JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. 2018, 83, 2166−2172
Article
pubs.acs.org/joc

Cycloaddition Reactions of Azomethine Ylides and 1,3-Dienes on the C_{2v}-Symmetrical Pentakisadduct of C_{60}

Radoslav Z. Pavlović,[†,∥] Aleksandra Mitrović,[†] William H. Coldren,[‡] Mira S. Bjelaković,[§] Christopher M. Hadad,[‡] Veselin R. Maslak,*[,†] and Dragana R. Milić*[,†]

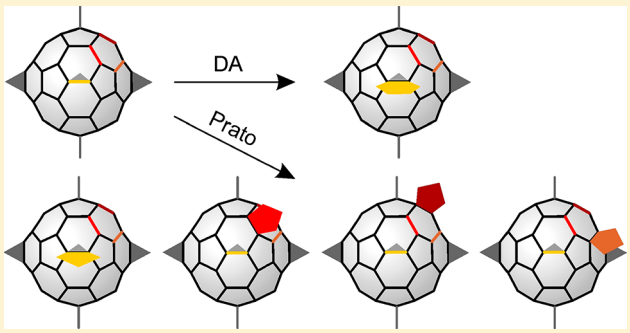
[†]Faculty of Chemistry, University of Belgrade, Studentski trg 16, P.O. Box 51, 11158 Belgrade, Serbia

[‡]Department of Chemistry & Biochemistry, The Ohio State University, 100 West 18th Avenue, Columbus, Ohio 43210, United States

[§]Center for Chemistry, Institute of Chemistry, Technology and Metallurgy, University of Belgrade, Njegoševa 12, 11000 Belgrade, Serbia

Supporting Information

ABSTRACT: The reactivity of the C_{2v}-symmetric pentakisadduct of C_{60} with azomethine ylides and conjugated dienes was studied experimentally and computationally. This derivative possesses four [6,6] double bonds, each with unique electrophilicity. The Diels−Alder reaction studied is a regiospecific, kinetically and thermodynamically guided [4 + 2] process producing [5:1]-hexaadducts with an octahedral addition pattern. The kinetically controlled Prato reaction gives a mixture of regioisomeric [5:1]-hexaadducts. The synthesis of geometrically well-defined supramolecular architectures may benefit from these new types of highly functionalized [5:1]-hexaadducts.



INTRODUCTION

During the past few decades, the design and synthesis of many C_{60} multiadducts[1] have significantly contributed to the development of supramolecular, medicinal, and materials chemistry.[2] Regioselective, multiple cycloadditions are based on three important synthetic strategies: Diederich's tether-directed method,[3] the reversible template-mediated approach introduced by Hirsch,[4] and Sun's template-free modification of the Hirsch procedure.[5] However, only a few studies of cycloaddition reactions to Bingel multiadducts have been reported so far. Echegoyen and co-workers examined the regioselectivity of the Prato cycloaddition to the symmetric Bingel tetrakisadduct of C_{60} using different *N*-substituted glycines.[6] Interestingly, Fujiwara and Komatsu reported that the reaction of *N*-methylglycine, formaldehyde, and the C_{2v} symmetric pentakis-methanofullerene derivative in toluene afforded exclusively one symmetrically functionalized [5:1]-hexaadduct in excellent yield.[7] The regiochemical outcome of [4 + 2] cycloadditions on similar pentakisadducts has not been widely studied.

Therefore, an additional investigation of multiple cycloadditions seemed reasonable. To the best of our knowledge, this is the first extensive experimental and theoretical study of the Prato and Diels−Alder (DA) reactions with the C_{2v} symmetrical Bingel pentakisadduct. Complementary to a detailed investigation of the reactivity of a functionalized fullerene and the regioselectivity of its reaction with 1,3-dipoles and conjugated dienes, the preparation of a new series of [5:1]-hexaadducts (Schemes 1 and 2) was also achieved.

RESULTS AND DISCUSSION

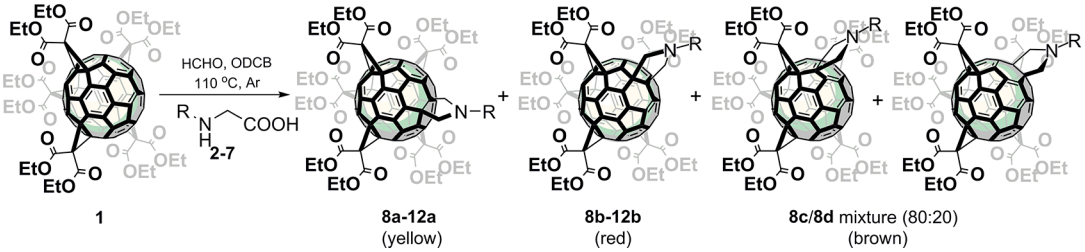
Following Hirsch's three-step protection−deprotection strategy,[8] pristine C_{60} was transformed to isoxazolinofullerene, which after 5-fold cyclopropanation to mixed hexaadduct and photochemical deprotection afforded pentakisadduct **1**. The efficiency and selectivity of Prato and DA cycloadditions to the starting compound **1** were investigated using six azomethine ylides obtained in situ from corresponding *N*-substituted glycines and formaldehyde (Scheme 1 and Table 1), as well as three conjugated dienes (Scheme 2).

Due to the C_{2v} symmetry of pentakisadduct **1**, four regioisomeric hexaadducts can be formed: one with symmetrically (octahedrally) derivatized [6,6] double bonds and three with unsymmetrically positioned addends. Only one position, the most distant from the existing addends (labeled as **a**, Figure 1), produces a highly symmetric product. Three sets of sites (**b**−**d**, Figure 1), each containing four equivalent bonds, all differing in distance and orientation to the cyclopropane subunits are available for the formation of the remaining products. Due to the inherent axial chirality, the asymmetric [5:1]-hexaadducts **b**−**d** exist in the form of racemic mixtures of clockwise and anti-clockwise enantiomers. As can be seen from

Received: December 6, 2017
Published: January 23, 2018

DOI: 10.1021/acs.joc.7b03083
J. Org. Chem. 2018, 83, 2166−2172

Scheme 1. Synthesis of the Regioisomeric Mixed [5:1]-Hexaadducts 8−12, Starting from C_{60} Symmetric Bingel Pentakisadduct 1[8] and Glycine Derivatives 2−7, All Performed in *o*-Dichlorobenzene at 110 °C



Scheme 2. Synthesis of Mixed Bingel−Diels Alder [5:1]-Hexaadducts 13a−15a

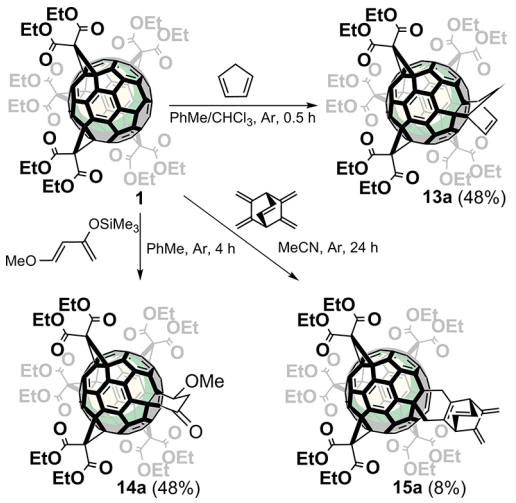


Table 1 and Scheme 2, statistical factors played a minor role, since the product distribution did not correlate with a 1:4:4:4 ratio.

The Prato reaction conditions were optimized by varying the solvent and heating source for the reaction between pentakisadduct **1**, *N*-methylglycine, and formaldehyde. Neither solvent nor heating source had an appreciable effect on regioselectivity, but both had a notable effect on the reaction time and product yield (Table S1 and Figures S1−S8, SI).

Consequently, *o*-dichlorobenzene (ODCB) and conventional heating below reflux (110 °C) were selected for all further reactions of glycine derivatives **2**−**7** (Table 1). Experimental results showed an influence of the glycine structure on the yield and distribution of regioisomeric hexaadducts. In almost all cases, the octahedrally functionalized product was formed preferentially (Table 1, entries 1, 2, 4, and 5). The presence of an amide functional group in the side chain resulted in a slight

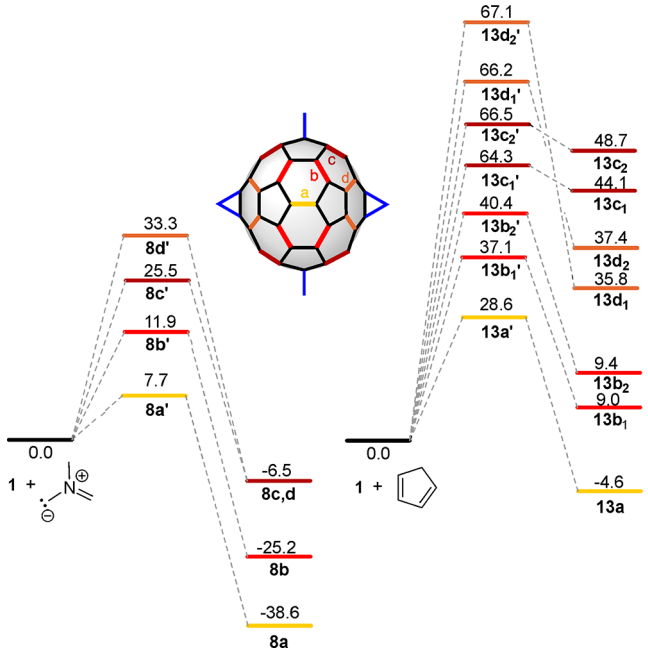


Figure 1. Schematic depiction of four different [6,6] C=C bonds on the fullerene derivative **1** and relative energy profiles (*E* in kcal/mol) of Prato and DA reactions obtained from B3LYP/6-31G* calculations.

predominance of the unsymmetrical red isomer **10b** (Table 1, entry 3). We attribute this to the possibility of hydrogen bond formation between the amide hydrogen and the two carbonyl oxygens of a proximal *e*-malonate subunit, which could help direct the cycloaddition on bond-**b**. With bulky tritylglycine **7**, no reaction was observed (Table 1, entry 6).

To determine the product distribution, each mixture of products was separated from the unreacted starting material **1** by flash column chromatography and analyzed by ^{1}H NMR spectroscopy (Table 1 and Figures 16−20, SI). Additional column chromatography afforded pure individual products,

Table 1. Prato's Reaction of 1 with *N*-Substituted Glycines 2−7

entry	glycines	R	time (h)	product and % yield[a] (% recovered **1**)	**a**:**b**:**c**[b] (per C=C)
1	**2**	Me	2	**8**, 62 (15)	57:37:6 (84:14:2)[c]
2	**3**	$(CH_2)_6NHBoc$	2	**9**, 37 (30)	55:45:0 (83:17:0)
3	**4**	$(CH_2)_3CONHCH_2COO^tBu$	2	**10**, 42 (25)	48:52:0 (79:21:0)
4	**5**	4-nitrophenyl	1	**11**, 16 (51)	52:48:0 (81:19:0)
5	**6**	4-methoxyphenyl	1.5	**12**, 33 (25)	80:20:0 (94:6:0)
6	**7**	Tr[d]	2	− (70)	−

[a]Isolated mixture of regioisomers. [b]Regioisomeric ratio, determined by ^{1}H NMR. [c]Due to low yield (<1%), no signals of **8d** were observed [Figure S1, Supporting Information (SI)]. [d]No reaction was observed with 3-trityloxazolidinone, as well, although with both substrates C_{60} afforded the *N*-trityl monoadduct (12% and 36%, respectively).

DOI: 10.1021/acs.joc.7b03083
J. Org. Chem. 2018, 83, 2166−2172

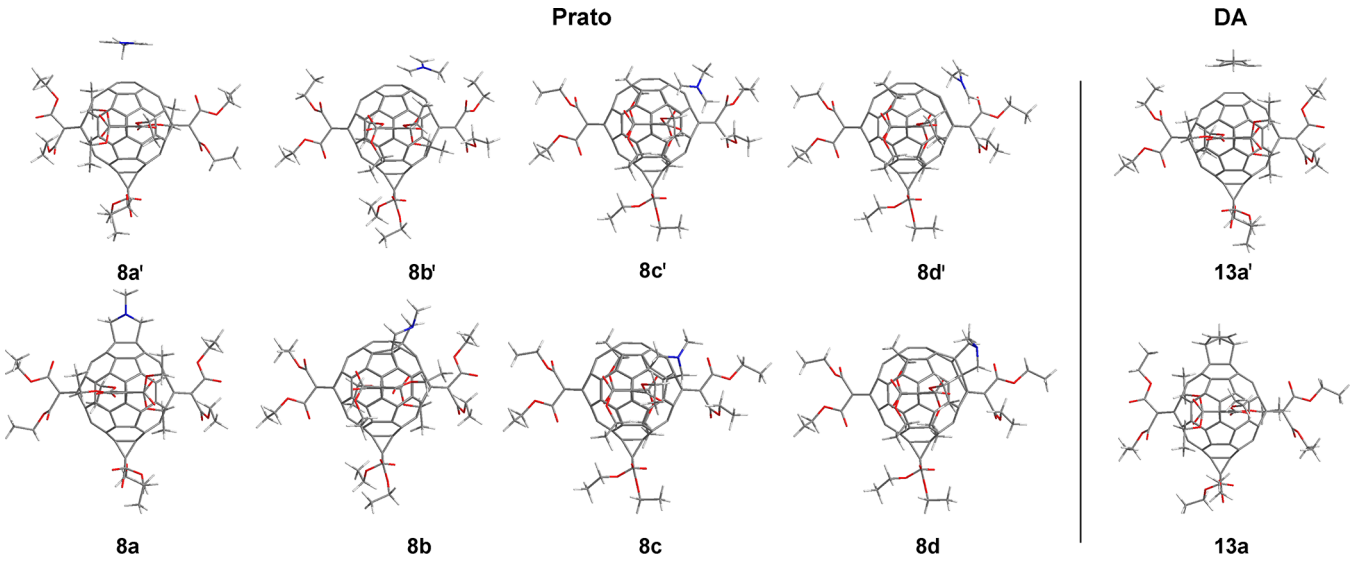


Figure 2. DFT-optimized geometries of transition states and products **8a−d** and **13a**.

except in the case of compounds **8**. In this case, two regioisomers were isolated in a pure form (yellow **8a** and red **8b**), and two remained as an inseparable mixture in very low yield (4%, brown **8c**/**8d** = 80/20). It should be noted that due to the very low concentration of **8d** in the mixture of products, the corresponding ^{1}H NMR spectrum had only three sets of pyrrolidine methylene protons assigned to **8a−c**. Detailed characterization of regioisomers **8−15** is given in the SI (pp S8−S15). Unambiguous proof for the addition pattern of regioisomers of compound **8** was provided by comparative analysis of their NMR (Figures S9−S11, SI) and UV−vis (Figures S12−S14, SI) spectra, as well as by spectral data comparison with known hexaadducts of fullerene. On the basis of NMR observations, the singlet form of the pyrrolidine protons for the yellow regioisomer **8a** can be attributed to an octahedral arrangement of the addends. On the other hand, asymmetric regioisomers **8b−d** (Figure S9, SI) exhibited two pairs of doublets attributed to the nonequivalent pyrrolidine methylene protons in the δ range of 3.0−4.4 ppm, which are diastereotopically shifted by 0.11/0.25 ppm (**8b**), 0.36/0.60 ppm (**8c**), and 0.63/0.92 ppm (**8d**). Importantly, the chemical environment of each pyrrolidine proton is influenced differently in each regioisomer as a result of the relative distance and orientation of both the C_{60} surface and diethyl malonate carbonyl groups. The diastereotopic shift of the doublets increases along the series of regioisomers **b** < **c** < **d**, which implies the weakest anisotropic influence of the carbonyl groups on the pyrrolidine protons of structure **8b**. This is consistent with the fact that product **8b** has the largest spatial distance between the pyrrolidine protons and the malonate carbonyls (see Figure 2). Furthermore, due to the dissimilar orientation of the cyclopropane rings and malonate carbonyls relative to the pyrrolidine moiety in the other two regioisomers, **8c** and **8d**, the effect is expected to be more prominent in structure **8d**, giving rise to the widest separation of diastereotopic ^{1}H pyrrolidine doublets. During the elucidation of the relative relationship between the addends of asymmetric regioisomers, when the NMR became more convoluted, the electronic absorption spectroscopy was of crucial importance. The spectra of the isomeric hexaadducts **8a−d** have unique absorptions in the visible region (Figure S12, SI). In the case of the yellow, C_{2v}-symmetric hexaadduct **8a**, the π-system has been reduced to eight isolated benzenoid rings, which is in line with the absence of weak absorptions in the visible region.[4a,8] As expected, the red regioisomer **8b** has a characteristic spectrum showing weak absorption maxima at 508 and 545 nm,[6a] while in the spectrum of the **8c**/**d** brown mixture the corresponding absorptions are more red-shifted (532 and 590 nm). The absorption spectra of the yellow products (**9a−15a**) are almost identical, and the red hexaadducts (**9b−12b**) also maintained similar features to one another, while the two series are spectroscopically distinct from one another due to the difference in electronic structure resulting from the type of addition pattern (Figures S13 and S14, SI).

The relative energetics of the *N*-methyl Prato and the cyclopentadiene DA reactions (Figure 1), as well as the optimized geometries (Figure 2) for all four possible transition states and resulting regioisomeric [5:1]-hexaadducts, were obtained from DFT calculations. The formation of **8a** is very exothermic (−38.6 kcal/mol, Figure 1) and the corresponding transition state **8a′** is very early on the potential energy surface (7.7 kcal/mol) and consistent with Hammond's postulate. The energy barrier leading to **8b** is also in agreement with this conclusion. On the other hand, the corresponding transition states that lead to **8c** and **8d** are much larger; note that **8d′** has the highest relative energy among the all transition states for the Prato reaction (Figure 1). Interestingly, Prato cycloaddition products **8c** and **8d** are found to be isoenergetic, indicating that only the difference in the corresponding activation barriers dictates the product ratio. Also, all products are calculated to be more thermodynamically stable than the reactants. Calculated energies of the corresponding transition states (**8a′−d′**, Figure 1), as well as regioisomeric ratios given in brackets in Table 1, clearly indicate the electrophilicity order of the corresponding LUMO orbitals located on the [6,6] C═C bonds at the nonfunctionalized part of the fullerene nucleus. Symmetric C═C bond-**a** is the most electrophilic, while the least electrophilic is bond-**d** (Figure 1). Bond-**a** has the lowest-energy LUMO, which is consistent with the well-known observation that *e*-attack becomes more selective with an increasing number of *e*-bonded addends.[1a] The exceptionally low electrophilic character of bonds-**c** and -**d** can be explained via the loss of

DOI: 10.1021/acs.joc.7b03083
J. Org. Chem. 2018, 83, 2166−2172

conjugation with the benzenoid ring (the *cis*-1 positions relative to those bonds are already cyclopropanated). Besides the electronic origin of high activation barriers for the formation of isomers **c** and **d**, the other significant contributors are destabilizing steric interactions between the 1,3-dipole and ethoxycarbonyl groups during the corresponding transition states formations (**8c′** and **8d′** in Figure 2).

This steric effect reflects directly the total absence of the unsymmetrical brown regioisomers **c** and **d** in reaction mixtures of all other cases (Table 1, entries 2−5) besides the reaction of *N*-methyl azomethine ylide with **1** (Table 1, entry 1). Also, strong steric repulsions between Ph and ethoxycarbonyl groups could be responsible for the lack of reactivity of the trityl substrate (Table 1, entry 6). An azomethine ylide with a *p*-methoxyphenyl group located at the nitrogen showed the best regioselectivity (Table 1, entry 5), which can be understood through the very good electronic complementarity of this 1,3-dipole and [6,6] double bond **a**.

Due to the thermodynamic stability of each product under thermal equilibrium, one would expect to obtain only **8a**. When the compounds **1** and **8b** were mixed together in ODCB at 110 °C for 100 h under an Ar atmosphere, there was no evidence of the formation of octahedral yellow regioisomer **8a**. This could be taken as additional proof of the pure kinetic guidance of the Prato reaction of **1** with azomethine ylides.

On the other hand, DA reactions showed very high regioselectivity with the exclusive formation of the Bingel−DA [5:1]-hexaadduct with an octahedral arrangement (Scheme 2). This experimental observation is in full agreement with the DFT-computed relative energies of the corresponding transition states, as well as the thermal energy of the products (Figure 1). It becomes very clear that the HOMO−LUMO gap between cyclopentadiene and C=C bond-**a** from **1** is larger in energy than the gap between the *N*-methyl azomethine ylide and the same bond from **1**. This is in accordance with the expected trend of energy of HOMO orbitals: 1,3-dienes < 1,3-dipoles.

This nucleophilicity order can likely be explained through stronger electronic repulsions between four π-electrons spread over the three-atom C−N−C unit in azomethine ylides in comparison with four π-electrons in 1,3-dienes spread over four C atoms. Also, only the formation of **13a** was computed to be an exothermic process, which strongly supports the experimentally obtained DA reaction results. Maximization of strain release by cycloaddition to double bond **a** is an additional reason for the preferred thermodynamic stability of symmetric [5:1]-hexakisadducts (**8a−12a** and **13a−15a**) in comparison with asymmetric [5:1]-hexakisadducts (**8b−12b**, **8c/d**; Figure S15, SI, **13b$_1$**, **13b$_2$**, **13c$_1$**, **13c$_2$**, **13d$_1$**, and **13d$_2$**) beside steric and electronic effects. This conclusion was also drawn for the Bingel−Hirsch cyclopropanation of fullerene pentakisadducts done by Hirsch's group.[3c]

CONCLUSION

In summary, new types of mixed [5:1]-hexaadducts were synthesized by Prato and DA reactions with symmetric C_{60} Bingel-pentakisadduct. On the basis of the experimentally obtained product distribution and DFT computations of corresponding transition states and products for both reactions, it can be concluded that the Prato reaction is fully kinetically controlled, leading to the regioselective formation of symmetric and asymmetric [5:1]-hexaadducts, while the DA reaction is kinetically and thermodynamically guided, thereby producing a sole regioisomer with an octahedral arrangement of addends. The synthesis of these new types of highly functionalized and geometrically well-defined compounds opens the possibility for their usage in synthetic organic, supramolecular, and materials chemistry.

EXPERIMENTAL SECTION

General Information. *N*-Methylglycine **2**, dicyclopentadiene, and Danishefsky's diene were purchased from Sigma-Aldrich and used without further purification. Glycine derivatives **3**,[9] **4**,[10] **5**,[11] **6**,[11] and **7**;[12] isoxazolinofullerene monoadduct;[13] the protected fullerene [5:1]-hexakisadduct;[8] the symmetrical pentakisadduct **1**;[8] and 2,3,5,6-tetramethylenebicyclo[2.2.2]oct-7-ene[14] were synthesized according to the literature procedures. Flash column chromatography (FCC) and dry-column flash chromatography (DCFC) were carried out with Merck silica gel 0.04−0.063 and 0.015−0.04 mm, respectively. Thin layer chromatography (TLC) was carried out on precoated silica gel 60 F_{254} plates. IR spectra (ATR) were recorded with a Perkin−Elmer-FT-IR 1725X spectrophotometer; ν values are given in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded with Bruker Avance (^1H at 500 MHz, ^{13}C at 125 MHz) and Bruker Ascend 400 (^1H at 400 MHz, ^{13}C at 100 MHz) spectrometers. Chemical shifts (δ) are expressed in ppm and coupling constants (J) in hertz. TMS was used as an internal reference. The following abbreviations were used for signal multiplicities (s = singlet, br s = broad singlet, br t = broad triplet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, dd = doublet of doublets, etc.). The homonuclear 2D (DQF-COSY and ROESY) and the heteronuclear 2D $^1H-^{13}C$ spectra (HSQC, HMBC) were recorded with the usual settings. UV spectra were recorded with a GBC-Cintra 40 UV/vis spectrophotometer. The high-resolution MS spectra were taken with Agilent 6210 LC ESI-MS TOF spectrometer. Reactions induced by microwave irradiation were performed in a Milestone MultiSynth microwave multimode oven by using a MonoPREP kit containing a sealed reaction vessel and a fiber-optic internal probe for the reaction temperature monitoring.

Synthesis of the Regioisomeric Bingel−Prato [5:1]-Hexaadducts ***8***. A mixture of **1** (50 mg, 0.033 mmol), paraformaldehyde (4 mg, 0.134 mmol, 4 mol equiv), and sarcosine **2** (4.4 mg, 0.049 mmol, 1.5 mol equiv) was heated at 110 °C in *o*-dichlorobenzene (4 mL) under argon for 2 h. The resulting mixture was cooled and the solvent was then evaporated to dryness. The residue was purified by FCC (SiO_2, 30 g) to give unreacted pentakisadduct (7.5 mg, 15%, PhMe/EtOAc 100:5) and a mixture of regioisomers **8** (32 mg, 62%, PhMe/EtOAc 100:15) (Figure S16, SI), which was separated by FCC (SiO_2, 20 g, PhMe/EtOAc 100:8 → 100:18): an inseparable mixture of **8c** and **8d** (2 mg, 4%; relative ratio **8c**/**8d** ∼ 80:20; see p S30, SI), **8a** as a yellow solid (10 mg, 19%), and **8b** as a red solid (15 mg, 29%). The pure **8b** was obtained after preparative TLC (PhMe/EtOc 8:2).

Compound **8a** (yellow): R_f = 0.33 (PhMe/EtOAc 8:2); ^1H NMR (500 MHz, $CDCl_3$) δ = 4.25−4.40 [m, 20H, CH_2(EtO)], 3.70 (s, 4H, CH_2^{pyrr}), 2.63 (s, 3H, CH_3−N), 1.27−1.38 [m, 30H, CH_3(EtO)]; ^{13}C NMR (125 MHz, $CDCl_3$) δ [164.1 (*t*-1), 163.9 (*eq*), 163.6 (*eq*), 10C, CO], [152.9, 146.2, 145.7 (2), 145.5, 145.1, 143.6, 141.8, 141.6, 140.0, 139.6, 139.2, 48C, C_{60}-sp^2], [70.0, 69.5, 69.2, 67.8, 10C, C_{60}-sp^3(cp)], 69.7 (2C, CH_2^{pyrr}), 68.2 [2C, C_{60}-sp^3(pyrr)], [62.9, 62.8, 62.7, 62.6, 10C, CH_2(EtO)], [45.4 (*eq*), 45.0 (*eq*), 41.2 (*t*-1), 5C, OCCCO], 41.3 (CH_3−N), [14.1, 14.0, 10C, CH_3(EtO)]; IR $\tilde{\nu}$ = 1744, 1265, 1220 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{98}H_{57}NO_{20}$ 1568.3547, found 1568.3501; UV/vis (PhMe) λ_{max} 284, 308 nm.

Compound **8b** (red): R_f = 0.28 (PhMe/EtOAc 8:2); ^1H NMR (500 MHz, $CDCl_3$) δ = 4.22−4.46 [m, 20H, CH_2(EtO)], 3.84 and 3.73 (2d, J = 10.0 Hz, 2H, CH_2^{pyrr}), 3.68 and 3.43 (2d, J = 10.0 Hz, 2H, CH_2^{pyrr}), 2.63 (s, 3H, CH_3−N), 1.24−1.42 [m, 30H, CH_3(EtO)]; ^{13}C NMR (125 MHz, $CDCl_3$) δ (164.2, 164.1, 164.0, 163.9, 163.8, 163.5, 163.2, 10C, CO), (152.0, 148.7, 147.6, 146.9, 146.8, 146.7, 146.2, 146.1, 145.8, 145.4, 145.3, 145.2, 145.0, 144.6, 144.4, 144.20, 144.15, 143.7, 143.5, 143.4, 143.2, 142.1, 141.9, 141.7, 141.4, 141.3, 140.8, 140.7, 140.2, 140.1, 139.93, 139.89, 139.7, 138.63, 138.59, 138.1, 137.8, 137.0, 134.8, 130.7, 125.4, 48C, C_{60}-sp^2), [71.1, 70.7, 69.8, 69.7,

DOI: 10.1021/acs.joc.7b03083
J. Org. Chem. 2018, 83, 2166−2172

69.4, 69.2, 68.8, 68.2, 66.3, 66.0, 10C, C_{60}-sp^3(cp)], (70.6, 70.0, 2C, CH_2^{pyrr}), [65.7, 63.1, 2C, C_{60}-sp^3(pyrr)], [62.93, 62.89, 62.84, 62.80, 62.7, 62.6, 62.5, 10C, CH_2(EtO)], (49.2, 45.5, 43.6, 43.4, 42.0, 5C, OCCCO), 41.2 (CH_3–N), [14.12, 14.07, 14.0, 10C, CH_3(EtO)]; IR $\tilde{\nu}$ = 1744, 1264, 1225 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{98}H_{57}NO_{20}$ 1568.3547, found 1568.3524; UV/vis (PhMe) λ_{max} 288, 508, 545 nm.

8c/**8d** mixture (**8c**/**8d** ~ 80:20) (brown): R_f = 0.47 (PhMe/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.05–4.55 [m, 20H, CH_2(EtO)], 4.12 and 3.49 (m and d, J = 9.5 Hz, 2H, CH_2^{pyrr}, **8d**), 3.99 and 3.07 (m and d, J = 9.0 Hz, 2H, CH_2^{pyrr}, **8d**), 3.96 and 3.36 (2d, J = 9.5 Hz, 2H, CH_2^{pyrr}, **8c**), 3.91 and 3.55 (2d, J = 9.0 Hz, 2H, CH_2^{pyrr}, **8c**), 2.51 (br s, 3H, CH_3–N), 1.15–1.47 [m, 30H, CH_3(EtO)]; ^{13}C NMR (125 MHz, $CDCl_3$) δ (165.2, 164.1, 164.04, 163.97, 163.9, 163.6, 10C, CO), (149.5, 149.0, 148.6, 148.0, 147.9, 147.7, 147.4, 147.1, 147.0, 146.8, 146.5, 145.9, 145.7, 145.4, 145.2, 144.9, 144.7, 144.2, 143.8, 143.5, 143.3, 143.0, 142.9, 142.7, 142.1, 142.0, 141.4, 141.3, 141.1, 140.4, 140.2, 139.43, 139.37, 138.43, 138.35, 137.6, 136.6, 129.3, 48C, C_{60}-sp^2), [71.1, 70.6, 70.2, 69.3, 69.0, 68.8, 68.3, 67.2, 67.1, 66.3, 10C, C_{60}-sp^3(cp)], (69.9, 66.8, 2C, CH_2^{pyrr}), [66.5, 58.2, 2C, C_{60}-sp^3(pyrr)], [63.04, 62.96, 62.90, 62.86, 62.8, 62.72, 62.67, 62.6, 62.5, 10C, CH_2(EtO)], (57.5, 52.2, 44.7, 43.8, 43.2, 5C, OCCCO), 40.7 (CH_3–N), [14.2, 14.1, 14.04, 14.00, 13.95, 13.9, 10C, CH_3(EtO)]; IR $\tilde{\nu}$ = 1744, 1260, 1225 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{98}H_{57}NO_{20}$ 1568.3547, found 1568.3488; UV/vis (PhMe) λ_{max} 288, 532 nm.

Synthesis of the Regioisomeric Bingel–Prato [5:1]-Hexaadducts ***9***. A mixture of **1** (100 mg, 0.066 mmol), paraformaldehyde (30 mg, 0.99 mmol, 15 mol equiv), and glycine derivative **3** (54 mg, 0.198 mmol, 3 mol equiv) in *o*-dichlorobenzene (4 mL) was heated at 110 °C under Ar for 2 h. The reaction mixture was purified by FCC (50g SiO_2) to give unreacted pentakisadduct **1** (30 mg, 30%) and a mixture of regioisomers (43 mg, 37%) (Figure S17, SI) using PhMe/EtOAc 100/8 and 100/15 as eluents, respectively. The pure regioisomers, yellow **9a** (14 mg, 12.1%) and red **9b** (17 mg, 14.6%), were isolated after another round of FCC on SiO_2 (20 g) using PhMe/EtOAc 100/14 and 100/18 as eluents, respectively.

Compound **9a** (yellow): R_f = 0.36 (PhMe/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.53 (br s, 1H, NH-Boc), 4.25–4.40 [m, 20H, CH_2(EtO)], 3.70 (s, 4H, CH_2^{pyrr}), 3.13 [m, 2H, CH_2(1)], 2.68 [br t, J = 7.0 Hz, 2H, CH_2(6)], 1.65 [m, 2H, CH_2(5)], 1.52 [quint, J = 7.0 Hz, 2H, CH_2(2)], 1.45 [s, 9H, CH_3(Boc)], 1.44 [m, 2H, CH_2(4)], 1.38 [m, 2H, CH_2(3)], 1.25–1.39 [m, 30H, CH_3(EtO)]; ^{13}C NMR (125 MHz, $CDCl_3$) δ [164.1 (*t*-1), 163.9 (*eq*), 163.7 (*eq*), 10C, CO], 156.0 [CO(Boc), (153.1, 146.2, 145.7, 145.6, 145.5, 145.1, 143.6, 141.8, 141.6, 140.0, 139.6, 139.1, 48C, C_{60}-sp^2], 79.0 [C(Boc)], [70.0, 69.4, 69.2, 67.8 (C_{60}-sp^3(cp), C_{60}-sp^3(pyrr)], 67.7 (CH_2^{pyrr}), [62.9, 62.74, 62.72, 62.6, 10C, CH_2(EtO)], 54.8 [CH_2(6)], [45.4 (*eq*), 45.0 (*eq*), 41.2 (*t*-1), 5C, OCCCO], 40.6 [CH_2(1)], 30.0 [CH_2(2)], 28.7 [CH_2(5)], 28.4 [CH_3(Boc)], 27.2 [CH_2(4)], 26.7 [CH_2(3)], 14.0 [10C, CH_3(EtO)]; IR $\tilde{\nu}$ = 3414, 1743, 1262, 1220 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{108}H_{76}N_2O_{22}$ 1753.4962, found 1753.4939; UV/vis (PhMe) λ_{max} 286 nm.

Compound **9b** (red): R_f = 0.30 (PhMe/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.54 (br s, 1H, NH-Boc), 4.22–4.47 [m, 20H, CH_2(EtO)], 3.92 and 3.64 (2d, J = 9.0 Hz, 2H, CH_2^{pyrr}), 3.74 and 3.36 (2d, J = 9.0 Hz, 2H, CH_2^{pyrr}), 3.13 [m, 2H, CH_2(1)], 2.70 [m, 2H, CH_2(6)], 1.68 [m, 2H, CH_2(5)], 1.52 [quint, J = 7.0 Hz, 2H, CH_2(2)], 1.45 [s, 9H, CH_3(Boc)], 1.44 [m, 2H, CH_2(4)], 1.38 [m, 2H, CH_2(3)], 1.25–1.42 [m, 30H, CH_3(EtO)]; ^{13}C NMR (125 MHz, $CDCl_3$) δ (164.2, 164.1, 164.0, 163.94, 163.87, 163.8, 163.5, 163.2, 10C, CO), 156.0 [CO(Boc)], (152.3, 148.7, 147.9, 147.0, 146.8, 146.6, 146.13, 146.09, 145.82, 145.80, 145.75, 145.43, 145.38, 145.3, 145.2, 145.1, 144.5, 144.34, 144.28, 144.1, 143.7, 143.5, 143.4, 143.1, 142.1, 142.0, 141.6, 141.5, 141.2, 140.7, 140.2, 140.1, 139.9, 139.7, 138.6, 137.96, 137.93, 136.8, 134.8, 130.7, 125.6, 48C, C_{60}-sp^2), 79.0 [C(Boc)], [71.0, 70.6, 69.8, 69.7, 69.4, 69.1, 68.8, 68.2, 66.3, 65.6 (10C, C_{60}-sp^3(cp)], (68.5, 68.1, CH_2^{pyrr}), [65.2, 62.4, C_{60}-sp^3(pyrr)], [62.92, 62.87, 62.82, 62.79, 62.72, 62.68, 62.6, 62.4, 10C, CH_2(EtO)], 54.6 [CH_2(6)], (49.2, 45.5, 43.6, 43.4, 42.0, 5C, OCCCO), 40.6 [CH_2(1)], 30.0 [CH_2(2)], 28.7 [CH_2(5)], 28.4 [CH_3(Boc)], 27.2 [CH_2(4)], 26.7 [CH_2(3)], 14.12, 14.06, 14.0, 10C, CH_3(EtO)]; IR $\tilde{\nu}$ = 3421, 1745, 1242 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{108}H_{76}N_2O_{22}$ 1753.4962, found 1753.4916; UV/vis (PhMe) λ_{max} 284, 508, 545 nm.

Synthesis of the Regioisomeric Bingel–Prato [5:1]-Hexaadducts ***10***. A mixture of pentakisadduct **1** (25 mg, 0.0165 mmol), glycine **4** (18 mg, 0.066 mmol, 4 mol equiv), and paraformaldehyde (9.9 mg, 0.330 mmol, 20 mol equiv) in *o*-dichlorobenzene (2.5 mL) was heated at 110 °C under Ar for 2 h. The mixture was cooled, and the solvent was evaporated. Separation of the recovered pentakisadduct **1** (6.2 mg, 25%) and the mixture of regioisomers **10a** and **10 b** (12.1 mg, 42%) (Figure S18, SI) was achieved by DCFC on silica gel using PhMe/EtOAc 100:4 and 70:30 as eluants, respectively. Regioisomers **10a** and **10b** were separated by preparative TLC (PhMe/EtOAc 6:4): **10a** (4 mg, 14%), **10b** (5 mg, 17%).

Compound **10a** (yellow): R_f = 0.34 (PhMe/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.37 (br t, J = 5.5 Hz, 1H, NH^{Gly}), 4.22–4.50 [m, 20H, CH_2(EtO)], 3.94 (d, J = 5.5 Hz, CH_2^{Gly}), 3.72 (s, 4H, CH_2^{pyrr}), 2.81 [t, J = 6.5 Hz, 2H, $CH_2(4)^{GABA}$], 2.45 [t, J = 7.0 Hz, 2H, CH_2(2)], 2.00 [quint, J = 7.0 Hz, 2H, $CH_2(3)^{GABA}$], 1.45 [s, 9H, CH_3(*t*Bu)], 1.22–1.40 [m, 30H, CH_3(EtO)]; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 172.8 (CO^{GABA}), 169.2 (CO^{Gly}), [164.1 (*t*-1), 163.93 (*eq*), 163.87 (*eq*), 163.7 (*eq*), 10C, CO], [153.0, 146.2, 145.7 (2C), 145.5, 145.2, 143.6, 141.8, 141.6, 140.0, 139.6, 139.2, 48C, C_{60}-sp^2], 82.0 (C^{tBu}), [70.1, 69.5, 69.2, 67.8, C_{60}-sp^3(cp)], 67.6 [C_{60}-sp^3(pyrr)], 67.3 (CH_2^{pyrr}), [62.9, 62.8, 62.7, 10C, CH_2(EtO)], 53.0 [$CH_2(4)^{GABA}$], [45.4 (*eq*), 45.0 (*eq*), 41.2 (*t*-1), 5C, OCCCO], 42.0 (CH_2^{Gly}), 33.8 [$CH_2(2)^{GABA}$], 28.0 [$CH_3(^tBu)$], 24.1 [$CH_2(3)^{GABA}$], [14.1, 14.0, 10C, CH_3(EtO)]; IR $\tilde{\nu}$ = 3414, 1744, 1674, 1265, 1221 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{107}H_{72}N_2O_{23}$ 1753.4599, found 1753.4561; UV/vis (PhMe) λ_{max} 284, 297, 308 nm.

Compound **10b** (red, mixture of two conformers proposed): R_f = 0.32 (PhMe/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.70 and 6.62 [two br t, J = 5.5 Hz, 1H, NH^{Gly}, two conformers in the relative ratio of 15:85 (**10b-II**/**10b-I**); see p S56, SI], 4.20–4.47 [m, 20H, CH_2(EtO)], 3.96 (dd, J = 2.5; 5.5 Hz, CH_2^{Gly}), 3.83 and 3.76 (2d, J = 9.0 Hz, 2H, CH_2^{pyrr}), 3.68 and 3.46 (2d, J = 9.0 Hz, 2H, CH_2^{pyrr}), 2.90 and 2.81 [2m, 2H, $CH_2(4)^{GABA}$], 2.47 [m (two overlapped t), 2H, CH_2(2)], 2.00 [m (two overlapped quint), 2H, $CH_2(3)^{GABA}$], 1.45 [s, 9H, CH_3(tBu)], 1.22–1.43 [m, 30H, CH_3(EtO)]; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 173.1 (CO^{GABA}), 169.2 (CO^{Gly}), (164.2, 164.1, 164.0, 163.92, 163.87, 163.8, 163.7, 163.5, 163.3, 10C, CO), (152.0, 148.7, 147.6, 146.9, 146.8, 146.6, 146.1, 145.9, 145.8, 145.6, 145.4, 145.33, 145.28, 145.2, 144.8, 144.4, 144.3, 144.2, 144.1, 143.7, 143.4, 143.1, 142.7, 142.1, 141.9, 141.8, 141.7, 141.6, 141.3, 140.8, 140.7, 140.3, 140.1, 140.0, 139.9, 139.7, 139.6, 139.3, 139.2, 138.6, 138.5, 138.0, 137.8, 136.7, 134.8, 130.6, 125.8, 48C, C_{60}-sp^2), 81.8 (C^{tBu}), [71.0, 70.7, 70.0, 69.8, 69.4, 69.2, 68.8, 68.1, 66.4, 66.0, C_{60}-sp^3(cp)], (67.7, 67.3, CH_2^{pyrr}), [65.1, 62.5, C_{60}-sp^3(pyrr)], [63.0, 62.9, 62.84, 62.80, 62.75, 62.6, 62.4, 10C, CH_2(EtO)], 52.1 [$CH_2(4)^{GABA}$], (49.2, 45.4, 43.6, 43.4, 42.05, 5C, OCCCO), 42.01 (CH_2^{Gly}), 33.6 [$CH_2(2)^{GABA}$], 28.1 [$CH_3(^tBu)$], 24.2 [$CH_2(3)^{GABA}$], [14.11, 14.07, 14.0, 10C, CH_3(EtO)]; IR $\tilde{\nu}$ = 3409, 1743, 1679, 1294, 1222 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{107}H_{72}N_2O_{23}$ 1753.4599, found 1753.4542; UV/vis (PhMe) λ_{max} 288, 506, 543 nm.

Synthesis of the Regioisomeric Bingel–Prato [5:1]-Hexaadducts ***11***. A mixture of **1** (20 mg, 0.013 mmol), glycine derivative **5** (7 mg, 0.034 mmol, 3 mol equiv), and paraformaldehyde (2.0 mg, 0.068 mmol, 5 mol equiv) in *o*-dichlorobenzene (2 mL) was heated at 110 °C under argon for 1 h. The mixture was cooled, and the solvent was evaporated. Separation of the recovered pentakisadduct **1** (11 mg, 51%) and the mixture of regioisomers **11a** and **11b** (3.6 mg, 16%) (Figure S19, SI) was achieved by DCFC on silica gel using PhMe/EtOAc 90:10 as an eluent. Regioisomers **11a** and **11b** were separated by preparative TLC (PhMe/EtOAc 90:10; **11a**, 1.5 mg, 6.7%; **11b**, 1.4 mg, 6.2%). The ^{13}C NMR spectrum of **11b** has a low-quality one with a low signal-to-noise ratio due to the small quantity of product.

Compound **11a** (yellow): R_f = 0.45 (PhMe/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.22 (d, J = 8.4 Hz, 2H, HC-Ar), 6.95 (d, J =

DOI: 10.1021/acs.joc.7b03083
J. Org. Chem. 2018, 83, 2166–2172

8.0 Hz, 2H, HC-Ar), 4.65 (s, 4H, CH_2^{pyrr}), 4.42−4.25 [m, 20H, CH_2(EtO)], 1.40−1.24 [m, 30H, CH_3 (EtO)]; ^{13}C NMR (100 MHz, $CDCl_3$) δ [164.0 (*t*-1), 163.8 (*eq*), 163.7 (*eq*), 163.6 (*eq*), 10C, CO], 152.4 (C−Ar), (151.7, 146.2, 146.1, 145.6, 145.5, 145.0, 143.4, 142.0, 141.8, 140.3, 139.6, 139.3, 48C, C_{60}-sp^2), 139.6 (C−Ar), 126.1 (2C, CH-Ar), 114.0 (2C, CH-Ar), [77.2, 70.2, 69.63 69.3, 68.0, 10C, C_{60}-sp^3(cp)], 66.5 [2C, C_{60}-sp^3(pyrr)], [63.02, 62.98, 62.93, 62.87, 62.8, 10C, CH_2(EtO)], 60.7 (2C, CH_2^{pyrr}), 45.1 (5C, OCCCO), [14.1, 14.05, 14.02, 10C, CH_3(EtO)]; IR $\tilde{\nu}$ = 2923, 1738, 1214, 1020, 753, 531 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{103}H_{58}N_2O_{22}$ 1675.3554, found 1675.3541; UV/vis (PhMe) λ_{max} 333, 356, 383 nm.

Compound **11b** (red): R_f = 0.39 (PhMe/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 (d, *J* = 8.4 Hz, 2H. HC-Ar), 6.99 (d, *J* = 8.4 Hz, 2H, HC-Ar), 4.74 (s, 2H, CH_2^{pyrr}), 4.60 (d, *J* = 11.2 Hz, 1H, CH_2^{pyrr}), 4.48−4.24 (m, 20H from CH_2(EtO), 4.40 (1H from CH_2^{pyrr}), 1.42−1.28 (m, 30H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (164.2, 164.1, 164.0, 163.9, 163.84, 163.79, 163.75, 163.7, 163.5, 163.2, 10C, CO), 150.8 (C−Ar), (149.2, 147.96, 147.93, 147.6, 146.9, 146.7, 146.1, 145.4, 145.0, 144.5, 144.3, 143.2, 142.9, 142.0, 141.7, 141.2, 140.9, 140.4, 48C, C_{60}-sp^2), 140.0 (C−Ar), 126.0 (2C, CH−Ar), 114.0 (2C, CH-Ar), 77.2, 64.0, [63.2, 63.1, 63.05, 63.02, 62.98, 62.96, 62.91, 62.87, 62.8, 62.6, 10C, CH_2(EtO)], {61.8 [C_{60}-sp^3(pyrr)], 61.6 (CH_2^{pyrr}), 61.4 [C_{60}-sp^3(pyrr)], 61.3 (CH_2^{pyrr}), from HSQC}, [14.2, 14.1, 14.0, 10C, CH_3(EtO)]; IR $\tilde{\nu}$ = 3479, 2925, 1744, 1596, 1258, 1021, 798, 533 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{103}H_{58}N_2O_{22}$ 1675.3554, found 1675.3540; UV/vis (PhMe) λ_{max} 212, 223, 243, 251, 295, 326, 341, 376, 502, 541 nm.

Synthesis of the Regioisomeric Bingel−Prato [5:1]-Hexaadducts ***12***. A mixture of **1** (20 mg, 0.013 mmol), paraformaldehyde (2.0 mg, 0.066 mmol, 5 mol equiv), and glycine derivative **6** (7.2 mg, 0.038 mmol, 3 mol equiv) in *o*-dichlorobenzene (2 mL) was heated at 110 °C under argon for 90 min. The mixture was cooled, and the solvent was evaporated. The reaction mixture was first purified by DCFC to give unreacted pentakisadduct **1** (5.0 mg, 25%) and a mixture of regioisomers (6.2 mg, 33%) (Figure S20, SI) using PhMe/EtOAc 90:10 as an eluent. The obtained mixture of regioisomers **12** was separated by preparative TLC (PhMe/EtOAc 90:10; **12a**, 3.6 mg, 19.2%; **12b**, 1.1 mg, 5.8%). The ^{13}C NMR spectrum of **12b** has a low-quality one with a low signal-to-noise ratio due to the small quantity of product.

Compound **12a** (yellow): R_f = 0.46 (PhMe/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.97 (d, *J* = 9.2 Hz, 2H, HC-Ar), 6.92 (d, *J* = 9.2 Hz, 2H, HC-Ar), 4.44−4.25 [m, 20H from CH_2(EtO); 4H from CH_2^{pyrr} at 4.37 ppm], 3.80 (s, 3H, CH_3O), 1.40−1.22 [m, 30H, CH_3(EtO)]; ^{13}C NMR (100 MHz, $CDCl_3$) δ [164.1 (*t*-1), 163.93 (*eq*), 163.88 (*eq*), 163.7 (*eq*), 10C, CO], (152.6, 146.2, 145.9, 145.8, 145.6, 145.1, 143.7, 141.9, 141.7, 140.1, 139.6, 139.2, 48C, C_{60}-sp^2), 117.7 (2C, CH-Ar), 114.8 (2C, CH-Ar), [77.2, 70.1, 69.5, 69.4, 67.9, 10C, C_{60}-sp^3(cp)], 67.0 [2C, C_{60}-sp^3(pyrr)], 63.6 (2C, CH_2^{pyrr}), [62.9, 62.80, 62.76, 10C, CH_2(EtO)], 55.6 (OCH_3), (45.5, 45.0, 5C, OCCCO), [14.1, 14.05, 14.03, 10C, CH_3(EtO)]; IR $\tilde{\nu}$ = 3523, 2926, 1738, 1598, 1263, 1020, 739, 531 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{104}H_{61}NO_{21}$ 1660.3809, found 1660.3777; UV/vis (PhMe) λ_{max} 209, 247, 264, 295, 306, 314, 326, 343 nm.

Compound **12b** (red): R_f = 0.44 (PhMe/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.00 (d, *J* = 8.4 Hz, 2H, HC-Ar), 6.91 (d, *J* = 8.8 Hz, 2H, HC-Ar), 4.55−4.20 [m, 23H, 20H from CH_2(EtO); δ values for signals of three pyrrolidine protons assigned from the HSQC spectrum: CH_2^{pyrr} at 4.48 and 4.41, and $1H^{pyrr}$ at 4.32], 4.10 (d, *J* = 9.6 Hz, $1H^{pyrr}$), 3.81 (s, 3H, CH_3O), 1.45−1.22 (m, 30H); ^{13}C NMR (100 MHz, $CDCl_3$) [the ^{13}C NMR of a small amount of this regioisomer (0.5 mg) was recorded over the weekend and spectrum was very poor with a low signal-to-noise ratio; thus, fullerene carbon signals were lost into the noise. Signals of C atoms of addends are given. On the basis of the HSQC spectrum (see SI) chemical shifts of pyrrolidine C atoms are given.] δ = 163.9 (10C, CO), 117.64, 117.58, 114.7, 77.2, (64.3 and 63.9, CH_2^{pyrr}, from HSQC spectrum), 63.05, 62.97, 62.92, 62.87, 62.82, 62.76, 62.5 [10C, CH_2(EtO)], 55.7 (OCH_3), [14.13, 14.07, 14.0, 10C, CH_3(EtO)]; IR $\tilde{\nu}$ = 2923, 1738, 1214, 1020, 791, 531 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{104}H_{61}NO_{21}$ 1660.3809, found 1660.3777; UV/vis (PhMe) λ_{max} 231, 215, 289, 307, 322, 506, 545 nm.

Prato Cycloaddition of Trt-Gly-OH ***7*** *on the Pentakisadduct* ***1***. A mixture of **1** (48.5 mg, 0.032 mmol), paraformaldehyde (10 mg, 0.32 mmol, 10 mol equiv), and Trt-Gly-OH **7** (30.5 mg, 0.096 mmol, 3 mol equiv) in *o*-dichlorobenzene (4 mL) was heated at 110 °C under argon for 2 h. The reaction mixture was purified by DCFC on SiO_2 to give unreacted pentakisadduct **1** (34 mg, 70%) and a more polar mixture of compounds that did not contain the expected isomers.

Synthesis of the Regioisomeric Bingel−DA [5:1]-Hexaadduct ***13a***. Freshly distilled cyclopentadiene (0.1 mL, 1.189 mmol, 100 mol equiv) was added to a solution of pentakisadduct **1** (18 mg, 0.0119 mmol) in a mixture of PhMe (2 mL) and $CHCl_3$ [1 mL, stabilized with EtOH (1%)]. After stirring for 30 min at 50 °C, the color changed from red to yellow. FCC, DCFC, and gravitational column chromatography did not give good separation of Diels−Alder hexaadduct and the starting pentakisadduct **1**. DA adduct **13a** (9 mg) was isolated in pure form by successive crystallizations of the reaction mixture from *n*-hexane/EtOAc and CH_2Cl_2/MeOH in a yield of 48%.

Hexaadduct **13a**: R_f = 0.26 (*n*-hexane/acetone 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.57 (s, 2H, HC═CH), 4.25−4.42 [m, 20H, CH_2(EtO)], 3.89 (br s, CH), 2.58 (d, *J* = 9.5 Hz, 1H, CH_2), 2.00 (d, *J* = 9.5 Hz, 1H, CH_2), 1.25−1.40 [m, 30H, CH_3(EtO)]; ^{13}C NMR (125 MHz, $CDCl_3$) δ [164.1 (*t*-1), 164.0 (*eq*), 163.8 (*eq*), 10C, CO], [154.9, 153.8, 146.3 (2), 145.9, 145.7, 145.59, 145.55, 145.5, 145.4, 145.2 (2), 145.1, 145.0, 141.8, 141.7 (2), 141.6, 139.8 (2), 139.7, 139.4, 139.0, 138.8, 48C, C_{60}-sp^2], 137.2 (CH═CH), 72.4 [2C, C_{60}-sp^3(DA)], [70.1, 69.9, 69.4 (2C), 69.2, 69.0, 67.9 (2C), 67.7 (2C), 10C, C_{60}-sp^3(cp)], [62.8, 62.7, 62.6, 10C, CH_2(EtO)], 56.6 (CH) 45.44 (CH_2), [45.42 (*e*-edge), 45.3 (*e*-edge), 45.1 (*e*-face), 41.2 (*t*-1), 5C, OCCCO], [14.1, 14.0, 10C, CH_3(EtO)]; IR $\tilde{\nu}$ = 1746, 1265, 1222 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{100}H_{56}O_{20}$ 1577.3438, found 1577.3424; UV/vis (PhMe) λ_{max} 284, 299, 312 nm.

Synthesis of the Regioisomeric Bingel−DA [5:1]-Hexaadduct ***14a***. Danishefsky's diene (18 mg, 21 μL, 0.106 mmol, 20 mol equiv) was added to a solution of pentakisadduct **1** (8 mg, 0.0053 mmol, 1 mol equiv) in PhMe (2 mL) in the dark under an Ar atmosphere. After stirring for 4 h at reflux, the color changed from red to yellow. The reaction mixture was purified by FCC. The starting compound **1** was eluted with *n*-hexane/EtOAc 7:3 (2 mg, 25%). The DA adduct **14a** was eluted with *n*-hexane/EtOAc 7:3 and further precipitated two times from CH_2Cl_2 solution with MeOH (4 mg, 47%).

Hexaadduct **14a**: R_f = 0.40 (*n*-hexane/EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.59 (br s, 1H, CH−OMe), 4.23−4.42 [m, 20H, CH_2(EtO)], 3.55 (s, CH_3O), 3.34 (m, 2H, C^{full}−CH_2−CO), 3.22 (m, 2H, CH−CH_2−CO), 1.24−1.40 [m, 30H, CH_3(EtO)]; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 207.6 (CO), (164.1, 163.9, 163.72, 163.66, 163.54, 163.51, 10C, EtOCO), (154.74, 154.69, 146.4, 146.3, 146.2, 146.1, 146.0, 145.9, 145.5, 145.4, 145.14, 145.07, 145.0, 144.5, 144.3, 143.8, 142.2, 142.1, 141.85, 141.76, 141.7, 139.9, 139.80, 139.78, 139.59, 139.56, 139.3, 139.1, 139.0, 138.7, 128.2, 125.3, 48C, C_{60}-sp^2), 86.8 (CH-OMe), (70.13, 70.08, 69.65, 69.62, 69.1, 67.7, 67.5, 67.4, 64.6, C_{60}-sp^3), [62.9, 62.84, 62.75, 62.6, 10C, CH_2(EtO)], 58.6 (CH_3O), 52.2 [C_{60}−CH_2−CO)], (45.51, 45.48, 45.1, 45.0, 40.5, 5C, OCCCO), 41.0 (CH−CH_2−CO), [14.1, 14.0, 10C, CH_3(EtO)]; IR $\tilde{\nu}$ = 1744, 1262, 1221 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{100}H_{58}O_{22}$ 1611.3492, found 1611.3472; UV/vis (PhMe) λ_{max} 286 nm.

Synthesis of the Regioisomeric Bingel−DA [5:1]-Hexaadduct ***15a***. Pentakisadduct **1** (20 mg, 0.013 mmol) was added to a solution of 2,3,5,6-tetramethylenebicyclo[2.2.2]oct-7-ene (4.0 mg, 0.026 mmol, 2 mol equiv) in acetonitrile (2 mL). The reaction mixture was heated to reflux in a sealed tube for 24 h. Volatiles were removed, and the residue was purified by DCFC with petroleum ether/acetone 1:1. Unreacted **1** (7.6 mg, 38%) was recovered and then the desired compound **15a** was collected (3.3 mg, 8%) as a yellow powder.

Hexaadduct **15a**: R_f = 0.51 (PhMe/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.56 (dd, *J* = 2.4, 3.2 Hz, 2H, HC-sp^2), 5.16 and 4.87 (2s, 4H, H_2C═C), 4.41−4.24 [m, 20H, CH_2(EtO)], 4.21 (t, *J* =

DOI: 10.1021/acs.joc.7b03083
J. Org. Chem. 2018, 83, 2166−2172

3.2 Hz, 2H, C*H*-sp^3), 3.48, 3.43 (ABq, J_{AB}= 11.2 Hz, 4H, CH_2-sp^3), 1.41−1.23 [m, 30H, CH_3(EtO)]; ^{13}C NMR (100 MHz, $CDCl_3$) δ (164.0, 163.9, 163.7, 10C, CO), 156.2, 155.6, 146.4 (2), 145.50, 145.48, 145.46, 145.1 (2), 144.9, 144.8, 143.7, 143.6 (2C, C═CH_2), 143.5, 141.92, 141.89, 141.8, 140.4 (2C, C═C), 139.7, 139.6, 139.2, 139.1, 139.0, 138.9, 134.4 (2C, CH═CH), 129.2, 102.7 (2C, CH_2═C), (70.11, 70.09, 70.04, 70.03, 69.6, 69.1, 69.0, 67.4, 63.2, 10C, C_{60}-sp^3-cp), 62.9 (2C, C_{60}-sp^3-DA), [62.8, 62.74, 62.71, 62.69, 62.6, CH_2(EtO)], 52.9 (2C, CH-sp^3), [45.3 (*e*-face), 45.2 (*e*-face), 45.0 (*e*-edge), 5C, OCCCO], 43.6 (2C, CH_2-sp^3), [14.1, 14.0, 10C, CH_3(EtO)]; IR $\tilde{\nu}$ = 2925, 1743, 1254, 713, 535 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{107}H_{62}O_{20}$ 1667.3907, found 1667.3901; UV/vis (PhMe) λ_{max} 214, 243, 291, 303, 318, 331.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b03083.

General information and optimization of reaction conditions, detailed characterization of products **8**−**15**, including their NMR and mass spectra, and computational results (Figures S1−S20 and Table S1) (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*V.R.M. e-mail: vmaslak@chem.bg.ac.rs.

*D.R.M. e-mail: dmilic@chem.bg.ac.rs.

ORCID

Dragana R. Milić: 0000-0002-5713-8815

Present Address

‖R.Z.P.: Department of Chemistry & Biochemistry, The Ohio State University, 100 West 18th Avenue, Columbus, Ohio 43210, United States.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work has been supported by the Ministry of Education, Science and Technological Development of Serbia (Project No. 172002). We thank the Ohio Supercomputer Center for providing generous allocations of computational resources.

■ REFERENCES

(1) (a) Hirsch, A.; Brettreich, M. *Fullerenes: Chemistry and Reactions*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004; Chapter 10, pp 289−344. (b) Hirsch, A.; Vostrowsky, O. *Eur. J. Org. Chem.* **2001**, *2001*, 829−848. (c) Yan, W.; Seifermann, S. M.; Pierrat, P.; Bräse, S. *Org. Biomol. Chem.* **2015**, *13*, 25−54. (d) Nierengarten, I.; Nierengarten, J.-F. *Chem. Rec.* **2015**, *15*, 31−51.

(2) (a) Muñoz, A.; Sigwalt, D.; Illescas, B. M.; Luczkowiak, J.; Rodríguez-Pérez, L.; Nierengarten, I.; Holler, M.; Remy, J.-S.; Buffet, K.; Vincent, S. P.; Rojo, J.; Delgado, R.; Nierengarten, J.-F.; Martín, N. *Nat. Chem.* **2016**, *8*, 50−57. (b) Braun, M.; Camps, X.; Vostrowsky, O.; Hirsch, A.; Endreß, E.; Bayerl, T. M.; Birkert, O.; Gauglitz, G. *Eur. J. Org. Chem.* **2000**, *2000*, 1173−1181. (c) Campisciano, V.; La Parola, V.; Liotta, L. F.; Giacalone, F.; Gruttadauria, M. *Chem. - Eur. J.* **2015**, *21*, 3327−3334. (d) Fortgang, P.; Maisonhaute, E.; Amatore, C.; Delavaux-Nicot, B.; Iehl, J.; Nierengarten, J.-F. *Angew. Chem., Int. Ed.* **2011**, *50*, 2364−2367. (e) Hörmann, F.; Brettreich, M.; Donaubauer, W.; Hampel, F.; Hirsch, A. *Chem. - Eur. J.* **2013**, *19*, 2814−2825. (f) Hörmann, F.; Hirsch, A. *Chem. - Eur. J.* **2013**, *19*, 3188−3197.

(3) (a) Isaacs, L.; Haldimann, R. F.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2339−2342. (b) Isaacs, L.; Diederich, F.; Haldimann, R. F. *Helv. Chim. Acta* **1997**, *80*, 317−342. (c) Beuerle, F.; Hirsch, A. *Chem. - Eur. J.* **2009**, *15*, 7447−7455.

(4) (a) Lamparth, I.; Maichle-Mössmer, C.; Hirsch, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1607−1609. (b) Witte, P.; Hörmann, F.; Hirsch, A. *Chem. - Eur. J.* **2009**, *15*, 7423−7433. (c) Seifermann, S. M.; Réthoré, C.; Muller, T.; Bräse, S. *Sci. Rep.* **2013**, *3*, 2817. (d) Brettreich, M.; Burghardt, S.; Böttcher, C.; Bayerl, T.; Bayerl, S.; Hirsch, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1845−1848. (e) Braun, M.; Hartnagel, U.; Ravanelli, E.; Schade, B.; Böttcher, C.; Vostrowsky, O.; Hirsch, A. *Eur. J. Org. Chem.* **2004**, *2004*, 1983−2001.

(5) (a) Li, H.; Haque, Sk. A.; Kitaygorodskiy, A.; Meziani, M. J.; Torres-Castillo, M.; Sun, Y.-P. *Org. Lett.* **2006**, *8*, 5641−5643. (b) Guerra, S.; Iehl, J.; Holler, M.; Peterca, M.; Wilson, D. A.; Partridge, B. E.; Zhang, S.; Deschenaux, R.; Nierengarten, J.-F.; Percec, V. *Chem. Sci.* **2015**, *6*, 3393−3401. (c) Riala, M.; Maxouti, K. L.; Ioannou, C. P.; Chronakis, N. *Org. Lett.* **2016**, *18*, 1132−1135. (d) Ramos-Soriano, J.; Reina, J. J.; Pérez-Sánchez, A.; Illescas, B. M.; Rojo, J.; Martín, N. *Chem. Commun.* **2016**, *52*, 10544−10546.

(6) (a) Ortiz, A. L.; Rivera, D. M.; Athans, A. J.; Echegoyen, L. *Eur. J. Org. Chem.* **2009**, *2009*, 3396−3403. (b) Ortiz, A. L.; Echegoyen, L. *J. Mater. Chem.* **2011**, *21*, 1362−1364. (c) Zhang, S.; Lukoyanova, O.; Echegoyen, L. *Chem. - Eur. J.* **2006**, *12*, 2846−2853.

(7) Fujiwara, K.; Komatsu, K. *Chem. Commun.* **2001**, 1986−1987.

(8) Hörmann, F.; Donaubauer, W.; Hampel, F.; Hirsch, A. *Chem. - Eur. J.* **2012**, *18*, 3329−3337.

(9) Mitrović, A.; Todorović, N.; Žekić, A.; Stanković, D.; Milić, D.; Maslak, V. *Eur. J. Org. Chem.* **2013**, *2013*, 2188−2193.

(10) Bjelaković, M.; Todorović, N.; Milić, M. *Eur. J. Org. Chem.* **2012**, *2012*, 5291−5300.

(11) Specklin, S.; Decuypere, E.; Plougastel, L.; Aliani, S.; Taran, F. *J. Org. Chem.* **2014**, *79*, 7772−7777.

(12) Barlos, K.; Papaioannou, D.; Theodoropoulos, D. *J. Org. Chem.* **1982**, *47*, 1324−1326.

(13) Langa, F.; de la Cruz, P.; Espíldora, E.; Gonzalez-Cortés, A.; de la Hoz, A.; López-Arza, V. *J. Org. Chem.* **2000**, *65*, 8675−8684.

(14) Uno, H.; Watanabe, H.; Yamashita, Y.; Ono, N. *Org. Biomol. Chem.* **2005**, *3*, 448−453.

DOI: 10.1021/acs.joc.7b03083
J. Org. Chem. 2018, 83, 2166−2172