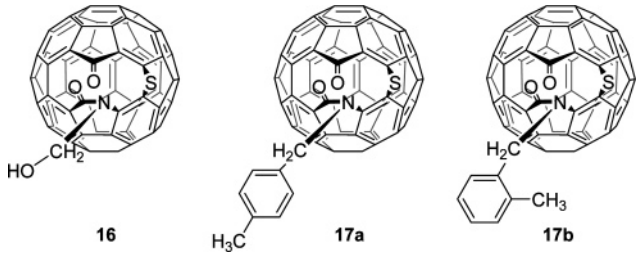


FIGURE 6. Molecular structures of **16**, **17a**, and **17b**.

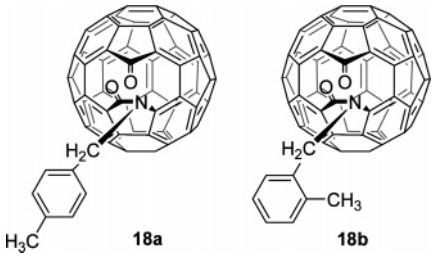


FIGURE 7. Molecular structures of isomers **18a** and **18b**.

by the electrophilic aromatic substitution reaction between toluene and the intermediate carbocation **13** at *para* and *ortho* positions, respectively (traces of the *meta* isomer were observed by ^{1}H NMR).

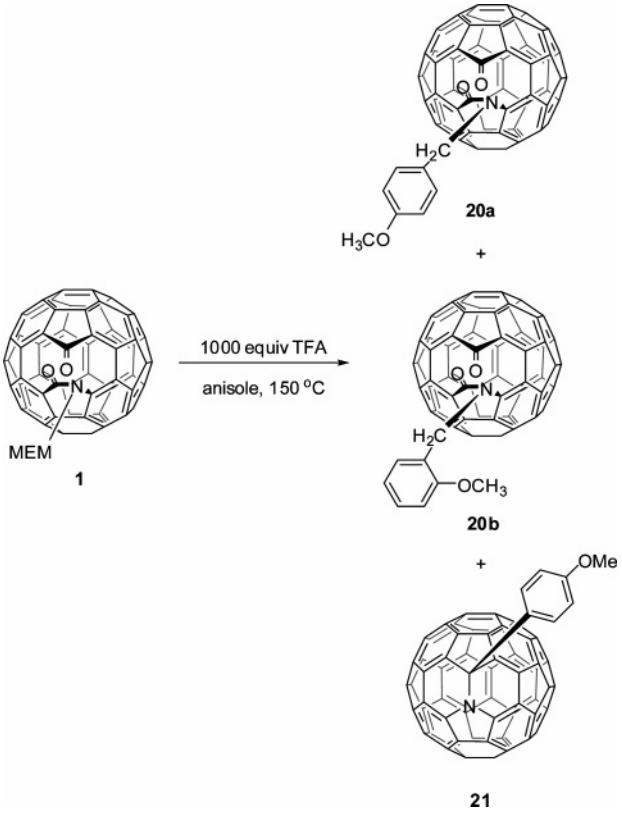
The reaction in chlorobenzene, after 3 days of heating at 60 °C, led to the formation of only one new derivative (determined by HPLC analysis), with exactly the same retention time as that for **14**, along with traces of starting material. Indeed, this was identified by ^{1}H NMR spectroscopy to be product **14**. Heating a mixture of *N*-MEM-S-ketolactam **4** with 600 equiv of trifluoroacetic acid in chlorobenzene at 100 °C for 2 h and 45 min afforded the fully deprotected *N*-MEM-S-ketolactam, which was purified and isolated in 90% yield. This procedure proved to be a more efficient way of producing adduct **14** than the one previously reported,[9f] due to its higher yield (90 versus 58%).

We must also note that, when *N*-MEM-S-ketolactam **4** was heated in toluene at 60 °C without any trifluoroacetic acid, it remained intact even after 4 days. In order to investigate the influence of pK_a on the removal of the MEM protective group, we replaced trifluoroacetic acid with acetic acid, a weaker acid. After heating the reaction for 18 h at 100 °C, the *N*-MEM-S-ketolactam moiety was intact in both toluene and chlorobenzene solutions, revealing that the use of strong acids, such as trifluoroacetic and *p*-toluenesulfonic, is crucial for the removal of the MEM protective group in these derivatives. Finally, we also carried out the deprotection of **4** by using milder conditions than those reported in our earlier work.[9f] Namely, **4** was treated with *p*-toluenesulfonic acid in ODCB, at 60 °C, instead of 150 °C. We anticipated that under these conditions removal of the MEM protective group may lead to the originally desired thioazafullerene dimer **12**. Unfortunately, we observed that derivative **14** was again the only product of the reaction.

We then also reduced the equivalents of the trifluoroacetic acid used to 50, 100, and 300 equiv in solutions of S-ketolactam **4** in toluene. The reaction mixtures were heated at 60 °C for 3 days; however, none of them gave any of the expected products (**14** or **17**) and only starting material **4** was present in the solutions. Therefore, at least 600 equiv of trifluoroacetic acid is necessary for the reaction to occur.

Our next step was to improve the yield of the new adduct **17** and reduce the reaction time. Accordingly, derivative **4** along with 600 equiv of trifluoroacetic acid were heated in toluene at 100 °C. The reaction was monitored by HPLC, and after 19 h, starting material had almost fully disappeared giving products **14** and **17** in a 2/3 ratio. In an effort to minimize the reaction time, we placed S-ketolactam **4** together with 1000 equiv of trifluoroacetic acid in toluene into a Schlenk tube. The reaction temperature was set at 150 °C. S-Ketolactam was completely consumed in 1 h and 40 min, affording again products **14** and **17** in a 2/3 ratio.

SCHEME 2. Reaction of the *N*-MEM-ketolactam Derivative of C_{60} 1 with Anisole



Similar reactions in PhCl and toluene were performed utilizing *N*-MEM-ketolactam **1** as starting material. After 3 days of heating at 60 °C in the presence of 600 equiv of trifluoroacetic acid, HPLC analysis on both reactions showed a single peak corresponding to the starting material. To make the conditions harsher, the reaction in toluene was placed in an oil bath at 100 °C and left overnight. HPLC analysis showed the appearance of a new peak. This new adduct was isolated as a mixture of the two isomers **18a** and **18b** (Figure 7), derived from the aromatic substitution of toluene by the electrophilic carbocation **7** on *para* and *ortho* positions, respectively (**18a**/**18b** $\approx$ 3/2; again, traces of the *meta* isomer were present in the mixture). When the reaction temperature was set at 150 °C and the equivalents of the trifluoroacetic acid were raised to 1000, complete consumption of **1** was observed within 5 h and adducts **18a** and **18b** were formed in 65% yield.

Next, we investigated whether electrophilic aromatic substitution reaction of *N*-methyl carbonium ions **7** and **13** can take place with the activated aromatic ring of anisole. Therefore, similar deprotection reactions were carried out in anisole as a solvent for **1** and **4**. Compound **4**, upon heating at 150 °C for

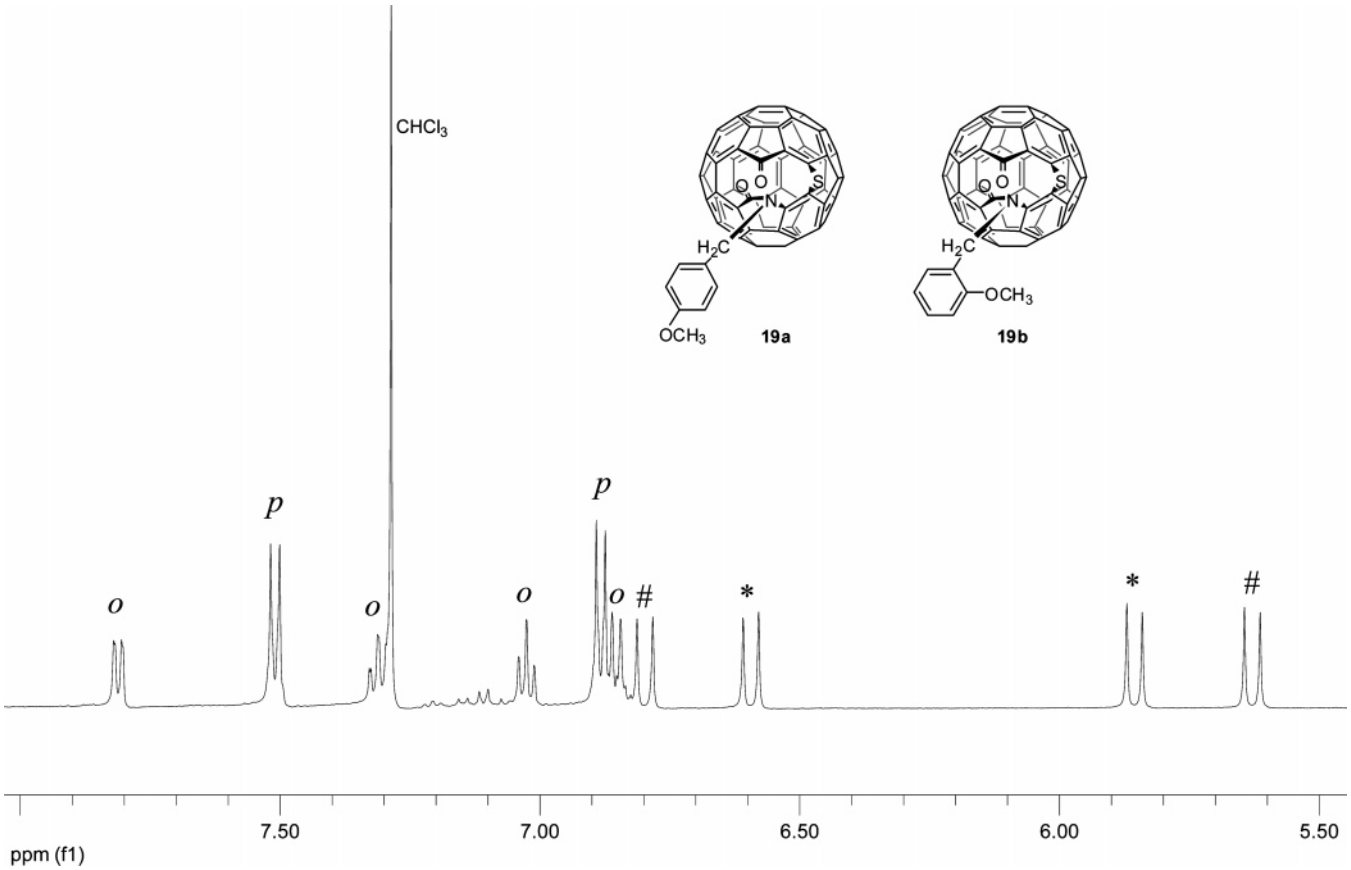


FIGURE 8. Expanded 5.5−8.0 ppm region of the ^{1}H NMR (500 MHz, $CDCl_3$) spectrum for **19a**, **19b** mixture (*o*, aromatic protons of the *ortho* isomer; *p*, aromatic protons of the *para* isomer; *, methylene protons of the *ortho* isomer; #, methylene protons of the *para* isomer).

1 h and 40 min in the presence of 1000 equiv of trifluoroacetic acid, was smoothly converted into the expected derivatives **19a** and **19b** (Figure 8) in quantitative yield. In this case, the *meta* isomer was not formed at all. The 5.5−8.0 ppm region of the ^{1}H NMR spectrum for the mixture of the isomers **19a** and **19b** is displayed in Figure 8 (for the whole spectrum, refer to Supporting Information). Two AB systems reveal the presence of two methylene carbons, whereas the aromatic region of the spectrum reveals the existence of both the *ortho* and the *para* isomers. The ratio of the two isomers was 1/1.

On the other hand, *N*-MEM-ketolactam **1** after 11 h of heating afforded the respective adducts **20a** and **20b** (1/1 ratio) in 48% isolated yield, along with the closed shell adduct **21** in 20% yield (Scheme 2). The latter reaction pathway has already been reported by Hirsch, under slight different reaction conditions (i.e., reaction of **1** with anisole in a refluxing 5:3 ODCB/anisol mixture in the presence of 50 equiv of *p*-toluenesulfonic acid).[15] This compound is the *para*-substitution product of anisole from the azafulleronium ion $C_{59}N^+$ (**9**, Scheme 1) and is also accessible through thermal treatment of the azafullerene dimer **11** with anisole in the presence of *p*-TsOH and air.[15] Most probably, due to steric hindrance factors, only the *para* isomer is observed in this case. A mechanistic study on the reactivity of azafulleronium ion **9** was published earlier by our research group.[16] On the basis of kinetic isotope effect (KIE) measurements, we proposed that the arenium cation is formed by electrophilic attack of $C_{59}N^+$ on the aromatic ring in the first step, followed by hydrogen abstraction in a rate-determining second step.

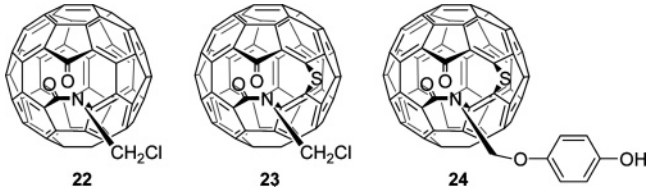
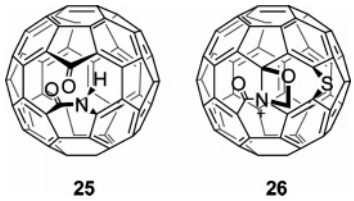


FIGURE 9. Molecular structures of the open-cage fullerene derivatives **22**, **23**, and **24**.

N-MEM-ketolactam **1** has been already known to afford the *N*-chloromethyl ketolactam **22** (Figure 9) by treatment with excess $TiCl_4$ in ODCB at room temperature.[14] When adduct **4** was treated with 5 equiv of $TiCl_4$ in ODCB at room temperature, *N*-chloromethyl S-ketolactam **23** was formed (Figure 9) after 2 h in 66% yield (Figure 9). This new compound was fully characterized by ^{1}H NMR, ^{13}C NMR, ^{1}H−^{1}H COSY, HMQC, and ^{13}C DEPT experiments as well as MS (MALDI), UV−vis, and FT-IR spectroscopy. By increasing the $TiCl_4$ equivalents and the reaction time, apart from the major product **23**, which was obtained in 40% yield, formation of the fully deprotected derivative **14** was also observed in 28% yield.

Finally, we attempted to trap carbocation **13** with hydroquinone, in accordance to the similarly reported reactivity for *N*-MEM-ketolactam **1**.[17] However, when *N*-MEM-S-ketolactam **4** was refluxed in an ODCB solution of excess *p*-toluenesulfonic acid monohydrate and hydroquinone under argon, the resulting

(15) Nuber, B.; Hirsch, A. *Chem. Commun.* **1998**, 405−406.
(16) Vougioukalakis, G. C.; Chronakis, N.; Orfanopoulos, M. *Org. Lett.* **2003**, *5*, 4603−4606.



25 **26**

FIGURE 10. Structures of the deprotected *N*-MEM-ketolactam (**25**) and the 1,3-oxazetidinium intermediate **26**.

reaction mixture was rather complicated and only traces of the desired hydroquinone ether **24** (Figure 9) were detected. The fully deprotected derivative **14** was only isolated from this mixture in 50% yield.

N-MEM-ketolactam **1** was unable, under any of the herein reported conditions, to afford the fully deprotected derivative **25** (Figure 10). On the other hand, *N*-MEM-S-ketolactam **4** was readily converted into **14** in most of the cases. According to Wudl and co-workers,[14] *N*-methyl carbonium ion **7** most probably forms the 1,3-oxazetidinium intermediate **8**, which leads to the azafullerene iminium cation **9** (Scheme 1) because the cyclopentanone carbonyl group and the *N*-methyl carbonium ion are parallel and buttressed against each other by the cage network. Our experiments suggest that the insertion of a sulfur atom in the rim of the orifice of **1** has disturbed this proper orientation for the two moieties, and thus, carbonium ion **13** does not form a corresponding 1,3-oxazetidinium intermediate **26** (Figure 10) toward the formation of the thioaza[60]fullerene dimer. In this case, the route to the fully deprotected adduct **14** is preferable.

Conclusions

Open-cage [60]fullerene derivative **5**, bearing two sulfur atoms on the rim of its 13-membered-ring orifice, has been isolated and characterized for the first time. Moreover, the chemical behavior of *N*-MEM-ketolactam **1**, as well as that of *N*-MEM-sulfur-ketolactams **4** and **5**, was extensively studied. Whereas thermal treatment of sulfur ketolactams **4** and **5**, under harsh acidic conditions, led to complete removal of the *N*-MEM group, this has been proved impossible for ketolactam **1**. It may very well be the case that for the latter the restoration of the [60]fullerene cage to the azafullerene iminium cation **9** is more favorable than the full removal of the *N*-MEM group, due to the feasible formation of the 1,3-oxazetidinium intermediate **8**. It has been also observed that, under milder conditions, **1** and **4** ketolactams afforded open-cage [60]fullerene adducts **17**, **18**, **19**, and **20**. The formation of these novel open-cage adducts was attributed to an electrophilic aromatic substitution reaction. Treatment of the open-cage [60]fullerene derivative **4** with $TiCl_4$ in ODCB yielded the corresponding *N*-chloromethyl sulfur ketolactam **23** in a similar way to *N*-chloromethyl ketolactam **22**.

Experimental Section

Synthesis of the Open-Cage Fullerene Derivative 5. Sixty-eight milligrams (0.08 mmol) of ketolactam **1** was dissolved in degassed HPLC grade ODCB (40 mL) together with 32.0 mg of S_8 (0.12 mmol) in a 100 mL round-bottomed flask under an argon atmosphere. Following the heating of the reaction mixture at 180 °C, tetrakis(dimethylamino)ethylene (30.5 μL, 0.12 mmol) was added. The reaction was stirred at 180 °C for 40 min, and the resulting solution was concentrated under reduced pressure to about 10 mL. The mixture was added to pentanes (100 mL) with vigorous stirring to give brown precipitates. The precipitates were dissolved in ODCB (6 mL), subjected to flash column chromatography (silica gel, 3% EtOAc in toluene), and the two isolated products (**4** and **5**) were washed three times with HPLC grade acetonitrile (centrifugation at 1500 c/min) to afford 50.0 mg (71%) of **4** (brown in solution) and 8.1 mg (11%) of **5** (orange in solution) as brown solids. **Data for 5:** IR (KBr, cm^{-1}) ν 1724, 1680, 1563, 1525, 1452, 1427, 1399, 1359, 1261, 1220, 1214, 1201, 1080, 1056, 1010, 841, 814, 794, 748, 610, 594, 560, 534, 477; UV−vis ($CHCl_3$, nm) λ_{max} 251, 320; MS (MALDI) *m*/*z* 920 (M^+); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (d, J = 10.5 Hz, 1H), 5.95 (d, J = 10.5 Hz, 1H), 4.07 (m, 2H), 3.70 (m, 2H), 3.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.84, 163.13, 152.24, 152.11, 149.85, 149.72, 149.50, 149.44, 149.33, 149.30, 148.98, 148.79, 148.48, 148.38, 148.19, 147.97, 147.47, 146.52, 145.76, 145.10, 144.79, 144.12, 143.78, 143.02, 141.46, 141.18, 141.06, 140.77, 140.21, 140.15, 139.67, 139.12, 139.10, 138.94, 138.71, 138.66, 138.60, 138.28, 138.07, 136.31, 136.15, 135.54, 133.46, 132.17, 132.02, 131.95, 131.84, 128.07, 126.90, 126.85, 122.72, 80.27, 72.14, 70.57, 59.56.

Synthesis of the Open-Cage Fullerene Derivative 6. A Schlenk tube was charged with 10.0 mg (0.01 mmol) of **5**, 0.9 mL of CF_3-COOH (∼1000 equiv), and 10 mL of chlorobenzene. Reaction progress was monitored by HPLC. The reaction mixture was stirred at 100 °C for 40 min. The solution was then concentrated to ∼2 mL and purified by flash column chromatography (silica gel, eluted with gradient ranging from toluene to 4% ethyl acetate in toluene). The isolated product was washed three times with HPLC grade acetonitrile (centrifugation at 1500 c/min) to yield 7.0 mg (78%) of **6** as a brown solid: IR (KBr, cm^{-1}) ν 1726, 1682, 1581, 1565, 1425, 1339, 1263, 1234, 1147, 1103, 1042, 924, 818, 801, 610, 559, 536; UV−vis ($CHCl_3$/ODCB: 60/1, nm) λ_{max} 263, 270, 277, 318; MS (MALDI) *m*/*z* 831 (M^+); ^{1}H NMR (500 MHz, ODCB-d_4) δ 9.48; a ^{13}C NMR spectrum of good quality was not acquired due to low solubility.

Synthesis of the Open-Cage Fullerene Derivatives 17a and 17b. A Schlenk tube was charged with 15.0 mg (0.02 mmol) of S-ketolactam **4**, 1.3 mL of CF_3COOH (∼1000 equiv), and 15 mL of toluene. The reaction mixture was stirred at 150 °C. Reaction progress was monitored by HPLC. After 1 h and 40 min, S-ketolactam was completely consumed, affording the two isomers **17a** and **17b** (giving a single peak in the HPLC analysis) along with derivative **14**. The solution was then concentrated under reduced pressure to ∼2 mL and purified by flash column chromatography (silica gel, eluted with gradient ranging from toluene to 3% ethyl acetate in toluene). The **17a**, **17b** fraction was collected first and the **14** fraction second. Separation of the two isomers **17a** and **17b** was impossible. This solution was stripped of solvent, and the resulting material was washed three times with HPLC grade acetonitrile (centrifugation at 1500 c/min) to yield a 7.0 mg (46%) mixture of **17a** and **17b**: IR (KBr, cm^{-1}) ν 1736, 1691, 1491, 1454, 1401, 1305, 1262, 1199, 1169, 1145, 1095, 1027, 801, 742, 705, 659, 639, 625, 617, 598, 576, 555, 544, 532, 521; UV−vis ($CHCl_3$, nm) λ_{max} 261, 323; MS (MALDI) *m*/*z* 903 (M^+). **17a:** ^{1}H NMR (500 MHz, $CDCl_3$/CS_2) δ 7.46 (d, J = 7.7 Hz, 2H), 7.16 (d, J = 7.7 Hz, 2H), 6.83 (d, J = 15.2 Hz, 1H), 5.65 (d, J = 15.2 Hz, 1H), 2.34 (s, 3H). **17b:** ^{1}H NMR (500 MHz, $CDCl_3$/CS_2) δ 7.44 (d, overlapped with the doublet of **17a**, 1H), 7.21 (m, 2H), 7.16 (overlapped with the doublet of **17a**, 1H), 6.79 (d, J = 15.9 Hz, 1H), 5.87 (d, J = 15.9 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$/CS_2) δ 189.44, 162.40, 149.72, 149.69, 149.27, 149.06, 148.64, 147.75, 147.72, 147.58, 147.42, 147.34, 147.07, 147.01, 146.98, 146.95, 146.87, 146.80, 146.50, 146.38, 146.01, 145.97, 145.96, 145.93, 145.80, 145.65, 145.59, 145.48, 145.42, 145.39, 145.35, 145.17, 145.13, 145.07, 145.05, 143.56, 143.54, 143.10,

(17) Keshavarz-K. M.; González, R.; Hicks, R. G.; Srdanov, G.; Sdarnov, V. I.; Collins, T. G.; Hummelen, J. C.; Bellavia-Lund, C.; Pavlovich, J.; Wudl, F.; Holczer, K. *Nature* **1996**, *383*, 147−150.

143.03, 142.98, 142.94, 142.58, 142.56, 142.29, 142.14, 141.82, 141.75, 141.67, 140.98, 140.79, 140.58, 140.55, 140.31, 140.28, 140.25, 140.10, 139.97, 139.66, 139.25, 138.32, 138.28, 138.16, 138.14, 137.92, 137.87, 137.83, 136.73, 136.70, 136.29, 136.13, 135.97, 135.76, 135.01, 134.95, 134.74, 134.00, 133.93, 131.95, 131.83, 131.27, 131.26, 130.02, 129.78, 129.48, 129.38, 129.19, 129.14, 129.03, 128.69, 128.58, 128.47, 126.81, 126.04, 125.96, 125.84, 125.77, 56.36 (CH_2 carbon of **17a**), 53.25 (CH_2 carbon of **17b**), 21.69 (CH_3 carbon of **17a**), 20.39 (CH_3 carbon of **17b**).

Synthesis of the Open-Cage Fullerene Derivatives 18a and 18b. A Schlenk tube was charged with 15.0 mg (0.02 mmol) of *N*-MEM-ketolactam **1**, 1.4 mL of CF_3COOH (~1000 equiv), and 15 mL of toluene. The reaction mixture was stirred at 150 °C, and the progress of the reaction was monitored by HPLC. *N*-MEM-ketolactam was completely consumed in 5 h, affording the two isomers **18a** and **18b** (a single peak in the HPLC chromatogram). The solution was then concentrated under reduced pressure to ~2 mL and purified by flash column chromatography (silica gel, toluene). Separation of the two isomers was impossible. **18a** and **18b** solution was stripped of solvent, and the resulting material was washed three times with HPLC grade acetonitrile (centrifugation at 1500 c/min) to yield a 10.0 mg (65%) mixture of **18a** and **18b**: IR (KBr, cm^{-1}) ν 1727, 1686, 1561, 1491, 1410, 1386, 1213, 1178, 768, 741, 615, 601, 578, 528, 522, 503, 492, 475, 457; UV−vis ($CHCl_3$, nm) λ_{max} 259, 319; MS (MALDI) *m*/*z* 871 (M^+). **18a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.42 (d, J = 15.0 Hz, 1H), 5.42 (d, J = 15.0 Hz, 1H), 2.36 (s, 3H). **18b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 7.5 Hz, 1H), 7.24 (m, 2H), 7.20 (overlapped with the doublet of **18a**, 1H), 6.37 (d, J = 15.5 Hz, 1H), 5.58 (d, J = 15.5 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3/CS_2$) δ 197.08, 162.86, 150.29, 150.26, 149.64, 148.20, 147.79, 147.68, 147.60, 147.17, 146.93, 146.82, 146.75, 146.59, 146.51, 146.46, 146.43, 146.28, 146.25, 146.18, 145.89, 145.81, 145.76, 145.72, 145.70, 145.58, 145.28, 145.25, 144.96, 144.91, 144.66, 144.64, 144.54, 144.52, 144.39, 144.21, 144.08, 143.94, 143.91, 143.86, 143.14, 141.98, 141.62, 141.41, 141.09, 141.02, 140.93, 140.26, 139.90, 139.57, 139.27, 138.50, 138.46, 137.09, 137.05, 136.43, 136.38, 136.11, 135.59, 135.53, 134.63, 134.34, 134.20, 134.14, 133.62, 133.56, 133.53, 132.70, 132.58, 132.50, 131.43, 130.20, 130.17, 129.49, 129.17, 129.10, 129.03, 128.89, 128.71, 126.94, 125.80, 54.39 (CH_2 carbon of **18a**), 51.53 (CH_2 carbon of **18b**), 21.75 (CH_3 carbon of **18a**), 20.38 (CH_3 carbon of **18b**).

Synthesis of the Open-Cage Fullerene Derivatives 19a and 19b. A Schlenk tube was charged with 10.0 mg (0.01 mmol) of S-ketolactam **4**, 0.9 mL of CF_3COOH (~1000 equiv), and 10 mL of anisole. The reaction mixture was stirred at 150 °C, and the progress of the reaction was monitored by HPLC. S-Ketolactam was completely consumed in 1 h and 50 min, affording the two isomers **19a** and **19b** (a single peak in the HPLC chromatogram). The solution was then concentrated under reduced pressure to ~2 mL and purified by flash column chromatography (silica gel, toluene). Separation of the two isomers was impossible. **19a** and **19b** solution was stripped of solvent, and the resulting material was washed three times with HPLC grade acetonitrile (centrifugation at 1500 c/min) to yield an 11.0 mg (>99%) mixture of **19a** and **19b**: IR (KBr, cm^{-1}) ν 1735, 1686, 1509, 1491, 1401, 1244, 1200, 1170, 1030, 821, 807, 793, 750, 521; UV−vis ($CHCl_3$, nm) λ_{max} 254, 319; MS (MALDI) *m*/*z* 919 (M^+). **19a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 15.1 Hz, 1H), 5.63 (d, J = 15.1 Hz, 1H), 3.69 (s, 3H). **19b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, J_1 = 7.5 Hz, J_2 = 1.1 Hz, 1H), 7.30 (m, 1H), 7.02 (m, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.59 (d, J = 14.9 Hz, 1H), 5.86 (d, J = 14.9 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.78, 189.75, 162.69, 162.61, 159.86, 158.17, 149.69, 149.66, 149.28, 149.23, 149.06, 149.02, 148.63, 148.60, 147.84, 147.75, 147.67, 147.64, 147.63, 147.54, 147.42, 147.36, 147.34, 147.31, 147.07, 147.00, 146.98, 146.97, 146.92, 146.86, 146.77, 146.72, 146.47, 146.43, 146.36, 146.32, 145.96, 145.89, 145.80, 145.77, 145.71, 145.61, 145.52, 145.42, 145.40, 145.37, 145.29, 145.15, 145.11, 145.06, 144.99, 143.53, 143.47, 143.03, 142.99, 142.96, 142.92, 142.64, 142.56, 142.52, 142.27, 142.23, 141.95, 141.74, 141.60, 140.92, 140.90, 140.53, 140.48, 140.32, 140.27, 140.22, 140.20, 140.09, 140.08, 139.65, 139.54, 139.20, 139.16, 138.29, 138.26, 138.16, 137.91, 137.88, 137.84, 137.81, 137.65, 137.05, 136.73, 136.65, 136.12, 135.91, 135.89, 134.99, 134.94, 134.92, 133.98, 133.57, 132.24, 132.12, 131.78, 130.49, 130.07, 129.86, 129.08, 129.04, 128.63, 128.60, 126.04, 125.90, 125.20, 121.12, 114.63, 114.26, 110.79, 56.15 (CH_2 carbon of **19a**), 55.73 (OCH_3 carbon of **19a**), 55.66 (OCH_3 carbon of **19b**), 52.47 (CH_2 carbon of **19b**).

Synthesis of the Open-Cage Fullerene Derivatives 20a and 20b. A Schlenk tube was charged with 10.0 mg (0.01 mmol) of *N*-MEM-ketolactam **1**, 0.9 mL of CF_3COOH (~1000 equiv), and 10 mL of anisole. The reaction mixture was stirred at 150 °C, and the progress of the reaction was monitored by HPLC. *N*-MEM-ketolactam was consumed in 11 h, affording the two isomers **20a** and **20b** (a single peak in the HPLC chromatogram), along with the less polar compound **21**. The solution was then concentrated under reduced pressure to ~2 mL and purified by flash column chromatography (silica gel, eluted with gradient ranging from toluene to 3% ethyl acetate in toluene). Compound **21** elutes first and the **20a**, **20b** fraction comes second. Characterization of **21** (2.2 mg was isolated, 20% yield) has already been reported (ref 15). The separation of the two isomers was impossible. **20a** and **20b** solution was stripped of solvent, and the resulting material was washed three times with HPLC grade acetonitrile (centrifugation at 1500 c/min) to yield a 5.0 mg (48%) brown solid: IR (KBr, cm^{-1}) ν 1728, 1682, 1609, 1560, 1511, 1493, 1249, 1176, 1119, 1031, 906, 731, 602; UV−vis ($CHCl_3$, nm) λ_{max} 259, 327; MS (MALDI) *m*/*z* 887 (M^+). **20a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 6.39 (d, J = 15.0 Hz, 1H), 5.39 (d, J = 15.0 Hz, 1H), 3.76 (s, 3H). **20b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 7.5 Hz, 1H), 7.35 (m, 1H), 7.04 (m, 1H), 6.89 (d, J = 8.5 Hz, 1H), 6.16 (d, J = 14.5 Hz, 1H), 5.61 (d, J = 14.5 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.69, 197.50, 163.15, 163.06, 160.00, 158.30, 150.27, 150.22, 149.65, 149.61, 148.18, 148.16, 147.78, 147.75, 147.72, 147.64, 147.15, 147.13, 147.06, 146.91, 146.81, 146.75, 146.71, 146.60, 146.55, 146.51, 146.49, 146.46, 146.43, 146.37, 146.29, 146.19, 146.18, 146.11, 145.88, 145.80, 145.74, 145.66, 145.55, 145.44, 145.29, 145.26, 145.23, 145.20, 144.89, 144.85, 144.62, 144.57, 144.53, 144.50, 144.46, 144.38, 144.35, 144.19, 144.13, 144.07, 144.03, 144.00, 143.89, 143.85, 143.81, 143.14, 143.09, 141.91, 141.86, 141.58, 141.52, 141.44, 141.38, 141.12, 140.99, 140.93, 140.91, 140.85, 140.78, 140.21, 140.17, 139.96, 139.93, 139.87, 139.56, 139.54, 139.25, 139.20, 138.45, 138.43, 137.10, 137.04, 136.42, 136.35, 136.31, 136.27, 136.05, 136.03, 135.55, 134.33, 134.26, 134.19, 133.86, 133.81, 133.53, 132.77, 132.57, 132.51, 132.10, 130.63, 130.35, 129.42, 129.10, 128.47, 124.15, 121.24, 114.80, 110.93, 55.78 (OCH_3 carbon), 55.69 (OCH_3 carbon), 54.15 (CH_2 carbon of **20a**), 50.40 (CH_2 carbon of **20b**).

Synthesis of the Open-Cage Fullerene Derivative 23. Ten milligrams (0.01 mmol) of S-ketolactam **4** dissolved in 10 mL of ODCB, HPLC grade, was added to a Schlenk tube. A 5-fold excess of $TiCl_4$ was added, and the resulting solution was stirred at room temperature. Reaction progress was monitored by HPLC. After 2 h and 50 min, the reaction mixture was washed with concd $NaHCO_3$ aqueous solution (10 mL), and the organic layer was concentrated to ~1 mL under vacuum. This crude product was purified by flash column chromatography (silica gel, toluene) to yield 6.3 mg (66%) of **23** as a brown solid: IR (KBr, cm^{-1}) ν 1737, 1712, 1561, 1492, 1428, 1401, 1355, 1258, 1199, 1142, 822, 814, 751, 728, 692, 625, 554, 532, 522; UV−vis ($CHCl_3$, nm) λ_{max} 254, 320; MS (MALDI) *m*/*z* 847 (M^+); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 10.7 Hz, 1H), 6.32 (d, J = 10.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.44, 162.11, 149.91, 149.32, 149.16, 148.73, 147.99, 147.79, 147.52, 147.35, 147.18, 146.96, 146.89, 146.85, 146.49, 146.44,

146.19, 146.12, 146.00, 145.84, 145.53, 145.50, 145.44, 145.41, 145.36, 145.31, 145.14, 145.06, 143.59, 143.40, 143.03, 143.01, 142.63, 142.31, 141.87, 140.94, 140.82, 140.41, 140.33, 140.14, 139.93, 139.37, 139.22, 138.79, 138.40, 137.97, 137.92, 136.64, 135.76, 134.52, 134.32, 133.67, 131.67, 129.14, 128.87, 126.47, 60.51 (CH_2 carbon).

Acknowledgment. This work was cofunded by the Greek Ministry of Education and the European Union, through research and education action programs PYTHAGORAS II and IRAKLITOS 2002. We thank Dr T. Drewello for his help in taking the MS spectra at the University of Warwick.

Supporting Information Available: ^{1}H and ^{13}C NMR, FT-IR, and UV−vis spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070796L