Regio- and diastereo-controlled double cycloaddition to [60]fullerene: One-step synthesis of *Cs* and C_2 chiral organofullerenes with new tris-annulating reagents

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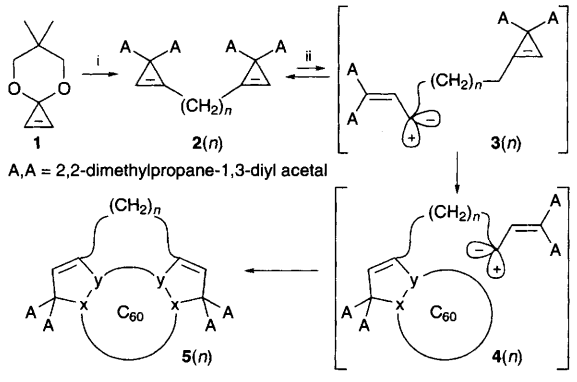
Double cycloaddition of new tris-annulation reagents to [60]fullerene creates a tricyclic system constructed on the [60]fullerene sphere, providing *Cs* symmetric and C_2 chiral non-racemic organofullerenes.

Organochemical modification of a number of double bonds of fullerene (*e.g.* 1,2-addition of an A–B reagent across a C=C bond) is posing new synthetic problems of spherical stereocontrol.[1,2] A more challenging yet much less explored issue is the control of the multiple addition of structurally complex reagents (A ≠ B). Uncontrolled additions would create a complex mixture of regioisomers,‡ and, in order to obtain a single isomer, selectivities must be achieved to control the position, orientation and absolute stereochemistry of the attachment of the A–B group to the sphere of fullerene.[3] Such control is not simply an intellectual challenge but will be practically useful for constructing large molecular structures bearing substituents with predefined spatial orientations. Here we report that the reaction of a new annulation reagent **2(*n*)** with [60]fullerene provides a route to regio- and stereo-selective functionalization of two double bonds of [60]fullerene. The double addition reaction created a new tricyclic system **5(*n*)** on the [60]fullerene sphere with *Cs* and C_2 symmetry. Most notably, the reagent bearing a chiral auxiliary **10** afforded C_2 chiral non-racemic fullerenes **11** and **12**.

The annulating reagents **2(*n*)** bearing a methylene carbon tether of a different number of carbon atoms (*n*) were prepared in a single step by coupling of a 1,ω-dihaloalkane with a lithiated cyclopropenone acetal (CPA)[4] (Scheme 1). The CPA moiety generates reversibly a minute amount of a nucleophilic vinylcarbene [*cf.* **3(*n*)**],[5] which undergoes [3 + 2] cycloaddition exclusively to the 6,6-juncture.[6] The bis CPA **2(*n*)** with an appropriate tether length hence undergoes cycloaddition to [60]fullerene to give initially **4(*n*)**, and then the bis-cyclopentene fused to a medium-sized central ring [**5(*n*)**]. The double cycloaddition was achieved by heating a mixture of **2(*n*)** (1.4–1.5 equiv.) and [60]fullerene (40–200 mg) at 150 °C in



Scheme 1 *Reagents and conditions*: i, BuLi in HMPA–THF at −70 °C followed by $I(CH_2)_nI$ at room temp.; ii, [60]fullerene, 150 °C in $1,2\text{-}Cl_2C_6H_4$, molecular sieves (4 Å)

$1,2\text{-}Cl_2C_6H_4$ (1.39–13.9 mmol dm^{-3}) in the presence of molecular sieves under nitrogen, and the desired double cycloadduct(s) **5(n)** was isolated by flash chromatography as a fraction(s) (silica gel, R_f = 0.4–0.6 with toluene) slower moving than recovered [60]fullerene (R_f = *ca.* 1.0).§

The yield and the product distribution were found to show remarkable dependence on the tether length (Table 1). Thus, the 3-carbon tethered reagent **2(3)** afforded a 38 : 62 mixture of two double cycloadducts **6** and **7** both of *Cs* symmetry in 37% combined yield. The yield diminished to 16% with the 4-carbon tethered **2(4)**, yet the reaction afforded a single *Cs* double cycloadduct assigned tentatively as **8**. On the other hand the reaction of the 6-carbon tethered **2(6)** afforded the double cycloadduct **9** of C_2 symmetry in 41% yield as a single double cycloadduct.

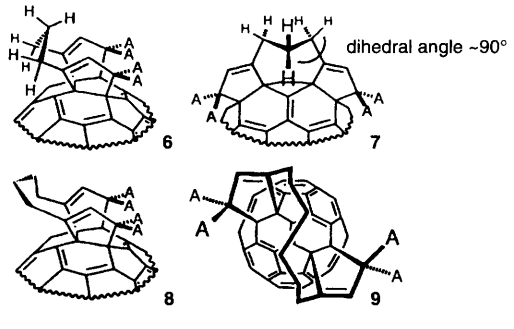
The reaction of the 5-carbon tethered **2(5)** gave none of the double adduct and, instead, afforded a hydrolysis product of the monoadduct **4(5)** likely due to the ring strain in the formation of a 9- or 10-membered ring structure which would be formed by the double addition. The reaction with an 8-carbon tethered **2(8)** afforded complex mixtures of double cycloadducts perhaps due to large conformational flexibility of the tether. Thus, the present tris-annulation reaction provided a viable synthetic route to the protected bis-cyclopentenones **5(*n*)** for *n* = 3, 4 and 6.

The above structural assignments of the double cycloadducts **5(*n*)** were achieved by careful analysis of ^1H and ^{13}C NMR data assisted by both empirical molecular modelling and computer-assisted coupling analysis based on conformers obtained by Monte-Carlo conformational search followed by MM2*

Table 1 Regioselective double [3 + 2] cycloaddition of **2(*n*)** to [60]fullerene

		Yield (%) of structural type[a]		
n	Equiv.	A	B	C
3	1.4	**6** 14 (23)	**7** 23 (38)	—
4	1.5	**8** 17 (30)	—	—
5	1.4	—	—	—
6	1.5	—	—	**9** 41 (55)

[a] Yield in parenthesis are based on recovered [60]fullerene.



optimization[7] (hereafter referred as the structural analysis). Fig. 1 shows the possibilities of topological connnectivity for **5(*n*)**. The structural analysis for **A–E** for n = 3-8 indicates that the 3- and 4-carbon tethers are too short to allow **C–E** to be feasible and the 6-carbon one too short for **E**. The C_2 symmetry of the double adduct with n = 6 thus indicated that the adduct was **9**.

For n = 3, both the two isomeric adducts formed were *Cs* symmetric, and hence they are in either **A** or **B** topology and coincidence of experimental and calculated NMR data led to the structural assignment. The minor product assigned to **6** showed four proton signals due to the tether methylene groups, which are fully coupled to each other. The major product, on the other hand, showed four signals of simpler coupling pattern, indicating the lack of vicinal proton couplings (*i.e.* 90° dihedral angle) between an allyl and a central methylene proton on the tether. The structural analysis indicated that compounds **6** and **7** exist in a single predominant conformer, and the calculated vicinal coupling constants based on the average of all conformers agreed well with the experimental values [calculated (experimental) values, *J* 0.3 (0), 0.3 (0), 9.3 (9.4), 11.2 (10.4) Hz for **6**, and *J* 2.6 (1.5), 2.8 (3.4), 3.9 (3.9), 13.2 (13.2) Hz for **7**]. The structure of *Cs* symmetrical product **8** was tentatively assigned since an alternative isomer of **B** topology suffers steric interactions between the two allylic methylene groups and is consequently less stable than **A**.

Having obtained the C_2 chiral double cycloadduct, we next examined the synthesis of a non-racemic double adduct without recourse to resolution.[8,9] To this end, the diol acetonide **10** of 89% ee was prepared from **1** and a chiral diiodide (synthesized by osmium asymmetric dihydroxylation of hex-3-ene-1,6-diol by AD-mix-β[10]) and allowed to react with [60]fullerene. The reaction gave a diastereoisomerically pure C_2 symmetric adduct **11** with a very large $[\alpha]_D^{24}$ value (−1875, 17% yield). The C_2 symmetry was indicated by the ^{13}C NMR and ^1H NMR spectra.¶ Finally, the chiral acetonide **11** was cleaved to obtain the non-racemic dialdehyde **12** with $[\alpha]_D^{24}$ value of −1872. The isolated yield of **12** was 26% based on **11**. Besides **11**, the cycloaddition of **10** to [60]fullerene afforded two C_1 isomers in 10 and 17% yields respectively hence indicating that the presence of the inflexible dioxolane unit in **10** affected the regio-directing effect of the 6-carbon tether. Further tuning of the tether structure will be the subject of further studies, and we envisage that derivatives provided by the double cycloaddition of the new annulation reagents will serve as useful tools in the studies of functional catalysis[11] and bioorganic applications (*e.g.* DNA interactions).[12]

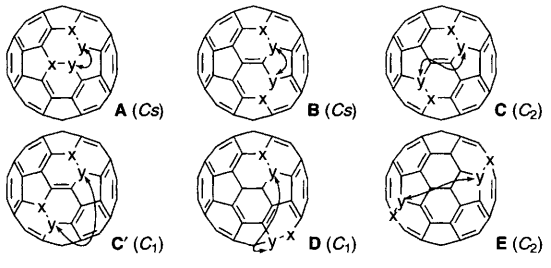
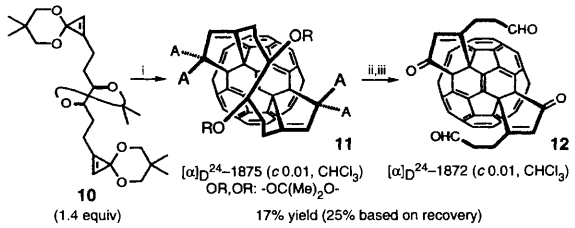


Fig. 1 Schematic representation of regioisomers formed by double cycloaddition with **2(*n*)**. The curved arrow indicates the *n*-carbon tether, and *x*–*y* indicates the points of attachment of the cyclopentene rings (*cf.* Scheme 1). Symmetry assignment disregards side chain conformation.



Scheme 2 *Reagents and conditions*: i, molecular sieves (4 Å), 1,2-$Cl_2C_6H_4$, 72 h, 150 °C; ii, H_2SO_4, H_2O, THF, 12 h, room temp.; iii, HIO_4, H_2O, THF, 4 h, 50 °C

Footnotes

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‡ Even the simplest double addition may afford 36 structural isomers.

§ Addition of **2** to 2 equiv. of fullerene did not take place because of the low concentration required. A small amount of mono-adduct (water-quenched product of **4**) was separated by chromatography.

¶ The relative stereochemistry in **11** between the C_2 acetonide and the C_2 fullerene core rests on the product analysis by the Monte- Carlo/MM2* optimization and is therefore tentative. Note that, owing to the C_2 symmetry of the tether, structures **A**, **B**, and **C′–D** produce C_1 products. The CD spectrum of **11** displayed a strong Cotton effect even in the 620–660 nm regions where there is only weak absorption in the UV–VIS spectrum. *Spectral data* for **11**. UV–VIS ($CHCl_3$) λ_{max}/nm (ε/dm³ mol⁻¹ cm⁻¹) 260 (72 800), 440 (2420), 463 (1730, 648 (425) an 716 (294); CD ($CHCl_3$) λ_{ext}/nm (Δε/dm³ mol⁻¹ cm⁻¹) 266 (+105 000), 276 (0), 288 (−75 000), 336 (0), 343 (+1300), 360 (+1300), 368 (0), 393 (−1430), 406 (−1410), 429 (0), 438 (+1610), 445 (0), 460 (−3750), 527 (0), 560 (+201), 577 (0), 603 (−737), 616 (0), 651 (+2350) and 720 (+4690); IR ν_{max}/cm⁻¹ (CCl_4) 2960, 2862, 2362, 2322, 1658, 1458, 1394, 1365, 1317, 1259, 1215, 1107, 1053, 1020, 557, 544 and 526; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 6 H, 2× CH_3), 1.24 (s, 6 H, 2× CH_3), 1.56 (s, 6 H, 2× CH_3), 2.17 (m, 2 H, CH_2), 2.95 (m, 2 H, CH_2), 3.73 (dd, *J* 2.0, 8.8 Hz, 2 H, equatorial OCH_2), 3.75 (dd, *J* 2.0, 8.8 Hz, 2 H, equatorial OCH_2), 4.03 (d, *J* 8.8 Hz, 2 H, axial OCH_2), 4.06 (d, *J* 8.8 Hz, 2 H, axial OCH_2), 4.10 [t, *J* 2.0 Hz, 2 H, two $CHOC(CH_3)_2$] and 7.05 (br s, 2 H, vinyl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.97 (CH_3), 22.86 (CH_3), 26.96 (two CH_3), 27.55 (CH_2), 30.17 [$C(CH_3)_2CH_2$], 33.91 (CH_2), 70.25*, 73.33 (OCH_2), 73.53 (OCH_2), 78.67*, 79.01 [$CHOC(CH_3)_2$], 109.89 [$OC(CH_3)_2O$], 113.91 (*C*CH=C), 125.88 (*C*H=C), 127.07*, 133.14*, 134.56*, 137.62*, 138.86*, 139.52*, 141.68*, 141.90*, 141.93*, 142.08*, 143.49*, 144.81*, 144.91 (C_{60}, 4 C), 145.57*, 145.61*, 146.18*, 146.25*, 146.31*, 146.35*, 146.49*, 147.53*, 147.74*, 147.88*, 148.73*, 149.04*, 149.40 (*C*=CH), 150.01* and 151.83*. $[\alpha]_D^{24}$ −1875 (*c* = 0.01, $CHCl_3$); HRMS calc. for $C_{85}H_{38}O_6$ (MH^+) *m/z* = 1155.2725, found *m/z* = 1155.2747. (Asterisked signals are assigned as fullerene carbon of 2 C intensity.)

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