Synthesis of Functionalized Polynorbornanes Employing 2,5-Bis(trifluoromethyl)-1,3,4-oxadiazole

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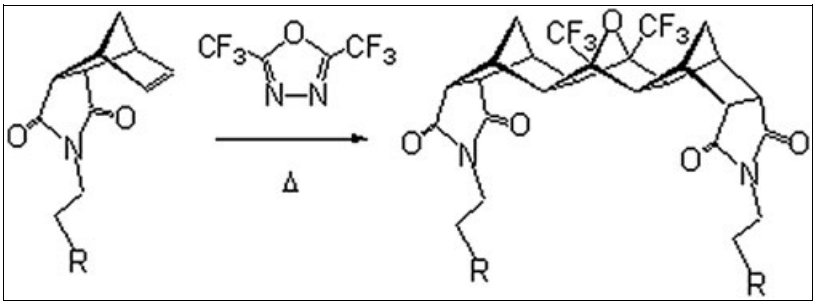

Cycloaddition reaction of 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole with strained olefinic bonds of norbornenes was used to synthetize functionalized polynorbornanes. This simple, one step procedure was more effective when reaction was carried out by classical heating, in comparison to microwave-assisted reactions. Various functional groups were stable in the reaction conditions (ester, imide, phthalimide, piperidyl, and carboxylic acid), whereas anhydride, *N*-Boc, or TMS functionalities do not withstand reaction conditions.

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INTRODUCTION

Polycyclic compounds have been found to be useful scaffolds in chemical structure manipulation in the development of multifunctional drugs [1]. They provide an excellent platform to tailor molecular diversity by appending desired substituents at selected positions around the molecular scaffold. The utilization of organic molecular scaffolds as a strategy for organization of polyfunctional groups [2] was achieved, for instance, by saccharides [3], calix[4]arenes [4], cholic acid [5], saturated polycyclic hydrocarbon structures [6] such as the bicylic norbornane [7], tricyclic adamantane, and tetracyclo [6.3.1.$1^{1.4}$.$0^{5.12}$] framework [8]. Conformational constraints imposed by norbornene scaffolds effectively serve as polypeptide β-sheet inducers [9,10]. The advantage of using norbornene derivatives as molecular scaffolds is that they have built-in U-shaped architectures delivering functional groups at desired geometrical positions [11,12]. Therefore, development of norbornene cycloaddition coupling protocols is of the crucial importance in the synthesis of polynorbornanes [13]. Amongst several available heterocyclic reagents, 2,5-bis (trifluoromethyl)-1,3,4-oxadiazole **1a** (OD) coupling plays one of the leading roles, where coupling was achieved by tandem Diels–Alder reaction/dinitrogen elimination/1, 3-dipolar cycloaddition sequence (Scheme 1) [14,15]. Isolation of intermediates was precluded by their high reactivity and nonstability.

The traditional conditions for OD coupling require strong heating and are not conductive for isolation of thermally sensitive materials [16]. High pressure facilitated coupling (at 1.4 GPa and RT) is advantageous in these cases, but reactions are limited to use of special high pressure equipment [14]. Therefore, the improvement of the OD coupling protocol in terms of using shorter reaction times and less vigorous conditions remained an important synthetic goal. In this respect, we investigated OD reactions under microwave (MW) conditions [17], and found that in the case of 7-oxanorbornene dienophiles, MW reactions were adventitious to classical heating in terms of reaction times and stereochemical outcomes [18]. In this article, we explore the utility of MW irradiated and thermal OD cycloadditions on the synthesis of functionalized polynorbornanes.

RESULTS AND DISCUSSION

The optimization of OD reaction with norbornenes under microwave conditions was carried out using substrate **5** as model compound. These results are collected in Table 1. All reactions carried out with **1a** were stereospecific, giving a single linear (*exo*,*exo*-) isomer. The observed stereospecificity of cycloadditions was explained previously in terms of the norbornene π-facial selectivity [15,18]. The inspection of results revealed that the yields of reactions are significantly lower than for the corresponding thermal reactions.

Scheme 1. OD coupling reaction.

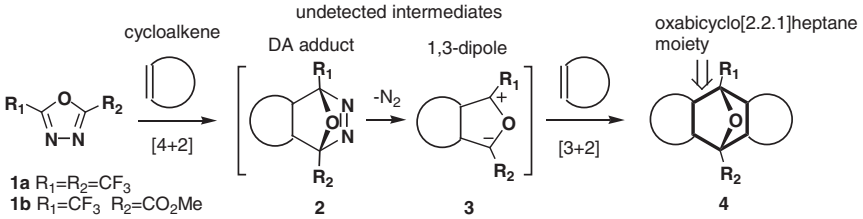
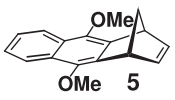
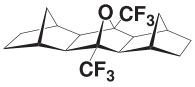
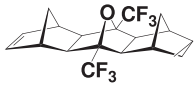
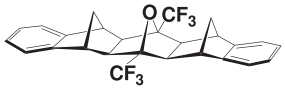
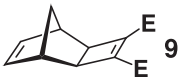
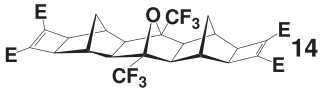
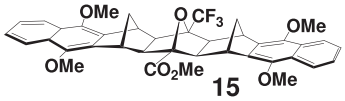


Table 1

Optimization of OD reaction with norbornenes under microwave conditions.

Entry	Substrate	Product	T/°C	t/min	Solvent	Yields/%[a]
1	 **5**	 **10**	150	30	—	10
2			150	120	—	15
3			170	30	—	15
4			120	30	—	8
5			150	30	CH_2Cl_2	8
6			150	30	CH_3CN	5
7			150	30	THF	8
8			150	30	dioxane	9
9			150	30	H_2O	12
10			150	24h	THF	95[b]
			150	30	THF	24
11	 **6**	 **11**				
			150	30	THF	21
12	 **7**	 **12**				
			150	30	THF	15
13	 **8**	 **13**				
			150	30	THF	15
14	 **9**	 **14**				
			150	30		98
15[c]	**5**	 **15**				
16[c]			150	48h	THF	96[b]

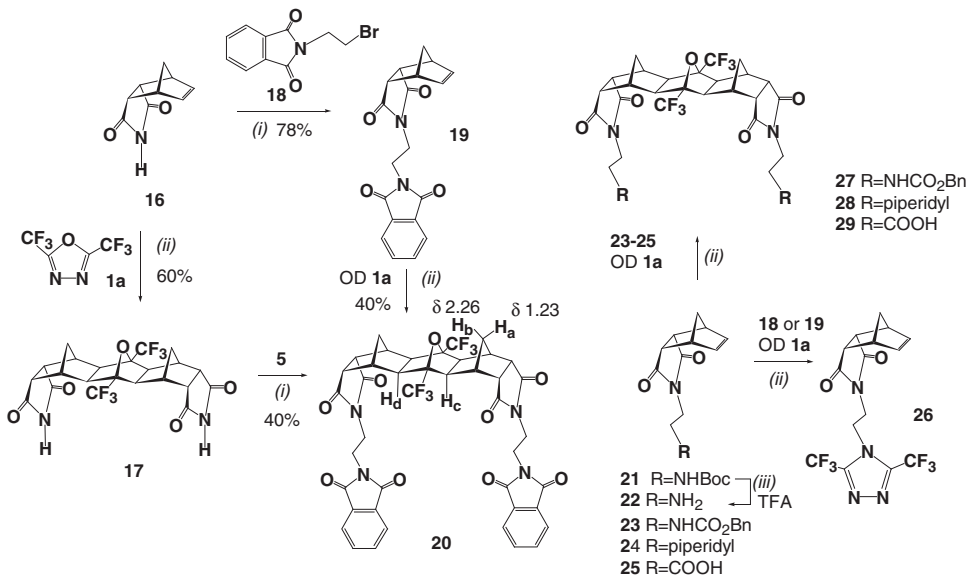
[a]Estimated from ^{1}H-NMR analysis; [b]classical thermal conditions; [c]2-carbmethoxy-5-trifluoromethyl-1,3,4-oxadiazole **1b**.

The best reaction yields were obtained in reactions carried out without solvent (in neat **1a**, Entries 1–4), whereas the presence of solvent decreases yields (Entries 5–9). The optimal reaction conditions were heating at 150°C, for 120 min (Entry 2). Similarly, low yields were obtained in OD reactions with model norbornenes **6–9** (Entries 11–14), which could be connected to the reaction times considerably shorter than used in classical thermal reactions (Entries 10 and 16). Observed lower reactivities compared with the 7-oxanorbornene dienophiles could be also explained in terms of stereoelectronic effects. Here, σ-π hyperconjugative orbital interactions with methylene bridge lower alkene frontier molecular orbitals, whereas oxygen bridge has smaller repulsive and steric interactions with incoming OD reagent [19].

The best reaction yield (98%) was obtained for the reaction of dimethoxynaphthalene substrate **5** with 2-carbmethoxy-5-trifluoromethyl-1,3,4-oxadiazole (Entry 15). In this case, MW reaction at 150°C gave quantitative conversion to cycloadduct **12** within 30 min. Comparable yield could be achieved by classical heating at 150°C for 48 h (Entry 16). This result indicates identical cycloaddition reactivity of methyl ester substituted OD as compared with the bistrifluoromethyl substituted OD. From this experimental observation, it is obvious that the presence of solid 1,3,4-oxadiazole reagent (compared with low-boiling point liquid OD), and the absence of solvent are highly advantageous. This solid state reaction is of particular interest for development of environmentally benign synthetic protocols [20].

Optimized MW reaction conditions were employed in subsequent synthesis of functionalized polynorbornanes (Scheme 2). For this purpose, ethylphthalimido protected substrate **19** was prepared in one step from the imide **16** (in 78% yield) by *N*-alkylation with *N*-(2-bromoethyl)phthalimide employing procedure analogous to literature (DMF, K_2CO_3) [21]. The *COC*-[3]polynorbornane bis-imide **17** was obtained according to literature starting from **16** [22]. Other substrates used in this study are known from literature (**21** and **22**) [23] and were prepared accordingly, whereas norbornenes **23** and **24** were synthetized for the first time. Thus, substrate **23** was prepared in 46% yield from 4-aminoethylnorbornene **22** and benzyl chloroformate, whereas **24** was prepared by microwave or classical heating of the mixture of *endo*-norborn-5-ene-2, 3-dicarboxylic anhydride and (1-aminoethyl)piperidine in 93% and 88% yield, respectively. Similarly, the heating of the mixture of *endo*-norborn-5-ene-2,3-dicarboxylic anhydride and β-alanine afforded substrate **25** [24]. Functionalities could be incorporated into the macrocylic ring either by their positioning onto norbornene substrate prior OD reaction, or by the post-cycloaddition functionalization. Hence, thermal cycloaddition reaction of phthalimide **19** with oxadiazole **1a** yielded bis-*N*-(2-ethyl)phthalimido *COC*-[3]polynorbornane **20** in 40% yield. In this product, two phthalimido functionalities are positioned on the same side of rigid polycyclic scaffold and their position locked. Adduct **20** could be also obtained by bis-*N*-alkylation of **17**, and its structure was deduced from NMR spectra. The most indicative signals in ^{1}H-NMR spectrum are those of the methylene bridge protons H_a and H_b. The close presence of the oxygen bridge atom causes their splitting to two doublets that are positioned at δ 1.23 and δ 2.26 (steric compression effect). ^{1}H-^{1}H COSY and NOESY correlations and C_{2v} symmetry of ^{13}C-NMR spectrum further support structure assignment, in particular indicative are strong NOESY correlations of *endo*-protons H_c and H_d. Coupling of phthalimide **19** with 2-carbmethoxy-5-trifluoromethyl-

Scheme 2. Reagents and conditions: (i) K_2CO_3, DMF, 65°C, **2d**; (ii) THF 150°C, **2d**; (iii) TFA, CH_2Cl_2.



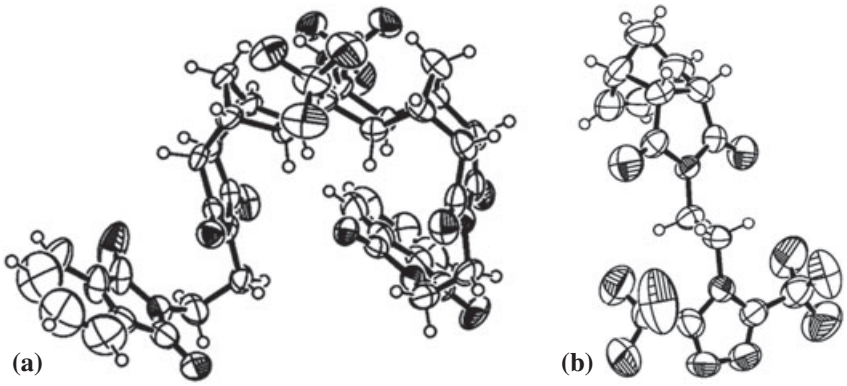


Figure 1. X-ray structures of (a) **20** and (b) **26**.

1,3,4-oxadiazole **1b** (at 150°C, MW, 2 h, no solvent) was less effective, just partial conversion to product was obtained (75% conversion, as deduced from the crude NMR spectra).

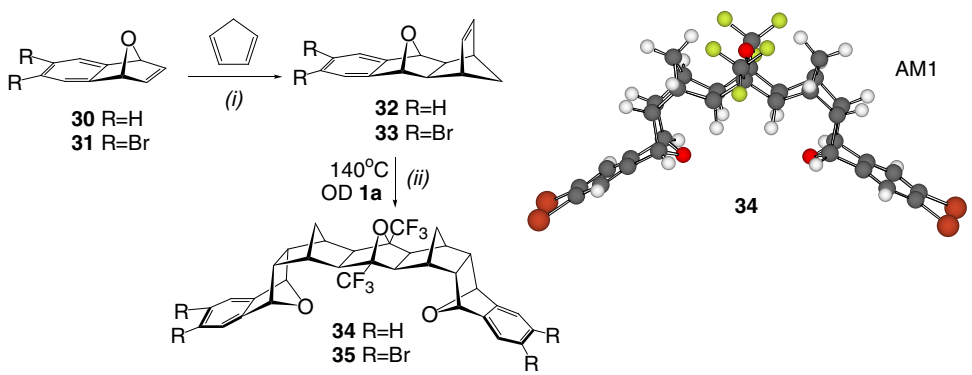
The assigned U-shaped structure of **20** was fully supported by the single crystal structural analysis, and its shape was presented in Figure 1(a). Of particular interest in this structure are the functionalities positioned at the *endo*-side of polynorbornene, whereas two trifluoromethyl substituents of polycyclic framework are pointed into *exo*-direction. Molecular modeling (AM1 method) of these alicyclophanes indicated that the N—N separation of the succinimide nitrogens in **17** is 6.30 Å, and that this distance expands to 6.63 Å upon conversion to the alicyclophane **20**. This calculated N—N distance agrees well with the value obtained from the X-ray structure of **20** (6.68 Å). Another structural point of interest is U-shaped curvature of *COC*-[3]polynorbornane, which is small, but evident.

The choice of substituents on the maleimide is limited because of their possible reactions with OD. It was found that much less effective were OD coupling reactions of *N*-Cbz, *N*-piperidyl, and carboxylic acid substrates **23–25**, where inseparable mixtures of adducts **27**, **28**, and **29** were obtained by heating at 150°C in THF. Equally inefficient were OD reactions with *N*-Boc substrate **21** and free amine **22** (Scheme 1). In these reactions, single product was isolated in high yield, whose ^{1}H-NMR spectra showed that norbornene C=C bond remained unchanged. Detailed spectral analysis showed that the 1,3,5-triazole derivative **26** was obtained in both cases as a sole product (in 86% and 90% yields, respectively). Even the high pressure reaction of **22** and OD conducted at lower temperature (THF, 100°C, 24 h, 4 kbar) produced **26** in 95% yield. Addition of bases such as triethylamine or crude K_2CO_3 into reaction vessel did not supress Boc deprotection. The structure of product **26** was unequivocally confirmed by the single crystal X-ray analysis (Figure 1(b)). Formation of triazoles by reaction of amines with oxadiazoles is a known process [25], and in the case of substrate **21** presumably takes place by the *in situ* deprotection of amine.

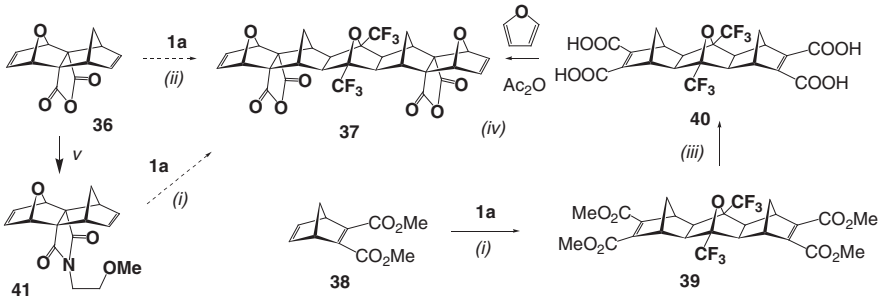
Alternative synthetic route to the end-functionalized U-shaped cavities presents OD cycloaddition with pentacyclic alkenes **32** and **33**, derived from 7-oxabenzonorbornenes **30** and **31**, by addition of cyclopentadiene (Scheme 3). Reactions proceed smoothly in high yield by heating at 140°C, for 2 days giving single isomers **34** and **35** (89% and 66%, respectively). Molecular modeling by AM1 method shows that the polycyclic skeleton of *COCOC*-[5]polynorbornane **34** and **35** positions substituents in more divergent manner than obtained by *COC*-[3]polynorbornane skeleton **20**.

Anhydride **36** [26] represents an experimental testing ground for establishing the site-selectivity and reactivity of olefinic bond in Diels–Alder reactions. Although in

Scheme 3. (i) $CHCl_3$, 80°C, 12 h, (ii) THF, 140°C, **2d**, ampoule.



Scheme 4. (i) THF 140°C, **1d**, (ii) THF 140°C, **2d**, (iii) KOH/MeOH, RT, 18 h, (iv) Ac_2O, furan, 60°C, 3 h, (v) Ac_2O, NaOAc, methoxyethylamine, 60°C, 24 h.



the Diels–Alder reactions with normal electron demand 7-oxanorbornene (or 7-aza) [27] π-bond is preferred reaction site, in the Diels–Alder reactions with reverse electron demand, such as OD addition, norbornene π-bond is the preferred reaction site. Simple frontier molecular orbital theory (FMO) analysis of **36** indicated that the HOMO is mostly located on the 7-oxanorbornene π-bond, and LUMO is on the norbornene π-bond. It was anticipated that selectivity will lead to the preferential formation of *OCOCO*[5]polynorbornene **37** (Scheme 4). However, it was found that anhydride **36** was not stable in the OD cycloaddition conditions. Instead, product **37** was prepared by three synthetic step procedure, starting with norbornadiene diester **38**. Its reaction with oxadiazole produced *COC*[3]polynorbornene **39** in 33% yield. KOH hydrolysis and the *in situ* formation of bis-anhydride of the tetraacid **40** was followed by trapping with furan to afford **37** (67%). Functionalization of anhydride **36** with methoxyethylamine gave imide **41**, which was subjected to OD reaction. It was found that synthesis of cycloadduct structurally related to **37** from **41** was not successful, because of the decomposition of substrate.

CONCLUSION

Inverse electron demand Diels–Alder reactions of 2,5-bis (trifluoromethyl)-1,3,4-oxadiazole with norbornenes were proven to be of synthetic value for the preparation of functionalized polynorbornanes. For this particular cycloaddition reaction and substrates, classical heating for prolonged time was more successful than microwave-assisted heating.

EXPERIMENTAL

The NMR spectra were recorded in $CDCl_3$ solutions containing tetramethylsilane as internal standard on Bruker AMX 300 or 600 MHz instruments. Melting points were determined using a Gallenkamp digital melting point apparatus and are uncorrected. The high-resolution mass spectra were recorded on a Micromass Platform II single quadrupole AutoSpec instrument (ESMS, electrospray mass spectrometry in CH_2Cl_2). Radial chromatography was carried out with a chromatotron, Model No. 79245T, using 1 mm thickness plates with silica gel $60F_{254}$ as the stationary phase. Chemicals were purchased from Aldrich (St. Louis, MO) and used without purification. Known procedures were used to prepare 2,5-trifluoromethyl-1,3,4-oxadiazole [28], 2-carbmethoxy-5-trifluoromethyl-1,3,4-oxadiazole [29] and **25** [24]. All new compounds gave ^{1}H-NMR and ^{13}C-NMR spectra and high-resolution mass spectra corresponding to their assigned structures.

4-(2′-Ethylphthalimido)-1α,2α,6α,7α-4-azatricyclo[5.2.1.0^{2,6}] deca-8-ene-3,5-dione (19). Mixture of imide **16** (1.0 g, 6.13 mmol), *N*-(2-bromoethyl)phthalimide **18** (1.56 g, 6.13 mmol), and potassium carbonate (4.24 g, 30.6 mmol) in DMF (20 mL) was heated at 65°C for 48 h. Solvent was removed *in vacuo*, residue dissolved in dichloromethane and washed with water. Organic layers were separated, dried ($MgSO_4$), and solvent removed *in vacuo* to afford colorless solid. (1.60 g, 78%, mp 177–178°C). ^{1}H-NMR ($CDCl_3$), δ/ppm: 1.42 (1H, dd, J = 8.9 Hz, J = 2.1 Hz), 1.61 (1H, dd, J = 8.9 Hz, J = 2.1 Hz), 3.16 (2H, br s), 3.22 (2H, s), 3.61 (2H, t, J = 4.8 Hz), 3.69 (2H, t, J = 4.8 Hz), 5.95 (2H, s), 7.62–7.69 (2H, m), 7.72–7.80 (2H, m); ^{13}C-NMR ($CDCl_3$), δ/ppm:, HRMS (*m/z*): Calcd for $C_{19}H_{16}O_4N_2$: 336.1110 found: 336.1117.

4-(2′-Benzyloxycarbonylaminoethyl)-(1α,2α,6α,7α)-4-azatricyclo[5.2.1.0^{2,6}]deca-8-ene-3,5-dione (23). Mixture of 4-aminoethyl-4-aza-1α,2α,6α,7α-tricyclo[5.2.1.0^{2,6}]deca-8-ene-3,5-dione **22** [23] (1.00 g, 5 mmol), aqueous Na_2CO_3 (0.4 M, 25 mL) in dichloromethane (25 mL) was treated with benzyl chloroformate (1.5 mL, 7.5 mmol) at 0°C. Reaction mixture was stirred for 16 h at RT, then diluted with dichloromethane, washed with water, and solvent was removed *in vacuo*. Residue was subjected to column chromatography (petroleum ether/ethyl acetate 2:1, then solvent polarity was gradually increased to EtOAc) to afford colorless solid (780 mg, 46%, mp 144–146°C). ^{1}H-NMR ($CDCl_3$), δ/ppm: 1.46 (1H, dd, J = 6.9 Hz, J = 2.2 Hz), 1.67 (1H, dd, J = 6.9 Hz, J = 2.2 Hz), 3.15 (2H, s), 3.26 (2H, t, J = 6.9 Hz), 3.31 (2H, s), 3.47 (2H, t, J = 6.9 Hz), 5.03 (2H, s), 6.02 (2H, s), 7.24–7.33 (2H, m); ^{13}C-NMR ($CDCl_3$), δ/ppm: 37.7, 39.6, 44.8, 45.9, 52.2, 60.4, 66.7, 128.1, 128.2, 134.4, 136.5, 156.3, 177.6; HRMS (*m/z*): Calcd for $C_{19}H_{20}O_4N_2$: 340.1423 found: 340.1427.

4-(2′-Piperidinoaminoethyl)-(1α,2α,6α,7α)-4-azatricyclo [5.2.1.0^{2,6}]deca-8-ene-3,5-dione (24). Mixture of *endo*-norborn-5-ene-2,3-dicarboxylic anhydride (200 mg, 1.22 mmol) and (1-aminoethyl)piperidine (156 mg, 1.22 mmol) was heated at 150°C for 30 min in an open round bottomed flask. After cooling, residue was passed through a short silica column (eluted with ethyl acetate) to afford yellow colored oil. (88%, mp 128–131°C). Method B. Reaction mixture was heated in MW reactor for 1 h at 150°C (93%). ^{1}H-NMR ($CDCl_3$), δ/ppm: 1.31–1.32 (2H, m), 1.42–1.46 (6H, m), 1.63 (1H, dd, J = 8.8 Hz, J = 1.4 Hz) 2.23 (2H, t, J = 7.1 Hz), 3.15 (2H, s), 3.28 (2H, s), 3.36 (2H, t, J = 7.1 Hz), 5.99 (2H, t, J = 1.8 Hz); ^{13}C-NMR ($CDCl_3$), δ/ppm: 24.2, 25.9, 35.5, 44.8, 45.7, 51.9, 54.3, 55.6, 134.3, 177.5; HRMS (*m/z*): Calcd for $C_{16}H_{22}O_2N_2$: 274.1681 found: 274.1689.

General procedure for OD cycloadditions. Method A - microwave. Mixture of oxadiazole **1a** (60 mg, 0.25 mmol) and substrate (50–100 mg, 0.05 mmol) in appropriate solvent was subjected to microwave-assisted reaction at 140–170°C. Reactions were conducted in CEM Discover®LabmateTH/ExplorerPLS® single mode microwave reactor using closed reaction vessel technique (power = 125 W). Excess of solvent was removed *in vacuo*, and products were analyzed by either by TLC or ^{1}H-NMR spectroscopy. Radial chromatography (with petroleum ether–ethyl acetate) was used to isolate pure products.

General procedure for OD cycloadditions. Method B - thermal. Mixture of oxadiazole **1a** (100 mg, 0.42 mmol) and substrate (100–150 mg, 0.05–0.1 mmol) in THF (2–3 mL) was heated in a sealed glass tube. Upon cooling, solvent and escess reagent were removed *in vacuo*, and products were purified by radial chromatography (with petroleum ether–ethyl acetate).

1,11-Bis(2′-ethylphthalimido)-6,16-bis(ethyl)-1α,2β,3α,4α,8α,9α,10β,11α,12β, 13α,14α,18α,19α,20β-6,16-diaza-22-oxaoctacyclo[9.9.1^{1,11}.1^{3,9}.1^{13,19}.0^{2,10}.0^{4,8}.0^{12,20}.0^{14,18}]tricosane-5,7,15,17-tetraone (20). Method B with **16** (40%), (mp 263–264°C). ^{1}H-NMR ($CDCl_3$), δ/ppm: 1.23 (2H, dd, J = 7.5 Hz, J = 4.9 Hz), 2.26 (2H, dd, J = 7.5 Hz, J = 4.9 Hz), 2.79 (4H, s), 2.92 (4H, s), 3.55 (4H, t, J = 7.1 Hz), 4.01 (4H, t, J = 7.1 Hz); 7.57–7.97 (8H, m); ^{13}C-NMR ($CDCl_3$), δ/ppm: 28.1, 38.2, 38.7, 40.7, 48.2, 49.3, 88.5 (q, $^2J_{C,F}$ = 31.3 Hz), 123.4, 124.2 (q, $^1J_{C,F}$ = 278.1 Hz), 131.8, 134.2, 168.6, 176.9, HRMS (*m/z*): Calcd for $C_{42}H_{32}O_9N_4F_6$: 850.2073 found: 850.2077.

Bisalkylation method. Mixture of imide **17** (62 mg, 0.123 mmol), *N*-(2-bromoethyl)phthalimide **18** (80 mg, 0.316 mmol), and potassium carbonate (20 mg, 0.145 mmol) in DMF (1.5 mL) was heated at 65°C for 48 h. Solvent was removed *in vacuo*, residue dissolved in dichloromethane and washed with water. Organic layers were separated, dried ($MgSO_4$), and solvent removed *in vacuo* to afford colorless solid (98.3 mg, 94%).

4-(2′-(2,5-Bis(trifluoromethyl)-1,3,4-oxadiazolo)aminoethyl)-1α,2α,6α,7α-4-azatricyclo[5.2.1.0^{2,6}]deca-8-ene-3,5-dione (26). Method B with **22** (86%), method B with **23** (90%), (mp 177–178°C). ^{1}H-NMR ($CDCl_3$), δ/ppm: 1.58 (1H, dd, J = 8.6 Hz, J = 2.3 Hz), 1.93 (1H, dd, J = 8.6 Hz, J = 2.3 Hz), 3.30 (2H, s), 3.38 (2H, s), 3.78 (2H, t, J = 6.4 Hz), 4.33 (2H, t, J = 6.4 Hz), 6.08 (2H, s); ^{13}C-NMR ($CDCl_3$), 36.9, 44.5, 44.8, 45.9, 52.2, 67.9, 117.8 (q, $^1J_{C,F}$ = 293.1 Hz), 134.6, 146.9 (q, $^2J_{C,F}$ = 41.4 Hz), 175.9; δ/ppm:, HRMS (*m/z*): Calcd for $C_{15}H_{12}O_2N_4F_6$: 394.0864 found: 394.0861.

1,11-Bis(trifluoromethyl)-6,16-bis(2′-benzyloxycarbonylaminoethyl)-1α,2β,3α,4α,8α,9α,10β,11α,12β,13α,14α,18α,19α,20β-6,16-diaza-22-oxaoctacyclo[9.9.1^{1,11}.1^{3,9}.1^{13,19}.0^{2,10}.0^{4,8}.0^{12,20}.0^{14,18}]tricosane-5,7,15,17-tetraone dicarboxylate (27). Method A (50%), method B (30%), ^{1}H-NMR ($CDCl_3$), δ/ppm (obtained from crude mixture): 1.25 (2H, d, J = 8.6 Hz), 2.20 (4H, s), 2.30 (2H, dd, J = 8.6 Hz, J = 1.7 Hz), 2.74 (4H, s), 2.84 (4H, s), 3.25–3.27 (4H, m), 3.46 (4H, t, J = 6.0 Hz), 5.05 (4H, s), 7.25–7.39 (10H, m); HRMS (*m/z*): Calcd for $C_{42}H_{40}O_9N_4F_6$: 858.2699 found: 858.2701.

1,11-Bis(trifluoromethyl)-6,16-bis(2′-piperidinoaminoethyl)-1α,2β,3α,4α,8α,9α,10β,11α,12β,13α,14α,18α,19α,20β-6,16-diaza-22-oxaoctacyclo[9.9.1^{1,11}.1^{3,9}.1^{13,19}.0^{2,10}.0^{4,8}.0^{12,20}.0^{14,18}]tricosane-5,7,15,17-tetraone dicarboxylate (28). Method B (20%), ^{1}H-NMR ($CDCl_3$), δ/ppm (obtained from crude mixture): 1.33 (2H, d, J = 10.5 Hz), 1.72 (4H, s), 2.21 (2H, d, J = 10.5 Hz), 2.87 (8H, t, J = 7.1 Hz), 2.89 (4H, s), 3.19 (4H, s), 3.59 (4H, t, J = 6.6 Hz), 3.66 (4H, t, J = 6.6 Hz), 3.70 (4H, t, J = 7.1 Hz), 3.72 (8H, t, J = 7.1 Hz).

1,11-Bis(trifluoromethyl)-6,16-diethyl-1α,2β,3α,4α,8α,9α,10β,11α,12β,13α,14α,18α,19α,20β-6,16-diaza-22-oxaoctacyclo[9.9.1^{1,11}.1^{3,9}.1^{13,19}.0^{2,10}.0^{4,8}.0^{12,20}.0^{14,18}]tricosa-5,7,15,17-tetraone dicarboxylate (29). Method B (MeCN, 20%), ^{1}H-NMR ($CDCl_3$), δ/ppm (obtained from crude mixture): 1.39 (2H, d, J = 10.5 Hz), 2.23 (4H, s), 2.29 (2H, d, J = 10.5 Hz), 3.05 (4H, s), 3.09 (4H, s), 4.24 (4H, s), 7.35 (2H, br s).

1,16-Bis(trifluoromethyl)-5,12,20,27-tetramethoxy-(1α,2β,3α,4β,5α,12α,13β,14α,15β,16α,17β,18α,19β,20α,27α,28β,29α,30β)-33-oxadodecacyclo[14.14.1.1^{3,14}1.^{15,12}.1^{18,29}.1^{20,27}.0^{2,15}.0^{4,13}.0^{6,11}.0^{17,30}.0^{19,28}.0^{21,26}]pentatriaconta-4,6,8,10,12,19,21,23,25,27-decaene (10). Method A (15%), method B (95%), (mp 187–191°C). ^{1}H-NMR ($CDCl_3$), δ/ppm: 1.63 (2H, dd, J = 9.8 Hz), 2.33 (4H, s), 2.58 (2H, dd, J = 9.8 Hz), 3.95 (12H, s), 4.09 (4H, s), 7.41 (4H, dd, J = 6.0 Hz, J = 2.8 Hz), 8.01 (4H, dd, J = 6.0 Hz, J = 2.8 Hz); ^{13}C-NMR ($CDCl_3$), δ/ppm: 41.4, 42.0, 54.8, 61.2, 87.1 (q, $^2J_{C,F}$ = 31.5 Hz), 121.5, 124.9, 123.5 (q, $^1J_{C,F}$ = 276.8 Hz), 127.7, 133.5, 143.9; HRMS (*m/z*): Calcd for $C_{38}H_{32}O_5F_6$: 682.2154 found: 682.2157.

1-Methyl-16-trifluoromethyl-5,12,20,27-tetramethoxy-(1α,2β,3α,4β,5α,12α,13β,14α,15β,16α,17β,18α,19β,20α,27α,28β,29α,30β)-33-oxadodecacyclo[14.14.1.1^{3,14}.1.^{15,12}.1^{18,29}.1^{20,27}.0^{2,15}.0^{4,13}.0^{6,11}.0^{17,30}.0^{19,28}.0^{21,26}]pentatriaconta-4,6,8,10,12,19,21,23,25,27-decaene-1-carboxylate (15). Method A (98%), method B (96%), (mp 211–213°C). ^{1}H-NMR ($CDCl_3$), δ/ppm: 1.56 (2H, dd, J = 5 Hz, J = 2 Hz), 2.31 (2H, dd, J = 5 Hz, J = 2 Hz), 2.42 (2H, dd, J = 5 Hz, J = 2 Hz), 2.71 (2H, dd, J = 5 Hz, J = 2 Hz), 3.66 (4H, s), 3.95 (6H, s), 4.1 (6H, s), 4.2 (3H, s), 4.2 (4H, s), 7.41 (2H, dd, J = 5.0 Hz, J = 2.0 Hz), 8.00 (2H, dd, J = 5 Hz, J = 2 Hz); ^{13}C-NMR ($CDCl_3$), δ/ppm: 41.3, 42.1, 44.1, 52.0, 54.6, 54.8, 60.7, 61.0, 81.1, 87.2 (q, $^2J_{C,F}$ = 31.1 Hz), 121.3, 121.4, 124.6, 124.8, 123.7 (q, $^1J_{C,F}$ = 277.0 Hz), 127.8, 127.9, 133.4, 133.7, 143.8, 144.0, 161.6; HRMS (*m/z*): Calcd for $C_{39}H_{35}O_5F_3$: 640.2436 found: 640.2349.

(1α,2β,3β,6β,7β,8α)-15-Oxapentacyclo[6.6.1.1^{3,6}.0^{2,7}.0^{9,14}]tetradeca-4,9,11,13-tetraene (32). Solution of 7-oxabenzonorbornadiene **30** (1.00 g, 6.94 mmol) in chloroform (5 mL) and freshly cracked cyclopentadiene (2.00 g, 30.3 mmol) was heated at 70°C for 18 h in sealed glass tube. Solvent was removed *in vacuo*, and oily residue was separated by flash column chromatography (silicagel, petroleum ether, then solvent polarity was increased to 5% ethyl acetate) to afford colorless oil (1.30 g, 89.0%). ^{1}H-NMR ($CDCl_3$), δ/ppm: 1.38 (1H, d, J = 8.1 Hz), 1.56 (1H, td, J = 8.1 Hz, J = 1.7 Hz), 2.38 (2H, t, J = 1.7 Hz), 2.92 (2H, t, J = 1.4 Hz), 4.97 (2H, s), 6.14 (2H, t, J = 1.7 Hz), 7.09 (4H, dd, J = 5.4 Hz, J = 3.2 Hz), 7.18 (4H, dd, J = 5.4 Hz, J = 3.2 Hz); ^{13}C-NMR ($CDCl_3$), δ/ppm: 44.4, 49.4, 53.7, 80.2, 118.9, 126.5, 134.4, 148.4; HRMS (*m/z*): Calcd for $C_{15}H_{14}O_1$: 210.1045 found: 210.1046.

11,12-Dibromo-(1α,2β,3β,6β,7β,8α)-15-oxapentacyclo[6.6.1.1^{3,6}.0^{2,7}.0^{9,14}]tetradeca-4,9,11,13-tetraene (33). Solution of 4,5-dibromo-7-oxabenzonorbornadiene **31** (1.00 g, 3.33 mmol) in chloroform (5 mL) and freshly cracked cyclopentadiene (2.00 g, 30.3 mmol) was heated at 80°C for 18 h in sealed glass tube. Solvent was removed *in vacuo*, and oily residue was separated by flash column chromatography (silicagel, petroleum ether, then solvent polarity was increased to 5% ethyl acetate) to afford colorless solid (0.94 g, 77%, mp 213–214°C). ^{1}H-NMR ($CDCl_3$), δ/ppm: 1.36 (1H, d, J = 8.2 Hz), 1.55 (1H, td, J = 8.2 Hz, J = 1.6 Hz), 2.36 (2H, dd, J = 2.6 Hz, J = 1.3 Hz), 2.92 (2H, t, J = 1.6 Hz), 4.92 (2H, s), 6.09 (2H, t, J = 1.5 Hz), 7.41 (4H, s); ^{13}C-NMR ($CDCl_3$), δ/ppm: 43.9, 48.6, 53.3, 79.4, 121.8, 123.9,

133.9, 149.0; HRMS (*m/z*): Calcd for $C_{15}H_{12}O_1Br_2$: 365.9255 found: 365.9261.

1,16-Bis-trifluoromethyl-(1α,2β,3α,4α,5β,12β,13α,14α,15β,16α,17α,18β,19α,20β,27β,28α,29β,30α)-31,33,35-trioxadodecacyclo[14.14.1.1^{3,14}.1^{5,12}.1^{18,29}.1^{20,27}.0^{2,15}.0^{4,13}.0^{6,11}.0^{17,30}.0^{19,28}.0^{21,26}]pentatriaconta-6,8,10,21,23,25-hexaene (34). Method A (70%), method B (89%), (mp 243–245°C). ^{1}H-NMR ($CDCl_3$), δ/ppm: 1.22 (2H, d, J = 11.7 Hz), 2.02 (2H, s), 2.22 (2H, d, J = 11.7 Hz), 2.74 (4H, s), 5.13 (4H, s), 7.11–7.13 (4H, m), 7.23–7.28 (4H, m); ^{13}C-NMR ($CDCl_3$), δ/ppm: 39.0, 39.1, 48.3, 50.9, 77.6, 87.2 (q, $^2J_{C,F}$ = 31.3 Hz), 118.7, 123.0 (q, $^1J_{C,F}$ = 276.8 Hz), 126.3, 147.1; HRMS (*m/z*): Calcd for $C_{34}H_{28}O_3F_6$: 598.1943 found: 598.1951.

1,16-Bis-trifluoromethyl-8,9,23,24-tetrabromo(1α,2β,3α,4α,5β,12β,13α,14α,15β,16α,17α,18β,19α,20β,27β,28α,29β,30α)-31,33,35-trioxadodecacyclo[14.14.1.1^{3,14}.1^{5,12}.1^{18,29}.1^{20,27}.0^{2,15}.0^{4,13}.0^{6,11}.0^{17,30}.0^{19,28}.0^{21,26}]pentatriaconta-6,8,10,21,23,25-hexaene (35). Method A (40%), method B (66%), (mp 187–188°C). ^{1}H-NMR ($CDCl_3$), δ/ppm: 1.19 (2H, d, J = 10.4 Hz), 2.00 (4H, dd, J = 3.1 Hz, J = 1.8 Hz), 2.25 (2H, d, J = 10.4 Hz), 2.62 (4H, s), 2.73 (4H, s), 5.15 (4H, s), 7.43 (4H, s); ^{13}C-NMR ($CDCl_3$), δ/ppm: 39.0, 40.0, 48.5, 50.8, 78.5, 87.8 (q, $^2J_{C,F}$ = 30.9 Hz), 122.3, 124.4, 125.8 (q, $^1J_{C,F}$ = 280.3 Hz), 148.1; HRMS (*m/z*): Calcd for $C_{34}H_{24}O_3F_6Br_4$: 909.8363 found: 909.8358.

4,5,11,12-Tetramethyl-1,8-bis(trifluoromethyl)-(2β,3α,6α,7β,9β,10α,13α,14β)-16-oxahexacacyclo[6.6.1.1^{1,8}.1^{3,6}.1^{10,13}.0^{2,7}.0^{9,14}]heptadeca-4,11-diene-4,5,11,12-tetracarboxylate (39). Solution of diester **38** (2.20 g, 10.57 mmol) and OD (1.13 g, 5.49 mmol) in dichloromethane (2 mL) was heated at 140°C for 18 h. Solvent and excess reagent were removed under reduced pressure to afford a brown colored oil. Treatment of oil with cold methanol gave colorless solid, which was collected by filtration. Recrystallization from methanol gave colorless crystals (1.05 g, 33%, mp 201–203°C).

^{1}H-NMR ($CDCl_3$), δ/ppm: 1.50 (2H, d, J = 9.8 Hz), 2.27 (2H, d, J = 9.8 Hz), 2.45 (4H, s), 3.52 (4H, s), 3.78 (12H, s); ^{13}C-NMR ($CDCl_3$), δ/ppm: 40.9, 47.5, 52.0, 53.9, 86.1 (q, $^2J_{CF3}$ = 130.5 Hz), 124.1 (q, $^1J_{CF3}$ = 278.9 Hz), 149.4, 164.25; CHN analysis Calcd H 4.07%, C 52.51%, found: H 4.04%, C 52.43%; HRMS (*m/z*): Calcd for $C_{26}H_{24}O_9F_6$: 594.1325 found: 594.1329.

1,8-Bis(trifluoromethyl)-(2β,3α,6α,7β,9β,10α,13α,14β)-16-oxahexacacyclo[6.6.1.1^{1,8}.1^{3,6}.1^{10,13}.0^{2,7}.0^{9,14}]heptadeca-4,11-diene-4,5,11,12-tetracarboxylate (40). Solution of tetraester **39** (0.53 g, 0.89 mmol) in methanol (20 mL) was treated with 40% aqueous KOH (10 mL) and stirred at RT for 16 h. Reaction mixture was acidified with diluted hydrochloric acid to afford colorless solid that was collected by filtration (86%, mp 340–343°C).

^{1}H-NMR ($CDCl_3$/DMSO-d_6), δ/ppm: 0.95 (2H, d, J = 12.0 Hz), 1.72 (2H, d, J = 12.0 Hz), 1.99 (4H, s), 3.23 (4H, s); ^{13}C-NMR ($CDCl_3$/DMSO-d_6), δ/ppm: 48.3, 53.8, 53.9, 84.6 (q, $^2J_{CF3}$ = 127.6 Hz), 124.0 (q, $^1J_{CF3}$ = 280.2 Hz), 150.2, 166.0; HRMS (*m/z*): Calcd for $C_{22}H_{16}O_9F_6$: 538.0698 found: 538.0689.

1,12-Bis(trifluoromethyl)-(2β,3α,5α,8α,10α,13β,14α,16α,19α,20β,21α,22β)-23,25,27,29,32-pentaoxadodecacyclo[10.10.1.3^{4,9}.3^{15,20}1^{1,12}.1^{3,10}.1^{5,8}.0^{14,21}.0^{16,19}]tritiaconta-6,17-diene-28,30,31,33-tetraone (37). Tetraacid **40** (200 mg, 0.3 mmol) was dissolved in acetic anhydride (20 mL) in a stoppered flask, and furan (10 mL) was added. Reaction mixture was heated at 60°C for 3 h, then acetic anhydride was removed *in vacuo* to afford colorless solid. Radial chromatography (petroleum ether/ethyl acetate 5:1, then solvent polarity was gradually increased to 1:1) afforded colorless crystals (67%, mp 286–287°C).

^{1}H-NMR ($CDCl_3$), δ/ppm: 2.20 (2H, d, J = 11.7 Hz), 2.37 (4H, s), 2.70 (2H, d, J = 11.7 Hz), 3.24 (4H, s), 5.18 (4H, s), 6.62 (4H, s); ^{13}C-NMR ($CDCl_3$), δ/ppm: 34.6, 44.3, 52.1, 66.9, 83.5, 88.8 (q, $^2J_{CF3}$ = 128.4 Hz), 125.7 (q, $^1J_{CF3}$ = 237.8 Hz), 138.9, 170.1; HRMS (*m/z*): Calcd for $C_{30}H_{20}O_9F_6$: 638.1012 found: 638.1018.

X-ray structures. All XRD data was collected on an Oxford Diffraction Xcalibur CCD diffractometer, using Mo K_α (λ = 0.71073 Å) radiation, structure solution by SHELXS97 (Sheldrick, 1997).

CCDC 813953 and 813954 contains the supplementary crystallographic data for the structures **20** and **26**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336033; or e-mail: deposit@ccdc.cam.ac.uk.

20 Crystal data: CCDC 813953, $C_{42}H_{32}O_9N_4F_6$, M_r = 179.4, monoclinic, *C2/c*, a = 18.5522(5) Å, b = 10.5073(3) Å, c = 22.6702 (6) Å, β = 93.314(2)°, V = 103.909(2) Å^3, Z = 16, T = 298 K, density = 1.248 mg/m^3, crystal size = 0.78 × 0.18 × 0.03 mm^3.

26 Crystal data: CCDC 813954, colorless plates, $C_{15}H_{12}O_2N_4F_6$, M_r = 394.29, monoclinic, *P21/n*, a = 13.5873(11) Å, b = 13.1008 (15) Å, c = 19.650(2) Å, β = 104.007(9)°, V = 3393.8(6) Å^3, Z = 8, T = 293(2) K, density = 1.543 mg/m^3, crystal size = 0.78 × 0.18 × 0.03 mm^3.

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