(H,H) = 0.9 Hz, 1 H, 10 b-H), 5.07 (ddd, J(H,H) = 10.0 Hz, J(H,H) = 2.0 Hz, J (H,H) = 0.9 Hz, 1 H, 10 a-H), 5.75 (ddd, J (H,H) = 17.0 Hz, J (H,H) = 10.0 Hz, J (H,H) = 8.0 Hz, 1 H, 9-H), 7.02 (AA'BB', analyzed as AB, $\Delta\nu_{AB}$ = 54.0 Hz, J (H,H) = 9.0 Hz, 4 H, Ph-H), 7.54 (m, 1 H, 2-H). ^{13}C NMR (50.3 MHz, $C_2D_2Cl_4$, 100 °C): δ = 19.80* (C-6), 27.71* (C-5), 30.65 (C-7), 35.96 (C-4 a), 40.26 (C-4), 41.24 (C-8), 50.45 (OCH_3), 51.57 (OCH_3), 55.45 (Ph-OCH_3), 58.87 (C-1'), 59.73 (C-8 a), 93.47 (C-3), 114.6 (2 x C-4'), 115.8 (C-10), 128.8 (2 x C-3'), 129.1 (C-2'), 140.4 (C-9), 146.1 (C-2), 159.6 (C-5'), 167.9 (CO), 175.6. The asterisk indicates peaks that are not yet unambiguously assigned.

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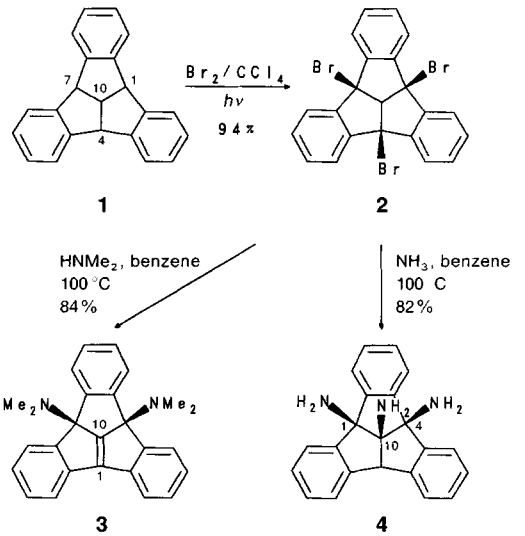
Three- and Fourfold Bridgehead-Substituted Tribenzotriquinacenes**

By *Andreas Schuster* and *Dietmar Kuck**

Dedicated to Professor Michael Hanack on the occasion of his 60th birthday

The threefold benzo-stabilized triquinacene **1**, one of the three prototypic centrotriindanes, provides, in contrast to the parent compound, an opportunity to study reactions at the four bridgehead positions through the formation of stable, well-crystallizing compounds. As we were recently able to show in collaboration with *de Meijere* et al.,[2] the threefold benzoannelation in the case of **1** also contributes considerably to the stabilization of anionic and olefinic derivatives of this system. We now present the particularly stable olefin **3**, which is readily accessible from **1** and which affords a variety of novel bridgehead-substituted tribenzotriquinacenes in some, in part, unusual reactions.

The tribenzoquinacene **1** is accessible via two routes[2, 3] and, despite its extremely poor solubility, can be converted almost quantitatively into the C_{3v} symmetrically substituted tribromo derivative **2** (Scheme 1). Aminolysis of **2** with di-



Scheme 1. Syntheses starting from tribenzotriquinacene **1**

methylamine affords the tribenzodihydroacepentalene **3**, also in high yields. In contrast to the analogously prepared dihydroacepentalenes,[6] crystalline **3** is absolutely air-stable—a remarkable property in view of the two strongly pyramidalized olefinic atoms C1 and C10.[7, 8] The analogous bis(trimethylsilyl) compound is likewise accessible from **1**, but is far less stable than **3**.[2, 9]

Surprisingly, *ammonolysis* of **2** leads to the triamino compound **4** with C_s symmetric substitution. The constitution of this compound, which is also obtainable in good yields, is unequivocally confirmed by its NMR spectrum (Table 1). The 1,4,10-triamine is thus the first triquinacene with heterosubstitution at the central bridgehead to be obtained in a direct synthesis.[10, 11] Attempts to explain the unexpected reaction of **2** with ammonia by further experiments were hitherto not very successful.[12] The intermediary analogue of **3** (H instead of Me, **3'**) is, in contrast to **3**, apparently not sufficiently kinetically stabilized.[13]

Two of the reactions of **3** carried out with 1,3-dipolar agents deserve special mention, namely those with azides (Scheme 2). **3** reacts smoothly with phenyl azide to give the regioisomer **9**, a triquinacene substituted by nitrogen at all four bridgehead atoms. Presumably, steric factors are mainly responsible here for the high regioselectivity. On the other hand, with trimethylsilyl azide we could not isolate the expected cycloaddition products, despite all measures to exclude moisture. Instead the 1-azido-4,7-bis(dimethylamino) derivative **6** was obtained in good yields, once again as a well-crystallizing compound. The NMR data and thermolysis results indicate that the three outer bridgehead atoms carry substituents (Table 1);[14] conclusive chemical proof (Scheme 2) was provided by the reduction of **6** with $LiAlH_4$ to give **7**, and the subsequent methylation according to *Eschweiler* and *Clarke* to give 1,4,7-tris(dimethylamino)tribenzotriquinacene **8**, whose C_{3v} symmetric constitution unambiguously followed from the ^{1}H and ^{13}C NMR spectra (Table 1).

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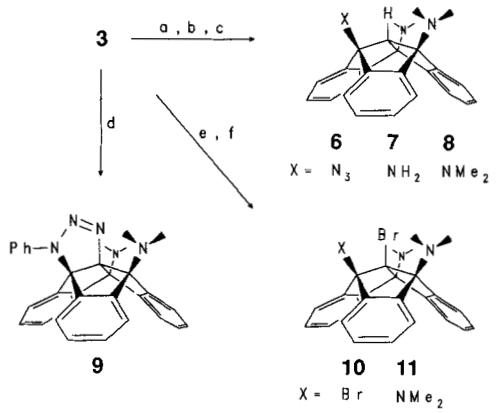
A number of fourfold heterosubstituted tribenzotriquinacenes can be prepared from the olefin **3**. Thus **3** reacts at low temperatures with bromine to give the dibromide **10** (Scheme 2), which can be converted as expected with dimethylamine into the, once again, C_{3v} symmetric 10-bromo-1,4,7-tris(dimethylamino)tribenzotriquinacene **11**. All attempts at the solvolysis of the C10–Br bond have so far failed.[15]

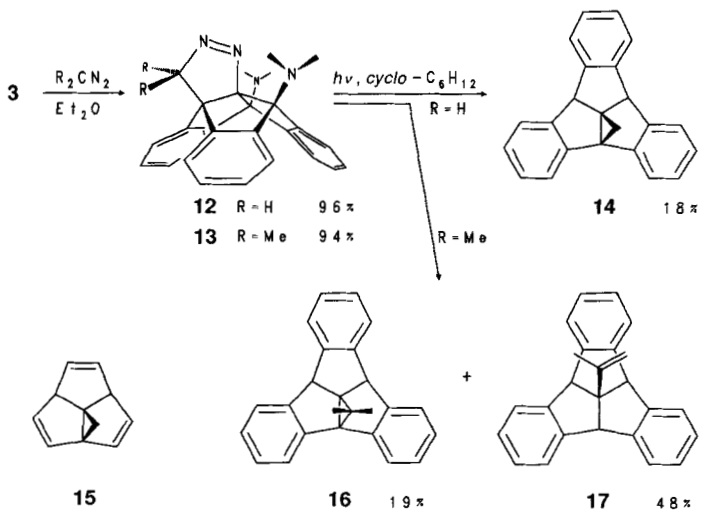


Schema 2. a) Me_3SiN_3/CH_2Cl_2, room temperature, 1 d (76 % **6**); b) $LiAlH_4$/THF, RT, 6 h (96 % **7**); c) $HCO_2H/CH_2O/H_2O$, 130 °C, 2 h (80 % **8**); d) PhN_3/CH_2Cl_2, RT, 1 d (94 % **9**); e) Br_2/CH_2Cl_2, −60 °C, addition over 6 h (85 % **10**); f) $HNMe_2/C_6H_6$, 100 °C, 1 d (54 % **11**).

Furthermore, we found an unexpected direct entry to 1,10-cyclopropa-annelated tribenzoquinacenes starting from **3**. Cyclopropatriquinacenes of type **15** are to our knowledge unknown so far; but several saturated derivatives have, however, been synthesized very recently from the dodecahedrane series.[16, 17] It therefore seemed interesting to check whether *tribenzo*triquinacene analogues are stable compounds despite the conjugation of the central cyclopropane ring with two π systems.[18]

The olefin **3** adds diazomethane and 2-diazopropane quantitatively with formation of the tetracyclic dihydropyrazoles **12** and **13**, respectively (Scheme 3). The similarly high yields and the almost identical NMR chemical shifts of the three *N*-substituted bridgehead atoms point to the same constitution of the two tetracyclic frameworks. Since considerable steric hindrance is assumed for the diazopropane adduct with a $C(CH_3)_2$ substituent on C10, **12** and **13** are assigned the structures shown, with a centro-N=N group.

Irradiation of a suspension of **12** in cyclohexane at room temperature (quartz filter) leads with complete deamination to the tetracycle **14**. Actually the product is formed in only 18 % yield, together with large amounts of polymeric material, but it can be isolated in pure form by medium pressure chromatography (MPLC) and slow crystallization. Surprisingly, it is very soluble compared to many other triben-



Scheme 3. Synthesis of cyclopropatriquinacenes.

Table 1. Physical data of selected compounds [IR(KBr), ^1H NMR ($CDCl_3$, 300 MHz), ^{13}C NMR ($CDCl_3$, 75 MHz), MS (EI, 70 eV)].

2: IR: $\tilde{\nu}$[cm^{-1}] = 3083, 3066, 3014, 1469, 1460, 1273, 1207; ^1H NMR: 3AA'BB' spin systems δ_A = 7.68 (6H), δ_B = 7.37 (6H), δ = 5.58 (s, 1H); ^{13}C NMR: δ = 143.6 (s), 130.6 (d), 125.1 (d), 89.2 (d), 67.1 (s); MS: *m/z* 435, 437, 439 ([*M* − Br]$^\oplus$; 51, 95, 51), 277 (78), 276 (68), 274 (21), 138 (100), 137 (33)

3: IR: $\tilde{\nu}$[cm^{-1}] = 3059, 2977, 2964, 2852, 2827, 2818, 1466, 1459, 1272, 1056; ^1H NMR: δ = 7.87 (d, 2H, ^3J = 6.1 Hz), 7.57 (d, 2H, ^3J = 6.4 Hz), AA'BB' spin system δ_a = 7.43 (2H), δ_B = 7.20 (2H), δ = 7.32–7.28 (m, 4H), 2.56 (s, 12H); ^{13}C NMR: δ = 164.1 (s), 154.4 (s), 153.8 (s), 144.1 (s), 139.3 (s), 127.8 (d), 126.7 (d), 126.6 (d), 124.8 (d), 122.2 (d), 78.2 (s), 41.5 (CH_3); MS: *m/z* 364 (*M*$^\oplus$, 1), 321 (14), 319 (8), 277 (26), 276 (100), 159 (2), 138 (9)

4: IR: $\tilde{\nu}$[cm^{-1}] = 3645, 3316 (br), 3064, 3025, 2872, 1476, 1453, 1219; ^1H NMR: δ = 7.64 (d, 2H, ^3J = 6.8 Hz), AA'BB' spin system δ_A = 7.59 (2H), $\delta_B \approx$ 7.25 (2H, masked), δ = 7.40 (d, 2H, ^3J = 6.7 Hz), 7.29–7.21 (m, 4H), 4.48 (s, 1H), 1.87 (br.s, 6H, NH_2); ^{13}C NMR: δ = 148.1 (s), 146.7 (s), 142.0 (s), 129.0 (d), 128.7 (d), 128.1 (d), 124.1 (d), 123.9 (d), 83.3 (s), 75.2 (s), 64.0 (d); MS: *m/z* 325 (*M*$^\oplus$, 57), 308 (69), 307 (33), 291 (100), 280 (22), 265 (18), 231 (10)

6: Colorless crystals, m.p. 203–208 °C (from CH_2Cl_2/MeOH); IR: $\tilde{\nu}$[cm^{-1}] = 3073, 3034, 2984, 2950, 2861, 2821, 2091 (N_3), 1476, 1454, 1242, 1235, 1225; ^1H NMR: masked AA'BB' and ABCD spin systems δ = 7.63–7.59 (m, 2H), 7.58–7.55 (m, 2H), 7.53–7.50 (m, 2H), 7.32–7.28 (m, 6H), 4.32 (s, 1H, 10-H), 2.26 (s, 12H, CH_3); ^{13}C NMR: δ = 146.3 (s), 144.8 (s), 142.6 (s), 129.7 (d), 129.1 (d), 124.7 (d), 124.5 (d), 123.3 (d), 83.7 (s), 80.6 (s), 55.3 (d), 41.0 (CH_3); MS: *m/z* 407 (*M*$^\oplus$, 2), 364 (20), 362 (24), 319 (62), 291 (100), 290 (88), 276 (13)

8: IR: $\tilde{\nu}$[cm^{-1}] = 3069, 3030, 2988, 2930, 2817, 2781, 1474, 1452, 1228, 1060, 1011, 769; ^1H NMR: 3AA'BB' spin systems δ_A = 7.53 (6H), δ_B = 7.22 (6H), δ = 4.37 (s, 1H, 10-H), 2.35 (s, 18H, CH_3); ^{13}C NMR: δ = 145.9 (s), 128.6 (d), 124.2 (d), 83.9 (s), 41.7 (CH_3); the signal for C10 presumably lies at δ = 77.8; MS (EI, 70 eV): *m/z* 409 (*M*$^\oplus$, 2), 365 (37), 364 (48), 321 (100), 320 (34), 277 (36), 276 (59), 160.5 (11), 138 (15)

9: IR: $\tilde{\nu}$[cm^{-1}] = 3089, 3067, 3029, 3005, 2986, 2940, 2875, 2840, 1596, 1488, 1473, 1462, 1270, 1224, 1003; ^1H NMR: δ = 7.57 (d, 2H, ^3J = 7.9 Hz), AA'BB' spin system δ_A = 7.54 (2H), $\delta_B \approx$ 7.30 (2H), δ = 7.43 (d, 2H, ^3J = 7.6 Hz), 7.39–7.23 (m, 5H), 7.14 (s, 4H), 2.83 (s, 6H, CH_3), 2.37 (s, 6H, CH_3); ^{13}C NMR: δ = 146.8 (s), 144.4 (s), 140.6 (s), 140.4 (s), 129.4 (d), 129.3 (d), 129.1 (d), 128.7 (d), 127.3 (d), 126.5 (d), 125.4 (d), 124.6 (d), 124.3 (d), 117.0 (s), 86.9 (s), 83.1 (s), 41.1 (CH_3), 39.7 (CH_3); MS: *m/z* 483 (*M*$^\oplus$, 5), 411 (16), 378 (100), 367 (84), 335 (40), 320 (20), 290 (24), 276 (49), 183.5 (7); UV/VIS (*n*-heptane, $c = 1.25 \times 10^{-4}$ M): λ_{max}[nm] (ε) = 295 (6280), 276 (8130), 268 (9180)

11: IR: $\tilde{\nu}$[cm^{-1}] = 3075, 3031, 2980, 2927, 2884, 2800, 1473, 1453, 1259, 1205, 1065, 757; ^1H NMR: 3AA'BB' spin system δ_A = 7.42 (6H), δ_B = 7.19 (6H), δ = 2.73 (18H, N-CH_3); ^{13}C NMR: δ = ca. 144 (s), 128.5 (d), 125.1 (d), 113.0 (s), 86.0 (s), 40.0 (CH_3); MS: *m/z* 487, 489 (*M*$^\oplus$; 16, 16), 443, 445 (21,20), 363 (10), 320 (23), 278 (17), 277 (21), 276 (53), 58 (100)

14: IR: $\tilde{\nu}$[cm^{-1}] = 3065, 3036, 3010, 2888, 1473, 1455, 1254, 1100, 755, 733; ^1H NMR: δ = 7.63–7.60 (m, 2H), 7.53–7.50 (m, 2H), 7.43–7.40 (m, 2H), 7.21–7.14 (m, 6H), 4.67 (s, 2H), 1.69 (s, 2H, CH_2); ^{13}C NMR: δ = 149.7 (s), 145.0 (s), 144.4 (s), 127.1 (d), 126.7 (d), 125.2 (d), 124.9 (d), 124.6 (d), 124.2 (d), 53.9 (d), 46.9 (s), 41.5 (s), 29.5 (t, CH_2); MS: *m/z* 292 (*M*$^\oplus$, 100), 291 (49), 289 (28), 280 (15), 276 (14), 215 (8), 146 (4), 138 (12); UV/VIS (*n*-heptane, $c = 4.45 \times 10^{-5}$ M): λ_{max}[nm] (ε) = 277 (2670), 270.5 (2760), ca. 264 (1800)

16: IR: $\tilde{\nu}$[cm^{-1}] = 3065, 3035, 3015, 2978, 2927, 2873, 1475, 1464, 1455, 752, 737, 721; ^1H NMR: AA'BB' spin system δ_A = 7.53 (2H), $\delta_B \approx$ 7.15 (2H, masked), δ = 7.43–7.40 (m, 4H), 7.18–7.12 (m, 4H), 4.52 (s, 2H), 1.06 (s, 6H); ^{13}C NMR: δ = 151.6 (s), 144.9 (s), 143.3 (s), 127.1 (d), 127.0 (d), 126.6 (d), 125.4 (d), 124.5 (d), 123.7 (d), 56.2 (s), 52.6 (d), 51.7 (s), 34.8 (s), 18.7 (CH_3); MS: *m/z* 320 (*M*$^\oplus$, 100), 305 (55), 289 (22), 279 (27), 278 (21), 277 (20), 276 (26), 178 (7), 144.5 (11), 138 (13); UV/VIS (*n*-heptane, $c = 5.0 \times 10^{-5}$ M): λ_{max}[nm] (ε) = 277 (3000), 270.5 (2740), ca. 264 (1920)

17: IR: $\tilde{\nu}$[cm^{-1}] = 3065, 3027, 2986, 2974, 2927, 1633, 1485, 1476, 1456, 1375, 875, 753, 733; ^1H NMR: 3AA'BB' spin systems δ_A = 7.45 (6H), δ_B = 7.18 (6H), δ = 5.05 (s, 1H), 4.92 (s, 3H), 4.87 (s, 1H), 1.90 (s, 3H, CH_3); ^{13}C NMR: δ = 148.3 (s), 145.0 (s), 127.5 (d), 124.1 (d), 108.1 (t), 70.2 (s), 60.6 (d), 20.1 (CH_3); MS: *m/z* 320 (*M*$^\oplus$, 100), 305 (44), 290 (10), 289 (15), 279 (16), 278 (27), 277 (18), 276 (23), 178 (11), 145 (11) 138 (14)

zotriquinacenes.[2-5] The ^{1}H NMR, ^{13}C NMR, and mass spectra unequivocally confirm the structure of **14** (Table 1).

Under the same conditions the diazopropane adduct **13** furnishes the tetracycle **16** in 19% yield; the main product, however, is the ring-opened 10-(propen-2-yl)tribenzotriquinacene **17**. Also these two compounds are spectroscopically unambiguously identifiable (Table 1) and like **14** are very stable in crystalline form. **17** is the first triquinacene with an unsaturated substituent on the central C atom and ought to be convertible into further, interesting C10-substituted tribenzotriquinacenes.[4, 5, 19]

The photolytic deamination of the cycloadducts **12** and **13** is surprising.[20] In the tribenzotriquinacenes this process is possibly facilitated by radicals generated in the course of the deazotization and is additionally favored by the formation of highly conjugated isoindene intermediates. Also consistent with this hypothesis is the ring-opening of **13** to give **17**.

The diaminoolefin **3** and the bridgehead-substituted tribenzotriquinacenes presented here for the first time prompt further investigations. Thus, the strictly ecliptic orientation of up to four vicinal substituents on the convex side of the molecule with the rigid triquinacene framework could lead to concerted dipolar interactions. The consequences of the particular stereochemistry of such highly functionalized spherical molecules for structure and reactivity should be studied in more detail.

Experimental Procedure for Selected Compounds

2: A suspension of tribenzotriquinacene **1** (560 mg, 2.00 mmol) in tetrachloromethane (100 mL) was treated dropwise at 50 °C with 6.00 mL of a 1.0 M solution of bromine in tetrachloromethane (6.00 mmol). The suspension was additionally irradiated with a photolamp (500 W). After very rapid uptake of the bromine (effervescence!), the solvent was removed and the yellow-brown residue recrystallized from toluene. **2** (970 mg; 94%) was obtained in the form of brownish platelets; m.p. 320–325 °C (decomp.).

3: **2** (517 mg, 1.00 mmol) was frozen in anhydrous benzene (10 mL) in a test tube (180 mm × 22 mm) containing a small stirring rod. Dimethylamine (20 mL) was condensed into the tube which was then placed in a steel autoclave (190 mm × 26 mm, Roth); the autoclave was sealed tight and the reaction mixture stirred magnetically in an oil bath at 100 °C for 20 h. After the reaction mixture cooled, the excess amine was removed and the contents of the test tube were diluted with 20 mL of dichloromethane and 20 mL of water. After extractive workup with CH_2Cl_2, drying with Na_2SO_4, and removal of the solvent, a light-brown crystalline residue was obtained, which upon recrystallization from CH_2Cl_2/MeOH afforded 305 mg (84%) of **3** in the form of colorless needles; m.p. 231 °C.

4: As described for **3**, **2** (517 mg, 1.00 mmol) was allowed to react in benzene (precooled to −40 °C) with liquid ammonia (10 mL) in a sealed tube. After workup and recrystallization from CH_2Cl_2/*n*-heptane **4** (266 mg, 82%) was obtained in the form of very fine, colorless needles; m.p. 248 °C (decomp.).

9: A solution of **3** (364 mg, 1.00 mmol) in dichloromethane (10 mL) was treated with phenyl azide (300 mg, 2.50 mmol) and the mixture stirred for 24 h at room temperature. Methanol was then added and the solution slowly evaporated down in a rotary evaporator until crystallization started. **5** (514 mg, 94%) was obtained in the form of colorless crystals; m.p. 251 °C.

10: To a solution of **3** (364 mg, 1.00 mmol) in anhydrous dichloromethane precooled to −60 °C was added dropwise a 50.0 mM solution of bromine (1.00 mmol) in dichloromethane (20 mL) over 6 h using a fine-bore dropping funnel. After warming to room temperature, the suspension was evaporated down in vacuo to a volume of 10 mL and treated with an equal amount of anhydrous ethyl acetate. The precipitated crystals were recovered by suction and recrystallized from CH_2Cl_2/EtOAc. **10** (445 mg; 85%) was obtained in the form of yellow crystals; m.p. 216 °C (decomp.).

11: Aminolysis of **10** (131 mg, 250 mmol), analogously to the reaction of **2** with dimethylamine, afforded a crude product, which, after recrystallization from CH_2Cl_2/MeOH, furnished **11** (65 mg; 54%) in the form of colorless crystals; m.p. 278 °C (decomp.).

14, **16**, and **17**: The cycloadducts **12** (m.p. 272 °C) and **13** (m.p. 330 °C) were obtained from **3** by standard methods.—Photolysis: In a falling film photoreactor (Normag, 400 mL volume, quartz glass cooling and immersion tubes, Hanau T 718Z1, 500 W mercury vapor lamp) a suspension of 500 μmol of **12** (204 mg) or **13** (217 mg) in 350 mL of cyclohexane (Uvasol, Merck) was purged of dissolved oxygen by passage of nitrogen for 10 min. After tempering to 20 °C, the photoreaction was started; after about 10 min the reaction mixture clarified, and after a further 40 min a renewed yellowish clouding was observed. Optimal yields were achieved after radiation for 90 min. The reaction mixture was evaporated to dryness in a rotary evaporator.—Isolation of **14**: The yellow residue was taken up in a little dichloromethane and filtered through silical gel. Finally, the nonpolar components (hydrocarbons) were isolated by MPLC (LiChroprep Si60, 40–60 μm, Merck, *n*-hexane/dichloromethane 4/1) as a yellow oil. Subsequent vapor-diffusion crystallization furnished up to 26 mg of **14** (18%) in the form of very fine needles; m.p. 272 °C.—Isolation of **16** and **17**: The yellow residue was taken up in a little dichloromethane and filtered with dichloromethane/*n*-hexane (1/1) through silica gel. The mixture of isomers (MS; 120 mg, 75%) was separated by MPLC with *n*-hexane/dichloromethane (5/1): 30 mg (19%) of **16** was obtained in the form of colorless crystals (m.p. 242 °C) and 76 mg (48%) of **17** as colorless needles (m.p. 161 °C).—All the new compounds gave satisfactory elemental analyses.

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1, 120022-86-8; **2**, 137041-65-7; **3**, 137041-66-8; **4**, 137041-67-9; **6**, 137041-68-0; **7**, 137041-69-1; **8**, 137041-70-4; **9**, 137041-71-5; **10**, 137041-72-6; **11**, 137041-73-7; **12**, 137041-74-8; **13**, 137041-75-9; **14**, 137041-76-0; **16**, 137041-77-1; **17**, 137041-78-2; phenyl azide, 622-37-7; trimethylsilyl azide, 4648-54-8; diazomethane, 334-88-3; 2-diazopropane, 2684-60-8.

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[2] D. Kuck, A. Schuster, B. Ohlhorst, V. Sinnwell, A. de Meijere, *Angew. Chem. 101* (1989) 626–628; *Angew. Chem. Int. Ed. Engl. 28* (1989) 595–597.
[3] D. Kuck, T. Lindenthal, A. Schuster, unpublished.
[4] The 10-methyl- and 10-ethyl-substituted tribenzotriquinacenes [3,5] are also readily substitutable threefold at the peripheral bridgehead atoms: A. Schuster, *Dissertation*, Universität Bielefeld 1991.
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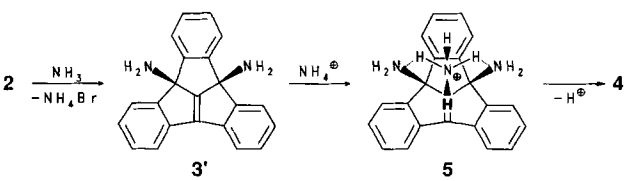
[8] According to force field calculations (MM2 (87)) the pyramidalization angles [7a] in **3** are Φ(C1) = 39.3° and Φ(C10) = 40.6°.
[9] B. Ohlhorst, *Dissertation*, Universität Hamburg 1989.
[10] Perchlorotriquinacenes have already been described: a) I. T. Jacobsen, *Acta Chem. Scand. 21* (1967) 2235–2246; b) *ibid. 26* (1972) 2477–2493; c) *Chem. Scr. 5* (1974) 174–192.
[11] a) P. Bischof, *Angew. Chem. 88* (1976) 609–610; *Angew. Chem. Int. Ed. Engl. 15* (1976) 556; b) L. A. Paquette, S. V. Ley, S. Maiorana, D. F. Schneider, M. J. Broadhurst, R. A. Boogs, *J. Am. Chem. Soc. 97* (1975) 4658–4667; c) R. C. Bingham, P. von R. Schleyer, *ibid. 93* (1971) 3189–3199; d) L. A. Paquette, *Top. Curr. Chem. 79* (1979) 41–165.
[12] Attempts to add NH_3 to **3** in NH_4Cl/NH_3 were unsuccessful [4].
[13] We presume that **3'** forms a chelate complex **5** with $NH_4^{\oplus}$, in which the ammonium proton orientated to the 1,10 double bond attacks electrophilically at C1.



[14] D. Kuck, A. Schuster, unpublished.
[15] No reaction was observed upon heating **11** with NH_3/benzene in an autoclave at 100 °C and with KOH/triethyleneglycol up to 120 °C.
[16] a) L. A. Paquette, T. Kobayashi, J. C. Gallucci, *J. Am. Chem. Soc. 110* (1988) 1305–1307; b) L. A. Paquette, T. Kobayashi, M. A. Kesselmayr, J. C. Gallucci, *J. Org. Chem. 54* (1989) 2921–2930.
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[18] The *increase* in reactivity of centropolyquinanes by benzoannelation has already been reported: a) see Ref. [2], b) B. Paisdor, D. Kuck, *J. Org. Chem. 56* (1991) 4753–4759.

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[20] Similar reductive C–N cleavages have been observed in the photolytic decomposition of simple alkylamines: a) M. Mousson-Canet. J. C. Mani: *Photochemistry and Molecular Reactions*, Israel Program for Scientific Translations, Jerusalem 1972, p. 76; b) H. Dürr, W. Bujnoch, H. Kober, *Methoden Org. Chem. (Houben Weyl) 4th ed 1952–*, Vol.4/5b, p. 1076.

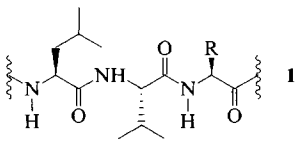
1,3-Dipolar Cycloaddition as the Key Reaction in the Synthesis of Potent Renin Inhibitors

By *Günter Benz,* Rolf Henning,* and *Johannes-Peter Stasch*

Dedicated to Professor Karl Heinz Büchel on the occasion of his 60th birthday

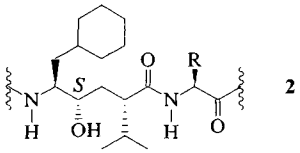
The renin–angiotensin system plays a central role in the pathogenesis of hypertension, mostly via the circulating vasoconstrictor angiotensin II. Although Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors) like captopril and enalapril[1] have already been introduced to therapy, emphasis has been directed toward renin inhibitors in recent years because of their supposedly better selectivity.[2] This increased interest has spurred synthetic work.

The most important reaction of renin is the proteolysis of the *N*-terminus of the globular protein angiotensinogen to the decapeptide angiotensin I. If the Leu-Val peptide bond in **1** cleaved in this reaction is replaced by an (*S*)-hydroxyethylene amide bond surrogate, renin inhibitors of the type **2** are obtained.[3] Because these molecules resemble the transition state for cleavage by aspartyl proteases they possess a high affinity for renin[4] but are not cleavable by the enzyme. Many renin inhibitors are rapidly degradated in vivo. This proteolysis should be hampered when the *C*-terminal amide bond is inverted. For this reason we propose renin inhibitors of the type **3** which has both modifications—the inverted peptide bond and the hydroxyethylene unit. To maintain the topology of the peptide chain the adjacent amino acid must have the D-configuration.



1

Leu Val



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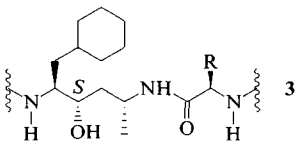

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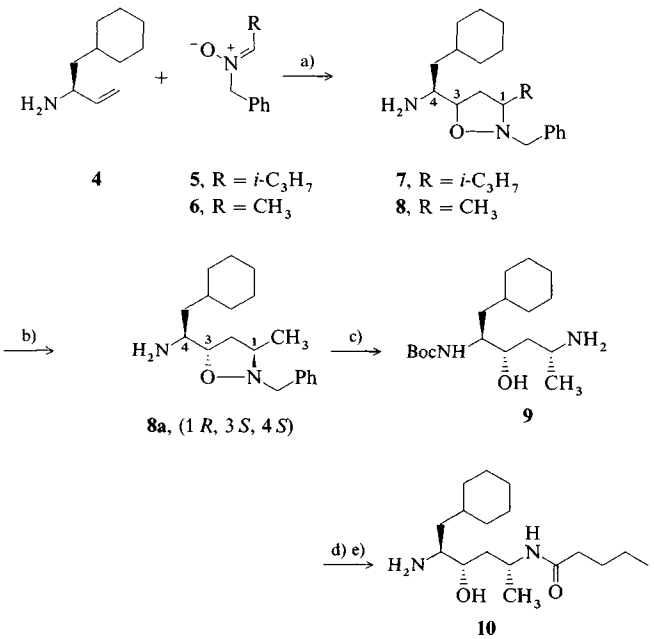
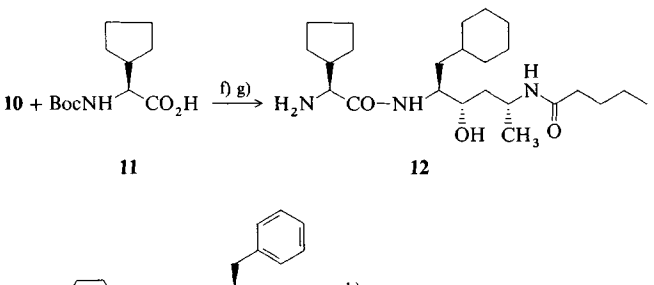
The 1,3-dipolar cycloaddition of allylamines with *N*-benzylnitrones[5] provides an easy access to this type of structure in which two stereocenters are generated early in the reaction sequence. The stereochemical course of the reaction can be influenced either by chiral nitrones[6] or by chiral allylamines.[7] The synthesis of the isoxazolidines and a potent renin inhibitor **14** is shown in Scheme 1.[8].

N-Boc-allylamine **4**[9] was prepared in four steps from *N*-Boc-phenylalanine. The subsequent reaction with benzylnitrone **5** at 140 °C in mesitylene led after 8 h to a mixture of four diastereomeric isoxazolidines **7**, in the ratio **7a** (1*R*, 3*S*, 4*S*) 0.75, **7b** (1*S*, 3*S*, 4*S*) 1.00, **7c** (1*S*, 3*R*, 4*S*) 0.60, **7d** (1*R*,



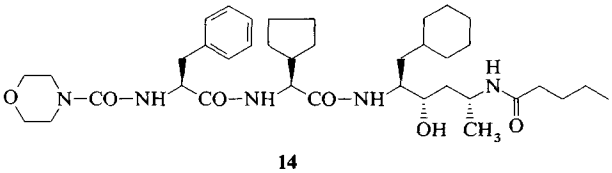
4 **5**, R = *i*-C_3H_7; **6**, R = CH_3 **7**, R = *i*-C_3H_7; **8**, R = CH_3

8a, (1*R*, 3*S*, 4*S*) **9** **10**



11 **12**

13



14

Scheme 1. a) Mesitylene, 140 °C, 8 h, 52% **7**; b) SiO_2, chromatography, *n*-hexane/ether 7:3; c) $NH_4^+HCO_2^-$, 10% Pd/C, CH_3OH, reflux, 60 min; d) $(n\text{-}C_4H_9CO)_2O$, NEt_3, CH_3OH; e) 4 N HCl, dioxane, 30 min; f) (*S*)-cyclopentylglycine **11**, dicyclohexylcarbodiimide (DCC), hydroxybenzotriazole (HOBT), diisopropylethylamine (DIPEA); g) 4 N HCl, dioxane, 30 min; h) morpholinocarbonyl-Phe **13**, DCC, HOBT, DIPEA.