Complete Control over Addend Permutation at All Six Pseudooctahedral Positions of Fullerene C_{60}

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The control of regioselectivity in fullerene additions has been a major obstacle in the exploration of their chemistry and properties.[1,2a] Among a practically infinite number of possible addition patterns provided by the spherical array of 30 functionalizable [6,6]-double bonds in I_h-C_{60}, hexakisadducts with a pseudooctahedral (T_h) symmetry have attracted particular interest, most recently for their peculiar luminescent properties.[2−6] While this general addition pattern has become accessible by several methods, the issue of spatial complexity, that is, achievement of control over the pseudooctahedral regiochemistry when *nonequivalent addends* are used, has drawn our interest for its potential in combinatorial chemistry.[6d] From this point of view, the near-spherical core of C_{60} can be considered as a "molecular super-stereogenic center", which is not only unique in organic stereochemistry,[7] but also more complex than its inorganic analogue, the octahedral framework of many transition metal complexes.[8] The T_h and O_h geometries have an important difference in that the six bonds that relay the ligands to the metal in the octahedral complexes are free to rotate, while the C═C bonds positioned perpendicularly to the vertexes of an octahedron in the T_h system are fixed in space. As a consequence, each octahedral diastereomer gives rise conceptually to a pair of *regioisomers* within the T_h scaffold of C_{60} (Figure 1), and there are 30 nonenantiomeric isomers at T_h locations compared to the 15 O_h stereoisomers when *six different addends* are used.[9] In this communication, we report a highly effective and versatile synthesis of a pair of C_{60} hexakisadducts **13a** and **13b** (Figures 3 and 4) as representative examples of the subtle topological relationship existing between regioisomers **2a** and **2b**.

So far, existing strategies to access T_h hexaadducts of C_{60} have taken advantage of the fact that the regioselectivity greatly enhances with each addition at the desired double bonds.[3−6] However, this general principle is far from sufficient in dealing with the *e-face* versus *e-edge* selectivity (see below) which challenged our ability to fully differentiate the hexakisaddition patterns **2a** and **2b** at the late stages of the synthesis.

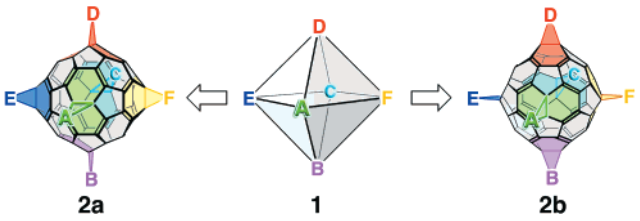

Figure 1. Stereoisomerism of C_{60} hexakisadducts: T_h and O_h topologies.

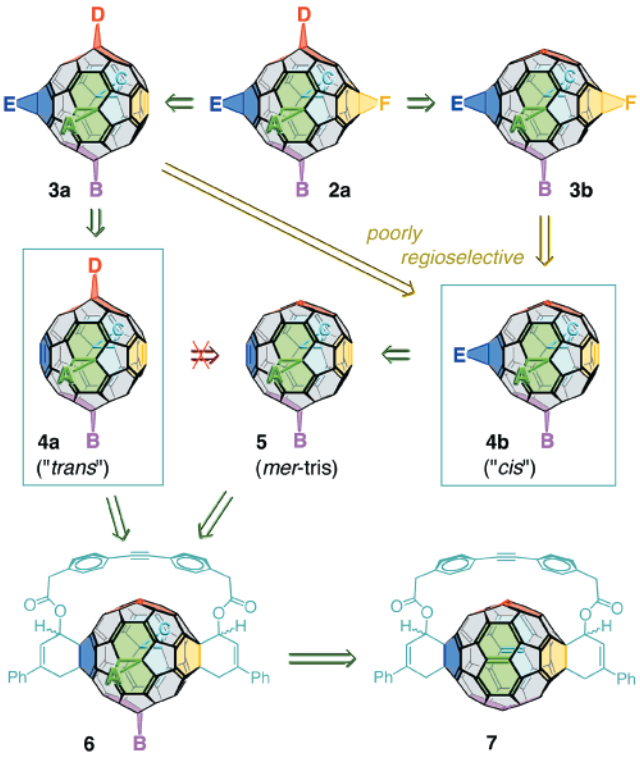

Figure 2. Control of regioisomerism at pseudooctahedral locations on C_{60}: *trans*-4+2 (via **4a**) versus *cis*-4+2 (via **4b**) strategies.

We have reported on a method to approach precise addition patterns as in **6** *via* a highly regioselective addition sequence on *trans-1* bisadduct **7** (Figure 2, A, B, C = $C(CO_2R)_2$).[6c] Subsequent one-pot deprotection[10] gives fully differentiated *e-face*, *e-edge*, *trans-1* trisadducts (**5**) in high yields. From there on, two main retrosynthetic pathways toward the final product **2a** can be taken (Figure 2). Model studies showed that the fourth most reactive location in **5** is the double *e-edge*/single *e-face* (polar) position which gives a *cis*-tetrakisadduct (**4b**) with no or very little *trans*-tetrakisadduct **4a**. However, the *fifth* addition to **4b** proved to be poorly regioselective, giving both isomers **3a** and **3b** that are extremely difficult to separate at this high degree of addition.[4b,6c] Although a judicious choice of addends with substantially different polarity could partially solve the separation problem,[6c,d] the effectiveness and generality of this synthetic route (via **4b**) is greatly limited. The only other possible pathway to **2a** is through the all-*e trans*-tetrakisadduct **4a** because the fifth attack on either side of the equator will give the same regioisomeric pentakisadduct **3a** in racemic form. Access to compound **4a** can be made by using noncovalent and covalent protections within the bridged

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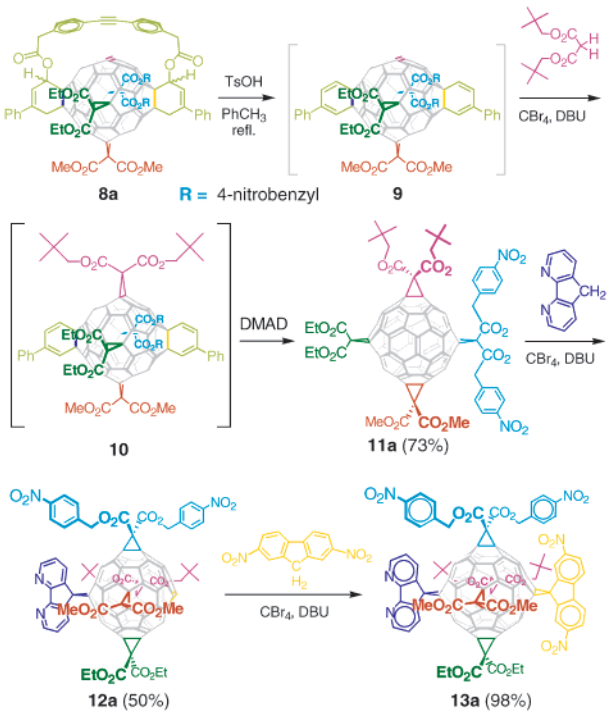

Figure 3. Regioselective synthesis of hexakisadduct **13a**.

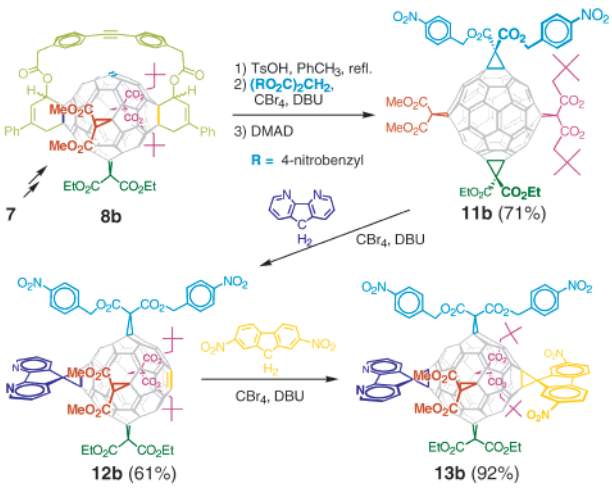

Figure 4. Regioselective synthesis of hexakisadduct **13b**.

precursor **7**, permitting the placement of symmetric addends in the sequential order ABC → ABCD → ABCDEF.

Selective sequential deprotection of **8a**[6c] (Figure 3) was carried out as follows:[9] First, elimination of the bridge of **8a** under acidic conditions (TsOH, toluene, reflux) unveiled the only reactive equatorial [6,6] double bond in **9**, which was functionalized by in situ addition of the fourth addend, neopentyl malonate, to give **10**. The temporary presence of the two thermally stable cyclohexadieno groups at both poles of **9** guaranteed the regiospecificity of this addition even when a large excess of neopentyl malonate was added. One serious concern had been the extreme sensitivity of cyclohexadienofullerenes toward air and light.[10] However, the $^1O_2$ quantum yield of C_{60} adducts decreases steadily with increasing degree of functionalization, being ~15% for a T_h hexaadduct.[11] Even so, **10** was not isolated and immediately allowed to react with an excess of dimethyl acetylenedicarboxylate (DMAD) to effect the Diels−Alder/*retro*-Diels−Alder sequence[10] that afforded the differentiated *trans*-tetrakisadduct **11a** in high overall yield (73% from **8a**). Treatment of **11a** with 1.2 equiv of 4,5-diazafluorene under in situ brominating conditions[12] gave 50% of **12a** as the only pentakisadduct, together with 12% of recyclable **11a** and 35% of the corresponding hexakisadduct. The last equatorial double bond was then blocked with 2,7-dinitrofluorene to give the hexakisadduct **13a** in nearly quantitative yield (98%).

Table 1. ^{1}H NMR Chemical Shift Comparison for **13a** and **13b**

	13a (ppm)	13b (ppm)	Δ(δ) (ppm)
t-Bu	0.86	1.00	−0.14
	0.87	1.02	−0.15
ethyl-CH_3	1.41	1.24	0.17
	1.43	1.26	0.17
MeO	3.78	4.006	−0.23
	3.79	4.010	−0.22
neopentyl-CH_2	3.85	3.97	−0.12
	3.87	4.17	−0.30
ethyl-CH_2	4.45	4.23	0.22
benzyl-CH_2	5.27, 5.40	5.19	0.21
	5.55	5.22	0.33
p-nitro-C_6H_4	7.55	7.33	0.22
	7.57	7.38	0.19
	8.179	7.94	0.24
	8.183	8.05	0.13

Red, groups facing both fluorenyl rings (shielded)
Green, groups at edge of both fluorenyl rings (deshielded)

The flexibility of this strategy was further demonstrated by the synthesis of the fully "permuted" isomer **13b**, carried out in a manner similar to **13a** starting from bridged bisadduct **7** (Figure 4).[9] Interestingly, compounds **13a** and **13b** can be readily distinguished by their ^{1}H NMR chemical shifts (Table 1). Each cyclopropyl substituent facing either the 2,7-dinitrofluorenyl or 4,5-diazafluorenyl groups is consistently shielded by 0.15−0.30 ppm. The reverse is seen for those groups at the edges of the aromatic rings. Although distances between substituents are too large in **13a** and **13b** to see NOE enhancements, 2D NMR techniques could prove useful in understanding the folding of peptidic chains built from these scaffolds.[13]

These results show that an exquisite control of the regiochemistry around the T_h coordination core of C_{60} can be achieved by the strategic planning of both covalent and noncovalent protections provided by the selective removal of the bridging moiety in **8a** and **8b**. This strategy overcomes a significant regioselection obstacle at the late stages of multifunctionalization. The pseudo-square-planar stereoisomerism of **11a** and **11b** is also interesting and can be regarded as the two-dimensional version of the topological relationship between hexakisadducts **13a** and **13b**. A semicombinatorial execution of this flexible strategy that will give fast access to all 30 isomers of type **2a/b** with a minimal average number of steps is currently underway.

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Supporting Information Available: Experimental procedures and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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