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New Cycloadditions of (*E*)-*N*,α-Dimethyl-α-(4-[2.2]paracylophanyl)nitrone

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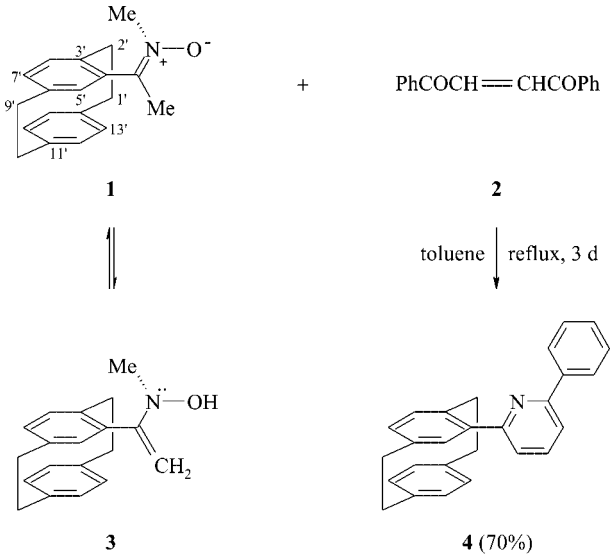
When *N*,α-dimethyl-α-(4-[2.2]paracyclophanyl)nitrone (**1**) is treated with dimethyl acetylenedicarboxylate (**5**), phenyl isocyanate (**9**), benzyne (**13**), or ethyl propiolate (**16**), the [2.2]paracyclophane-based pyrrole **6**, imidazole **10**, and isoxazole derivatives **14**, **15**, and **17** are formed in good yields. The stereoisomeric benzisoxazoles **14** and **15** obtained from the reaction between **1** and benzyne (**13**) could be separated and the structure of one of these stereoisomers, **15**, was assigned by X-ray structural analysis.

Introduction

Nitrones are well known to behave as 1,3-dipoles in thermal cycloaddition reactions.[1–3] However, we have recently obtained 2-(4′-[2.2]paracyclophanyl)-6-phenylpyridine (**4**)[4] from the reaction between *N*,α-dimethyl-α-(4-[2.2]paracyclophanyl)nitrone (**1**) and dibenzoylethylene (**2**) (Scheme 1). The unusual chemical behavior of our nitrone **1** is the result of the presence of its enamine form **3** in the decisive initial step of the cycloaddition. This formal hydroxy-enamine **3** can in principle induce the double bond of the dipolarophile to undergo Michael-type additions. To learn more about the mechanistic and preparative details of such cycloadditions, we decided to reinvestigate the chemistry of **1** towards other selected dipolarophiles such as dimethyl acetylenedicarboxylate (**5**), phenyl isocyanate (**9**), benzyne (**15**), and ethyl propiolate (**16**). This publication also represents an extension of our strategy to employ cycloaddition reactions for the synthesis of polycyclic and/or heterocyclic paracyclophanes.[5–7] The application of chiral [2.2]paracyclophanes, especially of heterocyclic derivatives, is becoming ever more widespread.[8,9]



1 **2** **3** **4** (70%)

Scheme 1. Cycloaddition between nitrone **1** and dibenzoylethylene (**2**).

Results and Discussion

In view of our previous results,[4] we expected another pyridine skeleton from the reaction between **1** and dimethyl acetylenedicarboxylate (**5**). On heating the two compounds together, though, we in fact isolated dimethyl 1-methyl-5-(4′-[2.2]paracyclophanyl)-1*H*-pyrrole-2,3-dicarboxylate (**6**) in 60% yield (Scheme 2). That **6** is a *N*-methylpyrrole-substituted [2.2]paracylophane derivative is shown by its spectroscopic data (see Exp. Sect.). Its ^{1}H NMR spectrum, for example, revealed four distinctive singlets in 1:3:3:3 ratio at δ = 6.75, 3.91, 3.90, and 3.50 ppm, corresponding to 4-H of the pyrrole ring, the two methyl ester moieties, and the *N*-methyl protons. In the ^{13}C NMR spectrum of **6**, the assignment of the carbonyl ester carbons was indicated at δ = 165.2 and 162.1 ppm, whereas the 4-CH carbon of the

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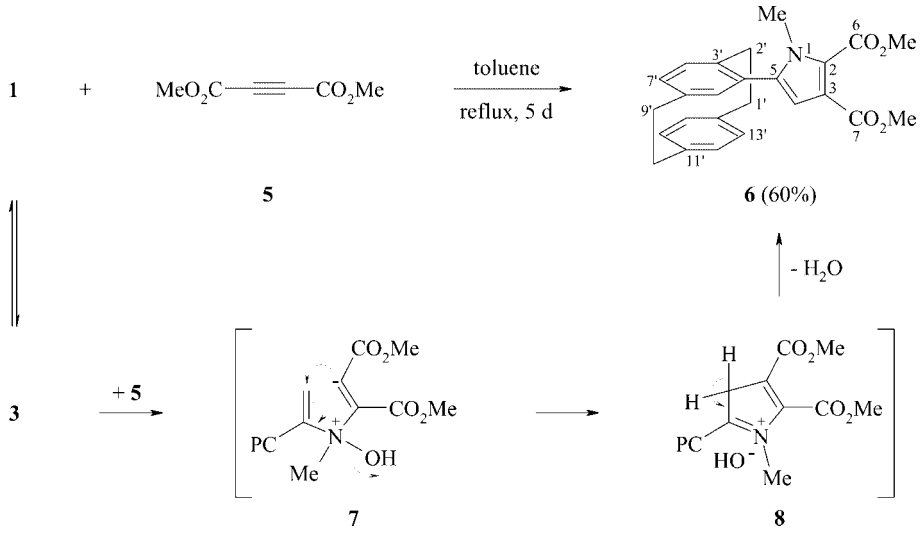
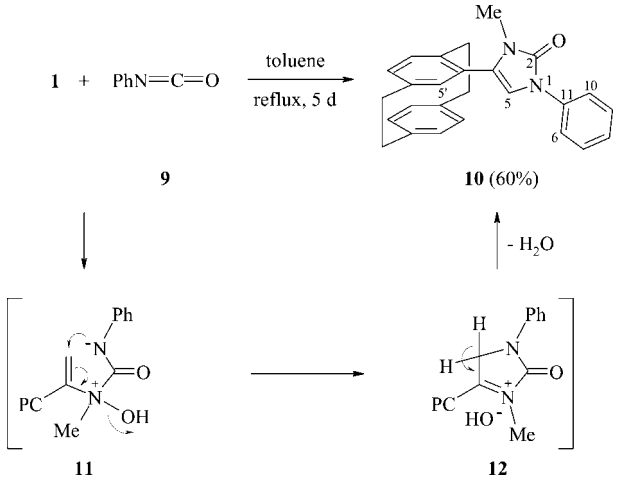


Scheme 2. Cycloaddition between nitrone **1** and dimethyl acetylenedicarboxylate (**5**); PC = 4-[2.2]paracyclophanyl.

pyrrole appeared at δ = 110.5 ppm. For the mechanism of the formation of **6**, we propose that the tautomer **3** initially attacks the activated triple bond of the dipolarophile **5** in a Michael-type reaction, thus resulting in the formation of the intermediate enolate **7**. The carbanion formed at the ethylenic diester can then attack the electrophilic exocylic double bond to form the salt **8**, which in the final step of the sequence eliminates one molecule of water to afford compound **6** (Scheme 2).

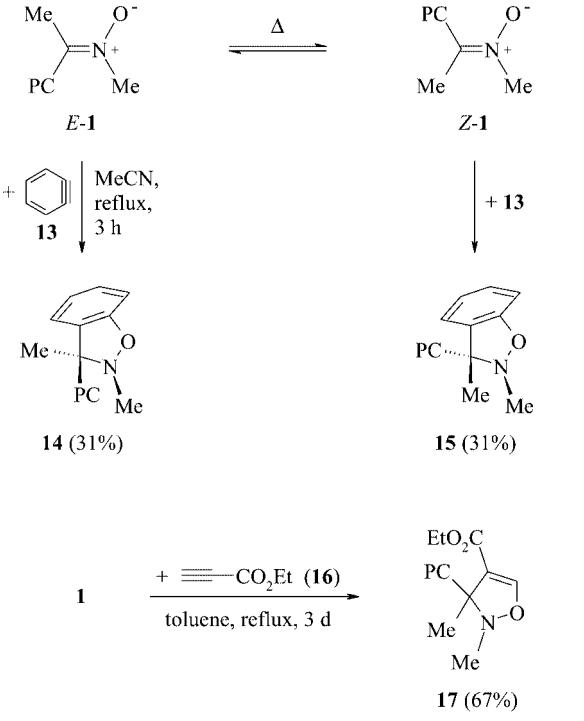
The reaction between **1** and phenyl isocyanate (**9**) gave 3-methyl-4-(4′-[2.2]paracyclophanyl)-1-phenyl-2,3-dihydro-1*H*-imidazol-2-one (**10**) in 60% yield by a similar mechanistic pathway (Scheme 3). In this case the reaction proceeds via formation of **11** and **12** (Scheme 3). The imidazolone structure of **10** is clearly indicated by its ^{1}H NMR spectrum, in which the NMe and 5-H protons appear at δ = 3.10 and 6.73 ppm, respectively (see Exp. Sect.). The structural assignment of **10** is also strongly supported by its ^{13}C NMR spectrum. The urea-type carbonyl group (C-2) absorbs at δ = 152.3 ppm and the imidazolone carbons C-4 and C-5 resonate at δ = 127.7 and 106.5 ppm, respectively. In a nuclear Overhauser (NOE) experiment, irradiation of 5′-H causes a strong enhancement of the imidazolone-5-H signal (see Exp. Sect.).



Scheme 3. Cycloaddition between nitrone **1** and phenyl isocyanate (**9**; PC = 4-[2.2]paracyclophanyl).

In a different manner, the reaction between **1** and benzyne (**13**) rapidly (within 3 h) gave the diastereomers (3*R**)-2,3-dimethyl-3-((4*S**)-4′-[2.2]paracyclophanyl)-2,3-dihydrobenzo[*d*]isoxazole (**14**) and (3*R**)-2,3-dimethyl-3-((4*R**)-4-[2.2]paracyclophanyl)-2,3-dihydrobenzo[*d*]isoxazole (**15**) in a 1:1 ratio (Scheme 4). Mass spectra and elemental analyses established the molecular formulas of both diastereomers as $C_{25}H_{25}NO$; the NMR spectra of these adducts are discussed in the next section. The formation of the two diastereomeric products can easily be explained by additions of **13** to the two diastereomers of nitrone **1**: (*E*)-**1** and (*Z*)-**1** (Scheme 4). The different behavior of the reaction between **1** and **13** in relation to the other dipolarophiles is attributed to the very high reactivity of the benzyne species.[10,11] The UV spectra exhibit two characteristic bands for each isomer, at λ_{max} = 285 and 242 nm for **14** and at λ_{max} = 280 and 238 nm for **15**. The structure of isomer **15** was furthermore confirmed by X-ray structural analysis (Figure 1). The molecule of compound **15**, as shown in Figure 1, indicates that the heterocyclic ring, selected dimensions of which are given in the caption, adopts an envelope conformation in which the nitrogen atom lies 0.45 Å out of the plane of the other four atoms (mean deviation 0.002 Å). Other dimensions may be regarded as normal.

Surprisingly, the reaction between **1** and ethyl propiolate (**16**) proceeded over 3 d at reflux in toluene to form the [2+3]cycloadduct **17** (Scheme 4), which was identified as a dihydroisoxazole paracyclophane derivative. This is analogous to the reported reaction between *N*,α-dimethylnitrone and ethyl propiolate.[12] This [2+3] cycloaddition behavior may be explained by the smaller steric requirements of ethyl propiolate in this type of reaction, in relation to the other



Scheme 4. Cycloaddition between nitrone **1** and dehydrobenzene (**13**) and ethyl propiolate (**16**); PC = 4-[2.2]paracyclophanyl.

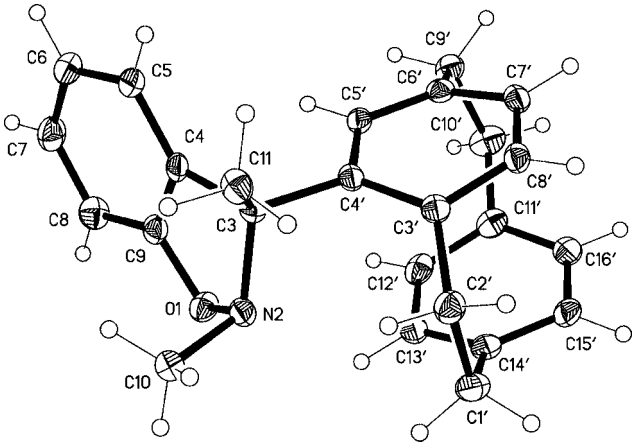


Figure 1. The molecule of compound **15** in the crystal. Ellipsoids represent 30% probability levels. Selected bond lengths [Å] and angles [°]: N2–C3 1.511(3), N2–O1 1.494(3), N2–C10 1.461(3), O1–C9 1.378(3), N2–O1–C9 105.7(2), C3–N2–O1 103.9(2).

dipolarophiles such as **5**. Moreover, because of the rigid structure of the phane nucleus, steric hindrance in the primary adduct cannot be released to the same extent as in an "open" system; *N*,α-dimethylnitrone, for example, is known to add to **16** in benzene within 10 h.[12,13] In the NMR spectra of **17**, the isoxazole 5-H proton is easily identifiable by its appearance as a singlet at δ = 7.71 ppm, whereas the isoxazole 5-CH has a chemical shift of δ = 154.8 ppm (see Exp. Sect.).

NMR Spectroscopy of 6, 10, 14, 15, and 17

NMR spectroscopy (^{1}H and ^{13}C) was the main tool used for the structural verification of the new products. The spectra of all of these compounds were assigned as fully as reasonably feasible by employment of the DEPT-135, H,H-COSY, C,H-HETCOR, and C,H-COLOC techniques. Details can be found in reference.[14] In some instances homonuclear decoupling was employed to distinguish *ortho*- and *meta*-correlations in the COSY spectra. NOE difference spectra were obtained for **10** and **14** in order to clarify the relative orientations of the different spin systems. The partial spectra of the [2.2]paracyclophane moieties were thus fully assigned for all compounds, but the near degeneracy of some bridge proton chemical shifts made the ^{1}H NMR spectra of the CH_2CH_2 fragments so tightly coupled that they were in some cases not analyzable with a reasonable amount of effort. The problems mainly concerned the spin systems of the protons at C-9′ and C-10′ (i.e., at the bridge remote from the substituent). The natures of the substituents themselves followed from their ^{1}H and ^{13}C chemical shifts and from the correlations between the nuclei within the substituents in the 2D NMR spectra. The point of attachment, C-α, of the substituents followed from $^3J_{CH}$ correlations between cyclophane C-4′ and H-β or between C-α and cyclophane 5′-H or from NOEs between cyclophane 5′-H and protons of the substituents. Compounds **14** and **15** showed ^{1}H NMR spectra with surprisingly different chemical shifts for a number of corresponding protons and so were initially believed to be constitutionally different, but all signal multiplicities and 2D correlations, importantly also those based on $^nJ_{CH}$ (n = 2, 3), are analogous for both isomers, thus showing them to be diastereoisomers differing in the relative configurations of the planar-chiral cyclophane system and the chiral center connected to C-4′. The relative configuration of **15** was established by X-ray diffraction (Figure 1), so that of **14** follows from the NMR evidence of identical constitution. The ^{1}H NMR spectra of **14** and **15** are shown in Figure 2; they differ most in the chemical shifts of 5′-H and 13′-H of the paracyclophane group. The proton 13′-H in **15** is shielded by 0.71 ppm relative to **14**, whereas 5′-H in **14** is shielded by as much as 1.24 ppm relative to **15**. As the relative configuration of **15** is known, these chemical shift effects may be interpreted qualitatively by assuming preferred conformations of **14** and **15** in which the aromatic ring of the dihydrobenzisoxazole group is oriented in such a way that the shielding region of its magnetic anisotropy affects 5′-H in **14**, while this instead applies for 13′-H in **15** (Scheme 5). There are also a number of considerable ^{13}C shift differences [δ_C(**15**) – δ_C(**14**)] between the diastereoisomers, the largest being those of C-3a, C*C*H$_3$, and C-5 in the benzisoxazole unit, amounting to +5.9, –3.1 and –2.2 ppm, respectively, and of C-5′ (–4.4 ppm) and C-3′ (+2.1 ppm) in the cyclophane moiety.

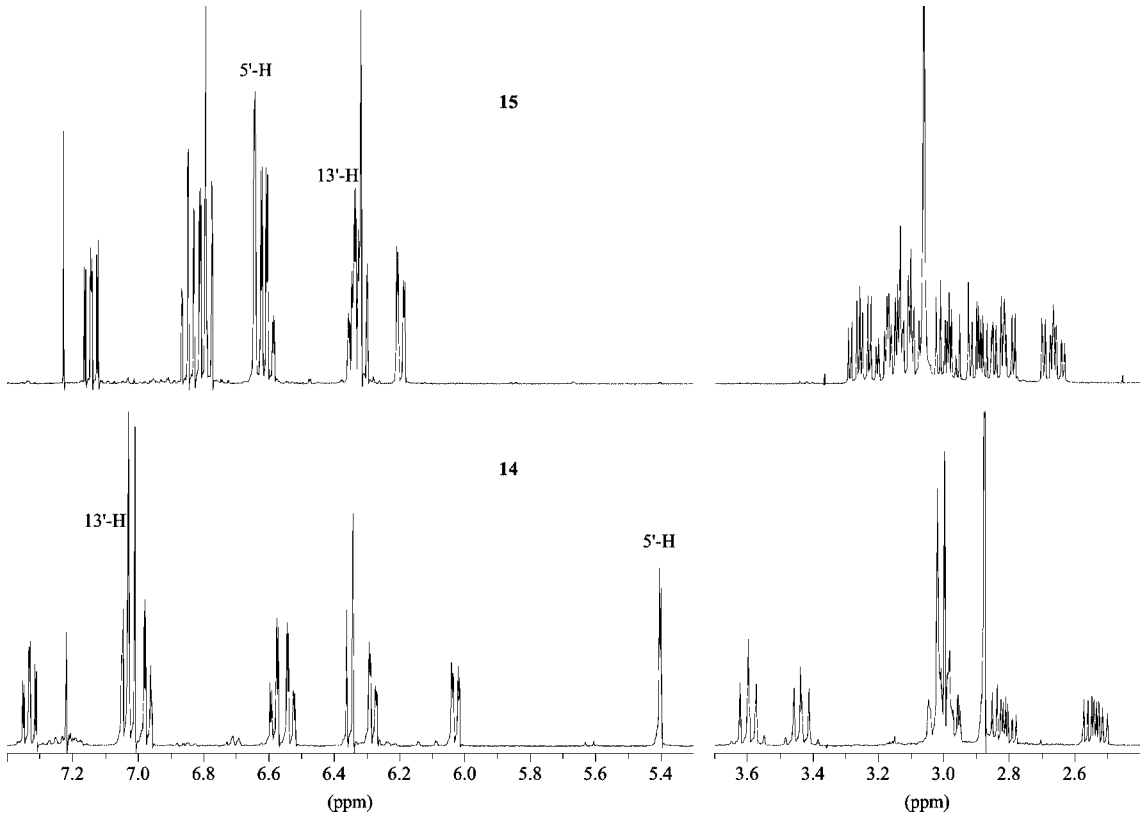
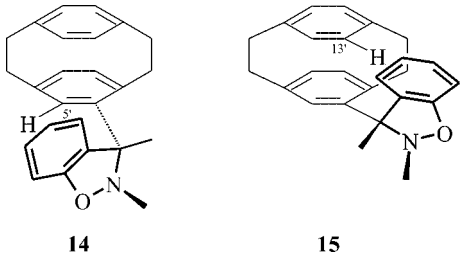


Figure 2. 400-MHz ^{1}H-NMR spectra of diastereomers **14** (bottom) and **15** (top); solvent: $CDCl_3$; reference: int. TMS. The signals of the *C*-methyl group at δ = 1.60 and 1.54 ppm for **14** and **15**, respectively, were omitted.



14 **15**

Scheme 5. Possible preferred conformations of **14** and **15** in which 5′-H and 13′-H, respectively, are shielded by the aromatic ring of the dihydrobenzisoxazole unit.

Experimental Section

General Remarks: Melting points: Kofler hot stage, uncorrected. NMR: Bruker AM-400, solvent: $CDCl_3$, internal standards: TMS (δ = 0.00) for ^{1}H, $CDCl_3$ (δ = 77.05) for ^{13}C. The subscripts in NMR spectroscopic data: *a* and *s* indicate bridge protons *anti* and *syn*, respectively, relative to the 4′-substituent at the paracyclophane system: The positions in the second paracyclophane ring are numbered such that C-12′ is pseudo-*geminal* to C-5′ etc. The results of NOE difference experiments are given in the form: irradiated signal → enhanced signal. The spin systems of the aromatic protons of **6** and **14** were analyzed iteratively by use of the Bruker WIN-DAISY program. The spin systems of both CH_2CH_2 bridges in **14** were also fully analyzed. When a complex ^{1}H multiplet comprising several protons was not analyzed, the individual proton chemical shifts obtained from the C,H-HETCOR spectra are given in parentheses following the δ-range of the multiplet. Chromatography columns were packed with silica gel 7714 (Merck). For preparative layer chromatography (PLC), glass plates (20 cm×x48 cm) were covered with a slurry of silica gel Merck PF_{254} and the solvents listed for development and air-dried. Zones were detected by the quenching of indicator fluorescence upon exposure to 254 nm UV light. Elemental analyses were performed at the Institut für Anorganische und Analytische Chemie, Technische Universität Braunschweig. MS: Finnigan MAT 8430 spectrometer at 70 eV. IR: Nicolet 320 FT-IR with KBr pellets and paraffin films. (*E*)-*N*,α-Dimethyl-α-(4-[2.2]-paracyclophanyl)nitrone (**1**) was synthesized by the procedure mentioned in ref.[4] The dipolarophiles dimethyl acetylenedicarboxylate (**5**), phenyl isocyanate (**9**), and ethyl propiolate (**16**) were bought from Fluka.

Dimethyl 1-Methyl-5-(4′-[2.2]paracyclophanyl)-1*H*-pyrrole-2,3-dicarboxylate (6): A mixture of **1** (279 mg, 1 mmol) and dimethyl acetylenedicarboxylate (**5**, 142 mg, 1 mmol) was heated at reflux in toluene (100 mL) for 5 d. The solvent was evaporated in vacuo and the residue was column chromatographed on silica gel with toluene to give **6** (240 mg, 60%) as yellow crystals. M.p. 68 °C (ethanol). ^{1}H NMR: δ = 2.74–2.93 [m, 3 H, shifts: 2.80 (2′-H_s), 2.84 (1′-H_a), 2.89 (1′-H_s)], 2.95–3.13 [m, 5 H, shifts: 3.00 (2′-H_a), 3.01 (9′-H), 3.09 (10′-H), 3.09, 3.11], 3.50 (s, 3 H, N*Me*), 3.90 (s, 3 H, 6-CO_2*Me*), 3.91 (s, 3 H, 7-CO_2*Me*), 6.46 (dd, 1 H, 12′-H), 6.51 (d, 1 H, 5′-H), 6.52 (d, 1 H, 8′-H), 6.54 (dd, 1 H, 7′-H), 6.56 (dd, 1 H, 15′-H), 6.63 (dd, 1 H, 16′-H), 6.68 (dd, 1 H, 13′-H), 6.75 (s, 1 H, 4-H) ppm; J_{HH} in the paracyclophanyl group fragment: $J_{5,7}$ = 1.9, $J_{7,8}$ = 7.9, $J_{12,13}$ = 7.9, $J_{12,16}$ = 2.0, $J_{13,15}$ = 2.0, $J_{15,16}$ = 7.8 Hz. ^{13}C NMR: δ = 33.52 (q, N*Me*), 33.54 (t, C-2′), 34.9 (t, C-1′), 35.0 (t, C-9′), 35.3 (t, C-10′), 51.7 (q, C-7-*Me*), 52.0 (q, C-7-*Me*), 110.5 (d, C-4), 120.1 (s, C-3), 125.1 (s, C-2), 129.6 (d, C-13′), 130.2 (s, C-4′), 132.0 (d, C-16′), 132.3 (d, C-12′), 133.3 (d, C-15′), 134.0 (d, C-5′), 134.2 (d, C-7′), 134.8 (d, C-8′), 139.1 (s, C-3′), 139.3 (s, C-14′),

139.4 (s, C-11′), 139.7 (s, C-5′), 140.3 (s, C-6′), 162.1 (s, C-6), 165.2 (s, C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3030–2988 (Ar–CH, s), 2880–2850 (aliph.-CH, m), 1597 (C=N, m), 1730 (CO, s), 1560 (C=C, s), 1280 (m), 980 (m), 760 (s) cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 350 nm (3.60). MS (70 eV): *m*/*z* (%) = 403 $[M]^+$ (100), 372 (10), 344 (12), 299 (12), 267 (38), 266 (30), 181 (24), 105 (10), 84 (10). $C_{25}H_{25}NO_4$ (403.48): calcd. C 74.42, H 6.25, N 3.47; found: C, 74.50, H 6.30, N 3.45.

3-Methyl-4-(4′-[2.2]paracyclophanyl)-1-phenyl-2,3-dihydro-1*H*-imidazol-2-one (10): A mixture of nitrone **1** (279 mg, 1 mmol) and phenyl isocyanate (**9**, 179 mg, 1.5 mmol) in chlorobenzene (150 mL) was heated to 100 °C for 5 d. The solvent was evaporated under vacuum and the residue was purified by column chromatography (silica gel) with dichloromethane to give **10** (230 mg, 60%) as colorless crystals. M.p. 150 °C (ethanol). ^{1}H NMR: δ = 3.10 (s, 3 H, N*Me*), 2.89–3.18 (m, 8 H, 1′,2′,9′,10′-H), 6.37 (dd, 1 H, 12′-H), 6.49 (d, 1 H, 5′-H), 6.56 (d, 1 H, 8′-H), 6.59 (dd, 1 H, 15′-H), 6.60 (dd, 1 H, 7′-H), 6.65 (dd, 1 H, 16′-H), 6.73 (s, 1 H, 5-H), 6.74 (dd, 1 H, 13′-H), 7.29 (m_c, 1 H, 8-H), 7.50 (m_c, 2 H, 7,9-H), 7.78 (m_c, 2 H, 6,10-H) ppm; J_{HH} in the paracyclophane fragment: $J_{5,7}$ = 1.9, $J_{7,8}$ = 7.8, $J_{12,13}$ = 8.0, $J_{12,16}$ = 1.9, $J_{13,15}$ = 1.8, $J_{15,16}$ = 7.9 Hz. NOEs: 5′-H → 5-H (very strong), 12′-H (very weak). ^{13}C NMR: δ = 28.5 (q, N*Me*), 33.6, 34.86, 34.88, 35.2 (4 t, C-1′,2′,9′,10′), 106.5 (d, C-5), 121.6 (d, 2 C, C-6,10), 125.7 (d, C-8), 127.7 (s, C-4), 128.3 (s, C-4′), 128.6 (d, C-13′), 129.2 (d, 2 C, C-7,9), 131.9 (d, C-12′), 132.1 (d, C-16′), 132.7 (d, C-5′), 133.4 (d, C-15′), 134.1 (d, C-7′), 135.1 (d, C-8′), 137.2 (s, C-11), 138.6 (s, C-3′), 139.2 (s, C-14′), 139.4 (s, C-11′), 140.3 (s, C-6′), 152.3 (s, C-2) ppm. IR (KBr): $\tilde{\nu}$ = 3135–3008 (Ar–CH, s), 2987–2851 (aliph.-CH, m), 1693 (C=O, s), 1618 (C=N, m), 1596 (C=C, m), 1220 (m), 980 (m) cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 260 nm (2.80). MS (70 eV): *m′z* (%) = 380 $[M]^+$ (18), 275 (40), 261 (10), 219 (60), 218 (100), 217 (40), 157 (10), 156 (30), 115 (10), 78 (8). $C_{26}H_{24}N_2O$ (380.49): calcd. C 82.06, H 6.36, N 7.37; found: C 82.15, H 6.40, N 7.25.

Reaction between Nitrone 1 and Benzyne (13): Benzenediazonium carboxylate (prepared from anthranilic acid) (10–15 mmol) was added slowly at gentle reflux over 1 h to a solution of **1** (460 mg, 2 mmol) in acetonitrile (150 mL). The reaction mixture was heated at reflux for 2 h and the reaction progress was followed by TLC. The solution was concentrated in vacuo and the residue was column chromatographed with toluene on silica gel. Two zones were isolated: the faster moving one contained compound **14**, while the slower one contained compound **15**.

(3*R)-2,3-Dimethyl-3-((4*R**)-4′-[2.2]paracyclophanyl)-2,3-dihydrobenzo[*d*]isoxazole (14):** 220 mg (31%) as colorless crystals. M.p. 140 °C (ethanol). ^{1}H NMR: δ = 1.60 (s, 3 H, 3-*Me*), 2.54 (2nd order ddd, 1 H, 9′-H_s), 2.81 (2nd order ddd, 1 H, 10′-H_a), 2.88 (s, 3 H, N*Me*), 2.95–3.05 [m, 4 H, shifts: 2.98 (10′-H_s), 3.01 (9′-H_a, –2′-H_a, –1′-H_a)], 3.44 (m_c, 1 H, 1′-H_s), 3.60 (m_c, 1 H, 2′-H_s), 5.41 (d, 1 H, 5′-H), 6.03 (dd, 1 H, 12′-H), 6.28 (dd, 1 H, 7′-H), 6.35 (d, 1 H, 8′-H), 6.54 (dd, 1 H, 16′-H), 6.58 (dd, 1 H, 15′-H), 6.97 (dd, *J* ≈ 6.8, 1.4 Hz, 1 H, 5-H), 7.00–7.07 [m, 3 H, shifts: 7.02 (8-H), 7.03 (6-H), 7.04 (13′-H)], 7.33 (td, *J* ≈ 7.6, 7.6, 1.4 Hz, 1 H, 5-H) ppm; J_{HH} in the paracyclophane fragment: $J_{5,7}$ ≈ 1.6, $J_{7,8}$ ≈ 7.5, $J_{12,13}$ = 7.9, $J_{12,16}$ = 1.7, $J_{13,15}$ = 1.8, $J_{15,16}$ = 7.7 Hz. NOEs: 12′-H → 13′-H, 5′-H; 5′-H → 9′-H_s, 6-H, 5-H, 12′-H; NMe → CMe, 2′-H_s, 13′-H; CMe → 5-H, 2′-H_s, NMe, 5′-H. ^{13}C NMR: δ = 24.0 (q, 3-*Me*), 34.7 (t, C-2′), 35.05 (t, C-9′), 35.07 (t, C-10′), 35.9 (t, C-1′), 40.3 (q, N*Me*), 73.0 (s, C-3), 106.7 (d, C-8), 121.3 (d, C-6), 125.4 (d, C-5), 129.0 (d, C-7), 129.5 (d, C-5′), 130.8 (s, C-4), 131.6 (d, C-16′), 131.8 (d, C-15′), 132.6 (d, C-7′), 132.8 (d, C-12′), 133.7 (d, C-13′), 137.1 (d, C-8′), 138.5 (s, C-3′), 138.9 (s, C-11′), 139.0 (s, C-6′), 139.8 (s, C-14′), 142.6 (s, C-4′), 157.1 (s, C-9) ppm. IR (KBr): $\tilde{\nu}$ = 3048–2998 (Ar–CH, s), 2850–2860 (aliph.-CH, m), 1580 (s), 1220 (m) cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 285 nm (2.92), 242 (2.50). MS (70 eV): *m*/*z* (%) = 355 $[M]^+$ (52), 340 (100), 325 (14), 251 (40), 236 (80), 221 (20), 208 (18), 144 (10), 115 (12), 104 (22), 78 (18). $C_{25}H_{25}NO$ (355.48): calcd. C 84.46; H 7.09, N 3.97; found C 84.46; H, 6.90; N, 3.97.

(3*R)-2,3-Dimethyl-3-((4*S**)-4′-[2.2]paracyclophanyl)-2,3-dihydrobenzo[*d*]isoxazole (15):** 220 mg (31%) as colorless crystals. M.p. 142 °C (ethanol). ^{1}H NMR: δ = 1.54 (s, 3 H, 3-*Me*), 2.67 (ddd, 1 H, 2′-H_a), 2.82 (ddd, 1 H, 1′-H_a), 2.89 (ddd, 1 H, 9′-H_s), 2.99 (ddd, 1 H, 10′-H_a), 3.06 (s, 3 H, N*Me*), 3.10 (ddd, 1 H, 1′-H_s), 3.13 (ddd, 1 H, 10′-H_s), 3.17 (ddd, 1 H, 9′-H_a), 3.26 (ddd, 1 H, 2′-H_s), 6.20 (dd, 1 H, 12′-H), 6.31 (d, 1 H, 8′-H), 6.33 (dd, 1 H, 13′-H), 6.34 (dd, 1 H, 7′-H), 6.60 (dd, 1 H 15′-H), 6.63 (dd, 1 H, 16′-H), 6.64 (d, 1 H, 5′-H), 6.76–6.87 [m, 3 H, shifts: 6.78 (8-H), 6.80 (5-H), 6.84 (6-H)], 7.14 (td, 1 H, 7-H) ppm; J_{HH} in the paracyclophane fragment: $J_{5,7}$ = 1.7, $J_{7,8}$ = 7.8, $J_{12,13}$ = 8.0, $J_{12,16}$ = 2.1, $J_{13,15}$ = 2.0, $J_{15,16}$ = 7.7, $J_{1a,1s}$ = –13.1, $J_{1a,2a}$ = 10.4, $J_{1a,2s}$ = 3.9, $J_{1s,2a}$ = 4.1, $J_{1s,2s}$ = 10.2, $J_{2a,2s}$ = –13.6, $J_{9a,9s}$ = –13.4, $J_{9a,10a}$ = 10.6, $J_{9a,10s}$ = 3.0, $J_{9s,10a}$ = 5.2, $J_{9s,10s}$ = 10.5, $J_{10a,10s}$ = –13.2 Hz; J_{HH} in the isoxazole fragment: $J_{5,6}$ = 7.5, $J_{5,7}$ = 1.3, $J_{5,8}$ = 0.5, $J_{6,7}$ = 7.5, $J_{6,8}$ = 0.9, $J_{7,8}$ = 8.0 Hz. ^{13}C NMR: δ = 20.8 (q, 3-*Me*), 34.0 (t, C-2′), 35.12 (t, C-9′), 35.17 (t, C-10′), 35.7 (t, C-1′), 38.8 (q, N*Me*), 71.5 (s, C-3), 107.3 (d, C-8), 121.1 (d, C-6), 123.1 (d, C-5), 128.0 (d, C-7), 130.1 (d, C-5′), 131.81 (d, C-12′), 131.84 (d, C-16′), 132.2 (d, C-13′), 132.4 (d, C-15′), 133.1 (d, C-7′), 136.8 (s, C-4), 136.9 (d, C-8′), 138.2 (s, C-4′), 138.8 (s, C-6′), 139.0 (s, C-11′), 140.1 (s, C-14′), 140.6 (s, C-3′), 155.9 (s, C-9) ppm. IR (KBr): $\tilde{\nu}$ = 3038–3008 cm^{-1} (Ar–CH, s), 2983–2774 (aliph.-CH, s), 1120 (s), 980 (m) cm^{-1}. UV (methanol): λ_{max} (lg ε) = 280 nm (3.00), 235 (3.10). MS (70 eV): *m*/*z* (%) = 355 $[M]^+$ (50), 340 (100), 325 (10), 251 (38), 236 (80), 221 (20), 208 (18), 144 (10), 115 (12), 105 (20), 78 (20). $C_{25}H_{25}NO$ (355.48): calcd. C 84.46, H 7.09, N, 3.97; found: C 84.58, H 6.94, N 3.97.

X-ray Crystal Structure Determination of Compound 15: *Crystal data*: Orthorhombic, space group $P2_12_12_1$, *a* = 9.709(2), *b* = 12.275(2), *c* = 15.656(2) Å, *Z* = 4, *T* = –100 °C. *Data collection*: A colorless prism ca. 0.7 × 0.4 × 0.4 mm was used to record 3194 intensities on a Stoe STADI-4 diffractometer (Mo-K_α radiation, $2\theta_{max}$ 55°). *Structure refinement*: The structure was refined anisotropically on F^2 (program SHELXL-97, G. M. Sheldrick, Univ. of Göttingen) to wR_2 0.113, R_1 0.047 for 246 parameters, 263 restraints (to *U* value components) and 2442 unique reflections. Friedel opposite reflections were merged. Methyl hydrogens were refined with use of rigid methyl groups, other hydrogens with a riding model.

CCDC-238143 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Ethyl 2,3-Dimethyl-3-(4′-[2.2]paracyclophanyl)-2,3-dihydroisoxazole-4-carboxylate (17): A solution of ethyl propiolate (**16**, 147 mg, 1.5 mmol) in toluene (30 mL) was added dropwise over 30 min to an ice-cold solution of **1** (279 mg, 1 mmol) in toluene (50 mL). The mixture was heated at reflux for 3 d. The solvent was evaporated under vacuum and the residue was subjected to column chromatography (silica gel, toluene). Compound **17** was obtained as a yellow oil, which solidified on addition of cyclohexane (20 mL) with stirring. Yield: 230 mg (67%) of **17** as colorless crystals. M.p. 65 °C (dichloromethane/pentane). ^{1}H NMR: δ = 1.23 (t, *J* =

7.1 Hz, 3 H, ester-*Me*), 1.59 (s, 3 H, 3-*Me*), 2.80 (2nd order ddd, 1 H, 9′-H_s), 2.86–3.00 [m, 3 H, shifts: 2.88 (s, 3 H, NMe), 2.90 (10′-H_a), 2.96 (2′-H_a), 2.98 (1′-H_a)], 3.07–3.16 [m, 2 H, shifts: 3.11 (10′-H_s)], 3.13 (9′-H_a), 3.25–3.46 [m, 2 H, shifts: 3.31 (1′-H_s), 3.41 (2′-H_s)], 4.09–4.23 (m, 2 H, ester-CH_2), 6.15 (d, J = 8 Hz, 1 H, 12′-H), 6.19 (br s, 1 H, 5′-H), 6.31 (dd, J = 7.6, ≥ 1.4 Hz, 1 H 7′-H), 6.32 (d, J = 7.6 Hz, 1 H, 8′-H), 6.56, 6.57 (unresolved m, 2 H, 16′-H, 15′-H, resp.), 6.76 (br d, J = 8 Hz, 1 H, 13′-H), 7.71 (s, 1 H, 5-H) ppm. ^{13}C NMR: δ = 14.3 (q, ester-*Me*), 22.2 (q, C-3-*Me*), 34.8 (t, C-2′), 35.1 (t, C-10′), 35.2 (t, C-9′), 35.7 (t, C-1′), 39.7 (q, NMe), 59.8 (t, OCH_2), 72.8 (s, C-3), 110.5 (s, C-4), 128.8 (d, C-5′), 131.7 (d, C-16′), 131.8 (d, C-15′), 132.5 (d, C-12′), 132.7 (d, C-7′), 133.1 (d, C-13′), 137.2 (d, C-8′), 137.8 (s, C-3′), 138.7 (s, C-6′), 139.1 (s, C-11′), 139.7 (s, C-14′), 141.0 (s, C-4′), 154.8 (d, C-5), 164.4 (s, COO) ppm. IR (KBr): $\tilde{\nu}$ = 3060–2998 (Ar–CH, s), 2870–2820 (aliph.-CH, m), 1730 (CO, m), 1700 (CO, s), 1560 (C=C, s), 1240 (m), 990 (m) cm^{-1}. UV (methanol): λ_{max} (lg ε) = 274 nm (2.90). MS (70 eV): *m*/*z* (%) = 377 $[M]^+$ (100), 346 (18), 331 (28), 272 (60), 258 (20), 208 (18), 115 (24), 105 (100), 78 (20). $C_{24}H_{27}NO_3$ (377.48): calcd. C 76.36, H 7.21, N 3.71; found C 76.48, H 7.14, N 3.71.

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