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Preparation and Characterization of Six Bis(*N*-methylpyrrolidine)−C_{60} Isomers: Magnetic Deshielding in Isomeric Bisadducts of C_{60}

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A series of isomers of bis(*N*-methylpyrrolidine)−C_{60} **2** (Prato bisadducts) was prepared by the 1,3-dipolar cycloaddition of *N*-methylazomethine ylide to C_{60}. Six isomers were separated and characterized by ESI-MS, UV/vis, and ^{1}H and ^{13}C NMR spectroscopy. The structures of these bisadducts were assigned based on (1) comparison of their molecular symmetries with their ^{1}H and ^{13}C NMR spectra, (2) comparison of their UV/vis spectra with those of corresponding Bingel−Hirsch bisadducts, and (3) the order of deshielding of the methylene and *N*-methyl ^{1}H NMR resonances. Prato bisaddition is less chemoselective than Bingel−Hirsch bisaddition to C_{60}.

Indroduction

The soccer ball-shaped molecule C_{60} appears to undergo reactions associated with poorly-conjugated electron-deficient alkenes.[1] However, a unique feature of C_{60} is that a large number of products may arise from polyaddition of even one reagent to C_{60} since it has 30 reactive [6,6] double bonds. Well-designed polyadducts of C_{60} with defined three-dimensional structures have potential for biological applications, such as molecular recognition.[2] For example, it has been reported that a water-soluble C_{60} derivative inhibits HIV protease and reverse transcriptase.[3,4] In order to be able to design three-dimensional structures based on C_{60}, it is important to control the chemoselectivity of the C_{60} polyaddition. The chemistry of C_{60} has been dominated, thus far, mainly with investigation of its monoaddition reactions. The synthesis of isomerically pure polyadducts of C_{60} has been reported in only a few cases.[5] For example, Hirsch et al.[5d] isolated and characterized seven isomers of bis(ethoxycarbonyl)methylene−C_{60}. In nucleophilic cyclopropanations of C_{60} (Scheme 1), attack at specific [6,6] double bonds is significantly preferred. The most favorable positions are at the equatorial and *trans*-3 positions relative to the addend already bound to the fullerene core (Figure 1).

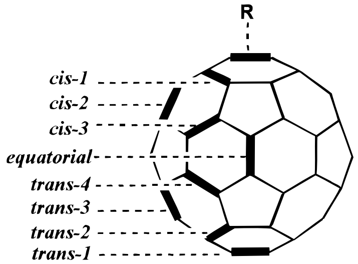
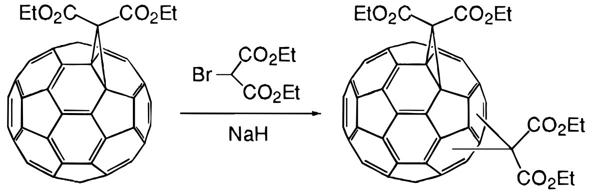


Figure 1. Positional relationships and Hirsch nomenclature of the eight different double bonds in a C_{60} bisadduct relative to the 6−6 bond carrying the first addend R.

Scheme 1



The 1,3-dipolar cycloaddition of azomethine ylides to C_{60} affording fulleropyrrolidines was reported by Prato and co-workers.[6] This high yield reaction occurs exclusively across [6,6] bonds. Since the addend is symmetrical in *N*-methylpyrrolidine−C_{60},[6a] there are again eight possibilities for bisaddition. We selected this reaction as another candidate for the investigation of the chemoselectivity of bisaddition to C_{60}. In this paper, we report the preparation, isolation, and characterization of six isomers of bis(*N*-methylpyrrolidine)−C_{60}. One would expect different proportions of isomeric bisadducts compared with that in Hirsch's reaction, since the two reactions proceed by totally different mechanisms.

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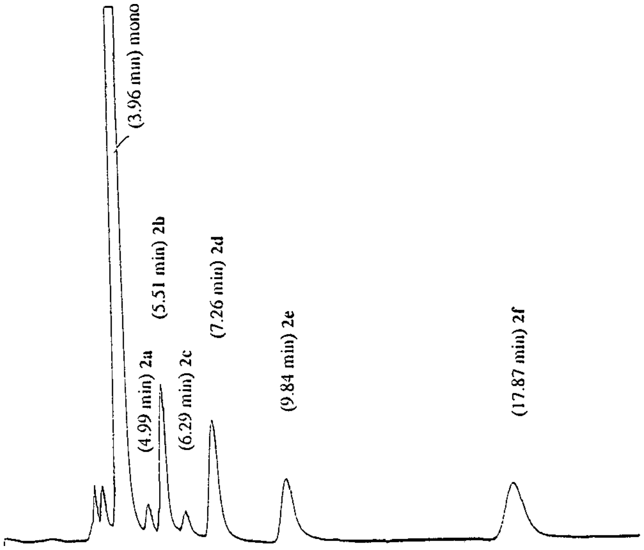
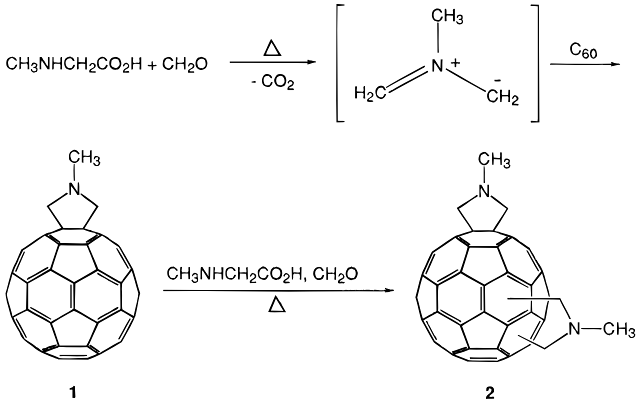


Figure 2. HPLC chromatogram of the mixture of isomeric bisadducts of bis(*N*-methylpyrrolidine)$-C_{60}$ **2a**−**f**. Conditions: 250 × 4.6 mm "Adsorbosphere Silica" column, 1000:1:1 toluene/EtOAc/Et_3N as mobile phase (1 mL/min), 4 μL injection, UV/vis detection at 340 nm.

Scheme 2



Results and Discussion

The monoadduct, *N*-methylpyrrolidine$-C_{60}$ (**1**), was prepared and isolated according to the reported procedure[6a] and was then subjected to the same reaction conditions (Scheme 2) to give bis(*N*-methylpyrrolidine)$-C_{60}$ isomers **2** (Prato bisadducts). Flash chromatographic separation on silica gel gave (in order of elution following **1**) a fraction containing four bisadducts **2a**−**d** and a mixed fraction containing two additional bisadducts **2e**,**f** as well as trisadducts. Further separation on a semipreparative "Econosil Silica" HPLC column led to isolation of six bisadducts **2a**−**f** in a 7.3:20:5.6:24:18:25 ratio. Electrospray ionization MS (ESI-MS) confirmed that all six components are *N*-methylpyrrolidine$-C_{60}$ bisadducts. Analysis of the original reaction mixture on an "Adsorbosphere Silica" HPLC column gave virtually the same isomer ratio as above (Figure 2). The fact that the ratio of bisadducts is not significantly time-dependent indicates similar reactivity of these bisadducts toward further reaction.

On the basis of comparison of the UV/vis spectra (Figure 3) of these bisadducts in the 400−700 nm region and their order of chromatographic elution with those of the isomers of bis(ethoxycarbonyl)methylene$-C_{60}$ (Hirsch bisadducts),[7] some tentative structure assignments could be made. On this basis, **2a**, **2b**, **2d** and **2f** were assigned as *trans*-1, *trans*-2, *trans*-3, and *cis*-3, respectively. The ^1H NMR spectra of these bisadducts match the assigned structures. Two singlets at δ 4.67 (CH_2) and δ 3.14 (CH_3) are observed in the spectrum of **2a**, consistent with the D_{2h} symmetry of *trans*-1. Four doublets at δ 4.64 (J = 9.3 Hz), δ 4.46 (J = 9.3 Hz), δ 4.32 (J = 6.6 Hz), and δ 4.30 (J = 6.6 Hz) along with one singlet at δ 3.05 (CH_3) are observed in the spectrum of **2b**; four doublets at δ 4.41 (J = 9.6 Hz), δ 4.32 (J = 9.6 Hz), δ 4.16 (J = 9.4 Hz), and δ 4.06 (J = 9.4 Hz) along with one singlet at δ 2.92 (CH_3) are observed in the spectrum of **2d**; and four doublets at δ 4.05 (J = 8.6 Hz), δ 4.03 (J = 8.6 Hz), δ 3.98 (J = 8.6 Hz), and δ 3.88 (J = 8.6 Hz) along with one singlet at δ 2.80 (CH_3) are observed in the spectrum of **2f**. These spectra are consistent with the C_2 symmetries of *trans*-2, *trans*-3, and *cis*-3. Each of these structures has two nonequivalent methylene groups possessing coupled diastereotopic protons, resulting in pairs of AB quartets.

Bisadduct **2e** was initially assigned as the *e* isomer according to its order of elution (its UV/vis spectrum in the 400−700 nm region does not match any of the UV/vis spectra of the Hirsch bisadducts), but its ^1H NMR spectrum rules out this assignment. Four doublets are observed at δ 4.30 (J = 10 Hz), δ 4.16 (J = 10 Hz), δ 4.06 (J = 9.6 Hz), and δ 4.03 (J = 9.6 Hz) along with one singlet at δ 2.88 (CH_3), consistent with either C_s or C_2 symmetry. The *e* bisadduct should have two equivalent methylene groups possessing nonequivalent protons coupled to each other, as well as two nonequivalent methylene groups with magnetically equivalent protons. Therefore, the ^1H NMR spectrum of the *e* isomer should consist of two doublets and three singlets (for two CH_2 and one CH_3 group).

The ^{13}C NMR spectrum of **2e** shows 35 signals (30 sp^2 fullerene carbons between δ 155 and δ 128, 2 sp^3 fullerene carbons at δ 69.81 and δ 69.58, two CH_2 groups at δ 70.05 and δ 69.39 and one CH_3 group at δ 41.38), compatible with the C_s symmetry of *trans*-4. Thus, on the basis of ^1H and ^{13}C NMR spectra, bisadduct **2e** was assigned as the *trans*-4 isomer (the only other possibility is *cis*-2, which is much less likely to be formed due to steric hindrance between the adjacent substituents).

Bisadduct **2c**, a minor product, is tentatively assigned as the *e* isomer based on its UV/vis spectrum in the 400−700 nm region. A similarity in UV/vis absorption in this region exists between **2c** and *e*-$C_{62}(CO_2H)_4$,[8] although no such similarity exists between **2c** and *e*-$C_{62}(CO_2Et)_4$ (Figure 3). The ^1H NMR spectrum of **2c** shows only one singlet at δ 4.03 for CH_2 and another singlet at δ 2.83 for CH_3. Apparently, the NMR spectrometer (even at 500 MHz) cannot sense the slight difference between the three magnetically nonequivalent methylene groups. This observation is not very surprising as a similar situation was noted in the Hirsch isomers. Only two multiplets at ca. δ 4.45 (CH_2) and δ 1.45 (CH_3) are observed in the ^1H NMR spectrum of *e*-$C_{62}(CO_2Et)_4$.[7] Attentive analysis of all ^1H NMR spectra of the Hirsch and Prato bisadducts indicates that when two addends on C_{60} approach the

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(7) We repeated the Hirsch bisaddition reaction, separated the regioisomeric bisadducts, and obtained ^1H NMR spectra for *trans*-2,*trans*-3,*trans*-4 equatorial and *cis*-3 isomers and UV/vis spectra for *trans*-1,*trans*-2,*trans*-3,*trans*-4 equatorial, *cis*-3, and *cis*-2 isomers, consistent with those reported in: Hirsch, A.; Lamparth, I.; Karfunkel, H. R. *Proc.*−*Electrochem. Soc.* **1994**, *94* (24) (Recent Advances in the Chemistry and Physics of Fullerenes and Related Materials), 734−46.

(8) For the UV/vis spectrum of *e*-$C_{62}(CO_2H)_4$ in the 400−600 nm region, see: Lamparth, I.; Hirsch, A. *J. Chem. Soc., Chem. Commun.* **1994**, 1727.

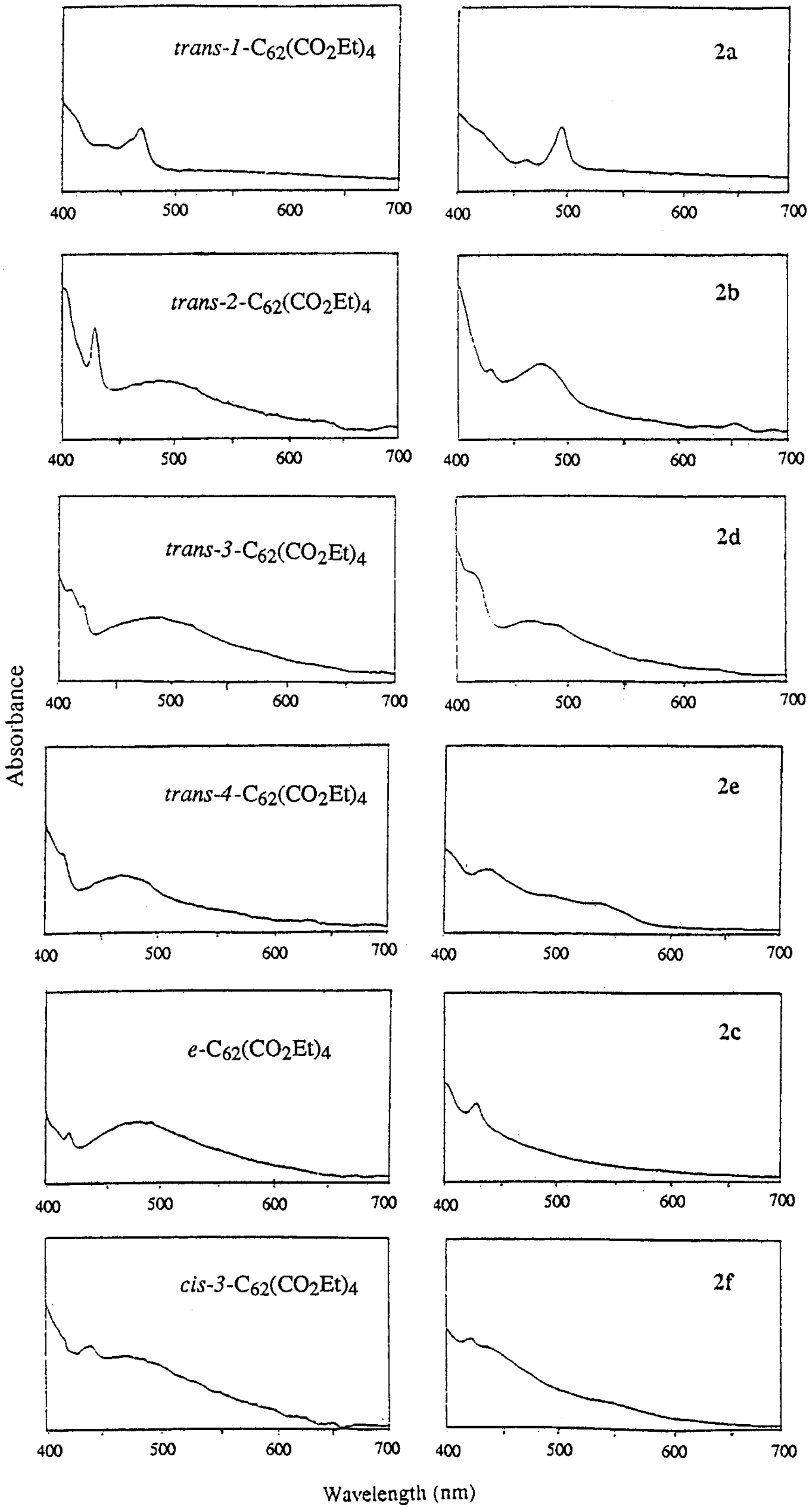

Figure 3. UV/vis spectra of regioisomeric bisadducts $C_{62}(CO_2Et)_4$ (Scheme 1) and UV/vis spectra of regioisomeric bisadducts bis(*N*-methylpyrrolidine)-C_{60} **2a**–**f**.

equatorial from the *trans*-1 orientation, chemical shift differences become smaller. Indeed, this phenomenon may be helpful in structure determination of C_{60} bisadducts.

The methylene and *N*-methyl resonances in **2a**–**f** are all downfield with respect to typical aliphatic pyrrolidines (for example, δ 2.32 for the *N*-methyl and δ 2.45 for the α-methylene groups in *N*-methylpyrrolidine) because of ring currents on the surface of the C_{60} cage.[9] It is interesting furthermore to compare the chemical shifts of the methylene and *N*-methyl resonances in the Prato bisadducts **2** (Table 1). The order of the chemical shifts of the methylene and N-methyl resonances *from trans-1*

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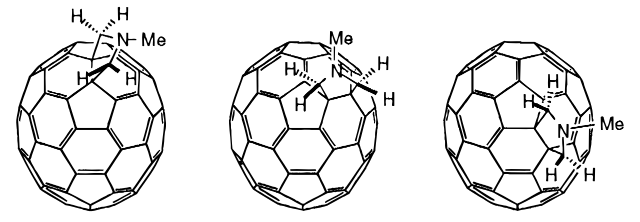

3a (1,9-isomer) **3b** (7,8-isomer) **3c** (22,23-isomer)

Figure 4. Structures of three *N*-methylpyrrolidine monoadducts of C_{70}.

Table 1. Order of the Chemical Shifts of the Methylene and *N*-Methyl ^{1}H NMR Resonances from *trans*-1 to *cis*-3 in Prato Bisadducts 2

compd	isomer	δ CH_2, ppm				δ NCH_3, ppm	deshielding order
2a	*trans*-1	4.67				3.14	1
2b	*trans*-2	4.64	4.46	4.32	4.30	3.05	2
2d	*trans*-3	4.41	4.32	4.16	4.06	2.92	3
2e	*trans*-4	4.30	4.16	4.06	4.03	2.88	4
2c	*e*	4.03				2.83	5
2f	*cis*-3	4.05	4.03	3.98	3.88	2.80	6

Table 2. Order of the Chemical Shifts of the Methylene and Methyl ^{1}NMR Resonances from *trans*-2 to *cis*-3 in Hirsch Bisadducts $C_{62}(CO_2Et)_4$ (Scheme 1)

isomer	δ CH_2, ppm			δ CH_3, ppm			deshielding order
trans-2	4.69		4.52	1.61		1.48	1
trans-3	4.56		4.46	1.52		1.44	2
trans-4	4.53		4.46	1.50		1.43	3
e	4.49	4.46	4.43	1.48	1.46	1.42	4
cis-3	4.48		4.42	1.46		1.40	5

to *cis*-3 can be attributed to differing ring currents associated with the overall π-bonding structure of isomeric C_{60} derivatives. The same deshielding order of the methylene and methyl resonances is observed in the Hirsch bisadducts (Table 2).[7] The structure assignments made above for *trans*-1, *trans*-2, *trans*-3, *trans*-4, *e* and *cis*-3 Prato bisadducts are strongly supported by this observation.

The chemical shifts of the methyl groups in the *N*-methylpyrrolidine monoadducts of C_{70} (Figure 4), at δ 2.74, δ 2.60 and δ 2.51 for **3a** (1,9-isomer), **3b** (7,8-isomer), and **3c** (22,23-isomer), respectively, indicate the influence of the curvature of the fullerene surface on the deshielding effect.[10] Deshielding of the methyl substituent is more pronounced at the region of sharper surface curvature. Deshielding in the polar region of C_{70} has been observed in isomeric C_{70} isoxazolines.[11] We suggest that the shape of the C_{60} sphere may be somewhat distorted after Prato bisaddition. Positioning of substituents on the regions of the C_{60} surface corresponding to variations in surface curvature, proceeding from *trans*-1 (most spherical) to *cis*-3 (most flat), could account for the deshielding order shown in Table 1. This relative order of chemical shifts may prove highly useful in structure assignments of other series of C_{60} bisadducts when the addends have groups which give distinct ^{1}H NMR signals.

It is worthy of note that Hirsch bisaddition (Scheme 1) is more chemoselective than Prato bisaddition (Scheme 2). Thus, *e*-$C_{62}(CO_2Et)_4$ and *trans*-3-$C_{62}(CO_2Et)_4$ are preferentially favored in Hirsch bisaddition, while *trans*-2, *trans*-3, *trans*-4, and *cis*-3 are the major isomers in Prato bisaddition (Figure 5).

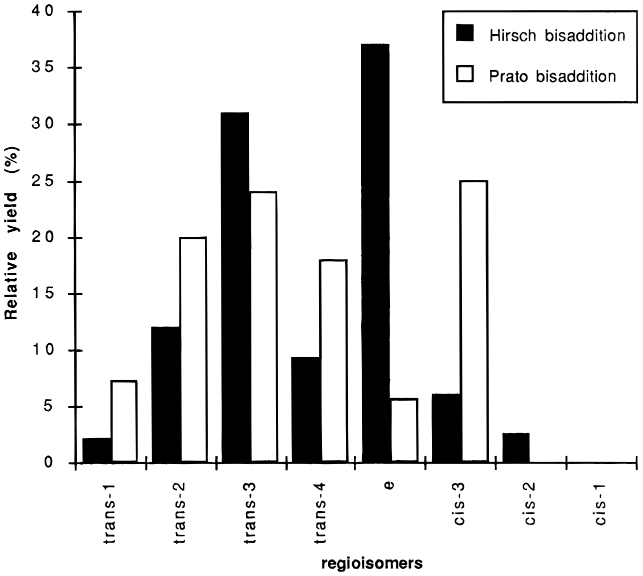

Figure 5. Chemoselectivities of Hirsch (Scheme 1) and Prato bisadditions (Scheme 2).

Summary

Prato bisadducts **2** were prepared by the 1,3-dipolar cycloaddition of *N*-methylazomethine ylide to C_{60}. Six isomers were separated and characterized by ESI-MS, UV/vis, and ^{1}H and ^{13}C NMR spectroscopy. The structures of these bisadducts were assigned on the basis of (1) comparison of their different molecular symmetries with their ^{1}H and ^{13}C NMR spectra, (2) comparison of their UV/vis spectra with those of the bisadducts from the Bingel–Hirsch cyclopropanation, and (3) the order of deshielding of the methylene and *N*-methyl ^{1}H NMR resonances. Prato bisaddition is less chemoselective than Hirsch bisaddition to C_{60}.

Experimental Section

General Information. Commercial reagents were used as received. C_{60} (>99%) was obtained from MER Corp.

Preparation of Mono(*N*-methylpyrrolidine)–C_{60} (1). A mixture of C_{60} (110 mg, 0.15 mmol), *N*-methylglycine (27 mg, 0.30 mmol), and paraformaldehyde (23 mg, 0.75 mmol) was heated at reflux in 200 mL of toluene under Ar for 2 h. The resulting brown solution was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (eluent: toluene and then toluene/triethylamine 100:1), affording 52 mg (45%) of the monoadduct: ESI-MS (TFA/toluene/MeOH) *m/z* 778 (M + H^+); ^{1}H NMR (200 MHz, $CDCl_3/CS_2$) δ 4.42 (s, 4H), 3.02 (s, 3H).

Preparation of Bis(*N*-methylpyrrolidine)–C_{60} (2a–f). *N*-Methylpyrrolidine bisadducts of C_{60} were synthesized from the monoadduct using the same experimental conditions as those described above. Flash chromatography on silica gel (eluent: 100:1 toluene/triethylamine then 100:5:1 toluene/EtOAc/triethylamine) was used for preliminary product separation. The first fraction contains bisadducts **2a**–**d**. The second fraction includes two further bisadducts, **2e** and **2f**, as well as trisadducts. A semipreparative 250 × 10 mm "Econosil Silica" HPLC column was used to isolate a total of six bisadducts, **2a**, **2b**, **2c**, **2d**, **2e**, and **2f**, in a 7.3:20:5.6:24:18:25 ratio [eluent: 1000:1:1 toluene/AcOEt/triethylamine for **2a**, **2b**, **2c** and **2d**; 1000:1:1 toluene/MeOH/triethylamine for **2e** and **2f** (3 mL/min); UV/vis detection at 340 nm].

2a: ESI-MS (TFA/toluene/MeOH) *m/z* 835 [M + H^+]; ^{1}H NMR (200 MHz, $CDCl_3/CS_2$) δ 4.67 (s, 4H), 3.14 (s, 6H); UV/vis (400–700 nm, CH_2Cl_2) see Figure 3.

2b: ESI-MS (TFA/toluene/MeOH) *m/z* 835 [M + H^+]; ^{1}H NMR (200 MHz, $CDCl_3/CS_2$) δ 4.64 (d, *J* = 9.3 Hz, 2H), 4.46

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(d, $J = 9.3$ Hz, 2H), 4.32 (d, $J = 6.6$ Hz, 2H), 4.30 (d, $J = 6.6$ Hz, 2H), 3.05 (s, 6H); UV/vis (400−700 nm, CH_2Cl_2) see Figure 3.

2c: ESI-MS (TFA/toluene/MeOH) *m*/*z* 835 [M + H^+]; ^{1}H NMR (200 MHz, $CDCl_3/CS_2$) δ 4.03 (s, 4H), 2.83 (s, 6H); UV/vis (400−700 nm, CH_2Cl_2) see Figure 3.

2d: ESI-MS (TFA/toluene/MeOH) *m*/*z* 835 [M + H^+]; ^{1}H NMR (200 MHz, $CDCl_3/CS_2$) δ 4.41 (d, $J = 9.6$ Hz, 2H), 4.32 (d, $J = 9.6$ Hz, 2H), 4.16 (d, $J = 9.4$ Hz, 2H), 4.06 (d, $J = 9.4$ Hz, 2H), 2.92 (s, 6H); UV/vis (400−700 nm, CH_2Cl_2) see Figure 3.

2e: ESI-MS (TFA/toluene/MeOH) *m*/*z* 835 [M + H^+]; ^{1}H NMR (200 MHz, $CDCl_3/CS_2$) δ 4.30 (d, $J = 10.0$ Hz, 2H), 4.16 (d, $J = 10.0$ Hz, 2H), 4.06 (d, $J = 9.6$ Hz, 2H), 4.03 (d, $J = 9.6$ Hz, 2H), 2.88 (s, 6H); ^{13}C NMR (500 MHz, $CDCl_3/CS_2$) δ 154.38 (2C), 152.45 (2C), 151.24 (2C), 150.75 (2C), 150.48 (2C), 149.51 (1C), 149.08 (2C), 148.19 (2C), 147.77 (2C), 147.27 (2C), 146.12 (2C), 145.98 (4C), 145.47 (2C), 145.83 (2C), 145.81 (2C), 144.51 (2C), 142.53 (2C), 142.03 (2C), 141.67 (2C), 141.65 (2C), 141.30 (2C), 141.16 (2C), 139.07 (2C), 138.53 (2C), 136.01 (2C), 135.33 (2C), 131.16 (1C), 128.91 (1C), 128.15 (1C), 70.05 (CH_2), 69.81 (2C-sp^3), 69.58 (2C-sp^3), 69.39 (CH_2), 41.38 (CH_3); UV/vis (400−700 nm, CH_2Cl_2) see Figure 3.

2f: ESI-MS (TFA/toluene/MeOH) *m*/*z* 835 [M + H^+]; ^{1}H NMR (200 MHz, $CDCl_3/CS_2$) δ 4.05 (d, $J = 8.6$ Hz, 2H), 4.03 (d, $J = 8.6$ Hz, 2H), 3.98 (d, $J = 8.6$ Hz, 2H), 3.88 (d, $J = 8.6$ Hz, 2H), 2.80 (s, 6H); UV/vis (400−700 nm, CH_2Cl_2) see Figure 3.

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Supporting Information Available: ^{1}H, ^{13}C NMR and ESI-MS spectra (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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