Sequential Peripheral Cyclopropanation as a Synthetic Approach to Cyclosubstituted Triangulanes

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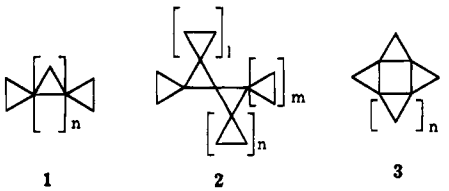
A general scheme for the synthesis of cyclosubstituted triangulanes has been developed, based on sequential bromocyclopropanation of the C=C bond and elimination, giving repeatedly the endomethylenecyclopropane framework with termination of the sequence of the cyclopropanation.

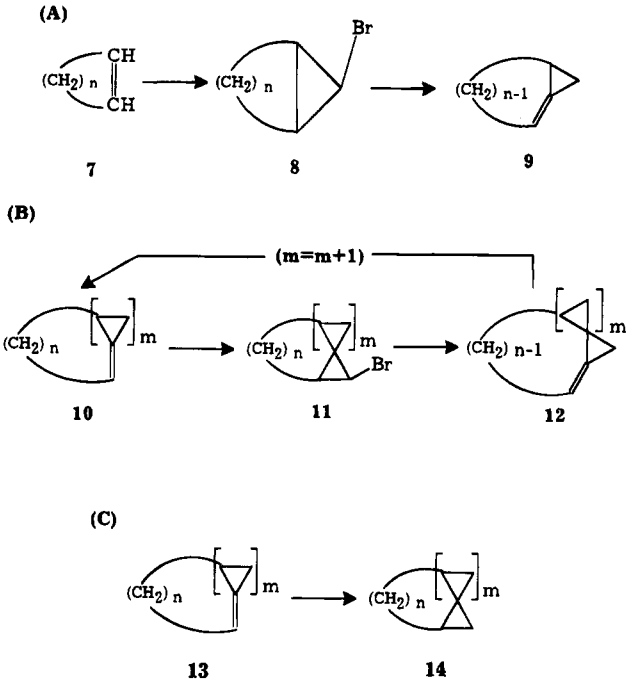
Triangulanes are a unique class of highly strained polycyclic hydrocarbons in which the skeleton is constructed from spiroannulated three-membered rings.[1-5] Two classes of triangulanes were considered in the literature: the chain[2] triangulanes, **1** (CHT), and the branched triangulanes, **2** (BT). We have elaborated a mathematical model for stereoisomerism in CHT and developed general approaches to their synthesis.[1] More recently, we,[3-5] as well as De Meijere and co-workers,[5,6] have proposed general strategies for the synthesis of BT.



1 **2** **3**

It is possible to imagine one more subclass of triangulanes, namely cyclic triangulanes, **3** (CT). Several members of CT with $n = 0-3$ possess severe strain,[7] but [8]-CT may be the member of this class which can be isolated. Insertion of methylene units will reduce the strain experienced by such cyclic systems, and *cyclosubstituted triangulanes* (CST) of types **5** and **6** represent more realistic synthetic targets.

Scheme 1



4 **5** **6**

Our first goal was to elaborate a synthetic pathway for the sequential incorporation of cyclopropane moieties into a cyclic framework in accordance with Scheme 1.[8]

The first (A) involves the transformation of the cycloalkanes **7** into a cyclopropanated cycloolefin **9**. The second step (B) is the application of the same synthetic sequence to incorporate cyclopropane moieties in accordance with pathway **10** → **12** (propagation step/s). The

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(2) This term was suggested by Dr. M. Klin. The previously used terms, either *nonbranched* or *linear* triangulanes, are not accurate and may be misleading.

(3) (a) Lukin, K. A.; Masunova, A. Yu.; Ugrak, B. I.; Zefirov, N. S. *Tetrahedron* **1991**, *47*, 5769. (b) Lukin, K. A.; Kozhushkov, S. I.; Zefirov, N. S. *Org. Magn. Reson.* **1991**, *29*, 774. (c) Lukin, K. A.; Kozhushkov, S. I.; Andrievsky, A. A.; Ugrak, B. I.; Zefirov, N. S. *Mendeleev Commun.* **1992**, 51.

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(6) Zoellner, S.; Bucholz, H.; Boese, R.; Gleiter, R.; de Meijere, A. *Angew. Chem.* **1991**, *103*, 1544.

(7) Dr. I. Baskin has calculated the following data: (a) simple force field calculations using PC Model (compound, heat of formation in kcal/mol, strain energy in kcal/mol, strain per C_2H_2-unit in kcal/mol): [4]-CT, 147.8, 165.3, 41.3; [5]-CT, 191.9, 214.4, 42.9; [6]-CT, 215.9, 243.4, 40.6; [8]-CT, 261.1, 298.4, 37.3. (b) AM-1 calculations with geometry optimization (compound, heat of formation in kcal/mol): [4]-CT, 249.96; [5]-CT, 267.75; [6]-CT, 225.65.

(8) Zefirov, N. S.; Kuznetsova, T. S.; Eremenko, O. V.; Kokoreva, O. V. *Mendeleev Commun.* **1993**, 91.

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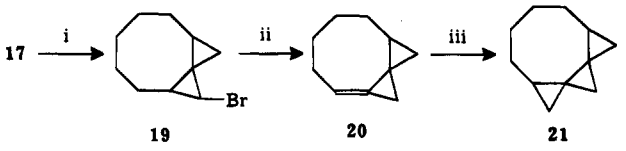
Scheme 2[a]



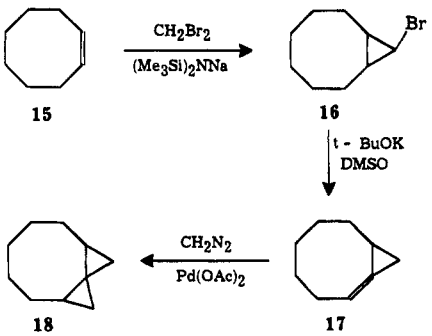
[a] Key: (i) $CH_2Br_2/(Me_3Si)_2NNa$; (ii) t-BuOK/DMSO; (iii) $CH_2N_2/Pd(OAc)_2$.

third step (C) is the cyclopropanation of the double bond, **13** → **14**, which terminates the process.

The goals of the present paper were (i) to develop the synthetic protocol for sequence A (**7** → **9**, Scheme 1) for cyclooctene and 1,5-cyclooctadiene, (ii) to elaborate the propagation steps **10** → **12** for these cases, and (iii) to apply this method for the synthesis of some eight-membered CST's of types **5** and **6**.

Results and Discussion

After many attempts to bromocyclopropanate cyclooctene[9] the conditions were found which provide a 45–50% yield of bromide **16** (mixture of two isomers in the ratio 20:1, as indicated by ^1H HMR). Dehydrobromination of **16** gave the olefin **17**.[10,11] Final cyclopropanation of **17** with CH_2N_2 in the presence of $Pd(OAc)_2$[1,12] gave CST **18**.

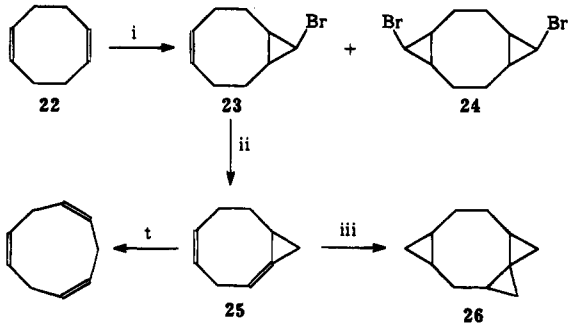


Repetition of the same reaction sequence with olefin **17** gave bromide **19** (45%), olefin **20**, and finally tetracyclo[8.1.0.0^{1,3}.0^{3,5}]undecane (**21**), which was isolated and purified by preparative GLC (Scheme 2).

Our attention was next focused on 1,5-cyclooctadiene (**22**). Bromocyclopropanation of **22** gave a mixture of monobromide **23** (36%) and dibromide **24** (5%) (Scheme 3). However, bromocyclopropanation of monobromide **23** gave 30–35% of dibromide **24**. Dehydrobromination of **23** gave diene **25** which was characterized by ^1H NMR. The diene **25** is not thermally stable, and heating to approximately 100 °C leads to its isomerization to 1,4,7-cyclononatriene.[13] Cyclopropanation of diene **25** with an excess of diazomethane gave the desired hydrocarbon **26** as a mixture of two possible isomers (4:1; 80% yield). These isomers were separated by preparative GLC and characterized by ^1H and ^{13}C NMR.

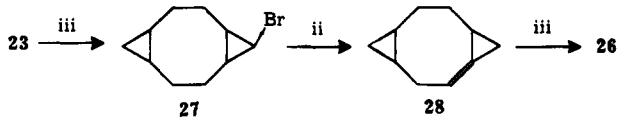
Alternatively, hydrocarbon **26** was obtained from bromide **23** *via* bromide **27** (Scheme 4).

Scheme 3[a]



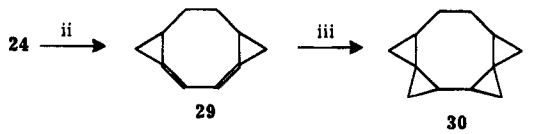
[a] Key: (i) $CH_2Br_2/(Me_3Si)_2NNa$; (ii) t-BuOK/DMSO; (iii) $CH_2N_2/Pd(OAc)_2$.

Scheme 4[a]



[a] Key: (ii) t-BuOK/DMSO; (iii) $CH_2N_2/Pd(OAc)_2$.

Scheme 5[a]



[a] Key: (ii) t-BuOK/DMSO; (iii) $CH_2N_2/Pd(OAc)_2$.

Finally, we have studied the dehydrobromination of dibromide **24** which gave a mixture where diolefin **29** is the major component. This mixture was treated without purification with diazomethane, and the isolated product (preparative GLC) was the hydrocarbon **30** (25% yield) (Scheme 5).

In conclusion, we have demonstrated that the methodology illustrated in Scheme 1 can be successfully applied to the synthesis of cyclosubstituted triangulanes containing an eight-membered ring. This study of the scope and limitation of this methodology for synthesis of cyclosubstituted and cyclic triangulanes as well as some theoretical considerations[14] are actively underway.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded on Telsa BS-467 and Bruker AC-200P and AM 300 spectrometers. Mass spectra were obtained with Varian MAT 311A and MX 1321A spectrometers. GLC analyses and separations were performed using silicone E-301 (15% on Inerton AW). All solvents and reagents were purified and dried by standard techniques. Pentane extracts were dried over $MgSO_4$.

General Procedure for Preparation of Bromides 16, 19, 23, and Dibromide 24. To a stirred mixture of olefin (2 equiv) and sodium hexamethyldisilylamide (1 equiv) in pentane under Ar at rt was added methylenedibromide (1 equiv) dropwise. The reaction mixture was stirred at rt during 1.5 h and then poured into cold water and extracted with pentane. The extract was washed with water and dried. After evapora-

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(14) (a) Mathematical model of chain triangulanes will be considered in a joint paper of M. E. Muzychuk (Bar-Lian University), M. H. Klin (Ben-Gurion University of the Negev), and N. S. Zefirov. (b) During the period of reviewing and improvement of this manuscript we successfully used this approach for the synthesis of CST's with four, five, and six cyclopropane rings (will be published).

tion of the solvent, the excess of the olefin and the bromides **16**, **19**, and **23** and dibromide **24** were isolated by distillation.

9-Bromobicyclo[6.1.0]nonane (16). Cyclooctene (10 g, 90 mmol) was converted into 4.7 g (52%) of **16** which is a 20:1 mixture of *endo*- and *exo*-isomers,[9] bp 58–60 °C/2 mm. Bp and ^{1}H NMR data are identical to those reported.[15]

2-Bromotricyclo[7.1.0.0^{1,3}]decane (19). Cycloalkene **17** (1.3 g, 10 mmol) was converted into 0.49 g (46%) of **19**, which is a 3:2 mixture of two isomers (as indicated by ^{1}H NMR), bp 81–83 °C/2 mm. ^{1}H NMR (300 MHz, CD_2Cl_2): (a) major isomer δ 0.75–0.8 (m, 1H), 0.90–0.95 (m, 1H), 1.3–1.8 (m, 10H), 1.84–2.05 (m, 2H), 3.44 (d, 1H, J = 6.56 Hz); (b) minor isomer δ 0.6–0.65 (m, 1H), 1.01–1.09 (m, 1H), 1.1–2.0 (m, 12H), 3.01–3.03 (m, 1H). ^{13}C NMR (CD_2Cl_2): δ 12.31 (CH_2), 13.23 (CH_2), 18.73 (CH), 20.57 (CH), 20.95 (CH_2), 22.67 (CH), 23.48 (CH_2), 23.61 (CH_2), 25.19 (CH_2), 25.3 (C), 28.10 (CH_2), 28.17 (CH_2), 28.34 (CH), 29.10 (CH_2), 29.49 (CHBr), 30.38 (CH_2), 31.36 (CH_2), 32.19 (CH_2), 33.73 (CHBr).[16] MS: *m/e* 214, 216 (4, M^+), 135 (60), 121 (22), 107 (27), 93 (83), 79 (60), 67 (100), 53 (23).

9-Bromobicyclo[6.1.0]non-4-ene (23) and 5,10-Dibromotricyclo[7.1.0.0^{4,6}]decane (24). Cyclooctadiene (4.3 g, 40 mmol) was converted into 1.4 g (36%) of **23** as mixture of isomers, bp 78–80 °C/2 mm (bp and ^{1}H NMR data of **23** are identical to those reported[17]) and 0.2 g (5%) of **24** which is a 6:1 mixture of isomers, bp 110–115 °C/2 mm, mp 74–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ major isomer 1.1–1.23 (m, 4H), 1.55–1.72 (m, 4H), 1.95–2.1 (m, 4H), 3.34 (t, 2H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 17.83 (CH), 22.87 (CH_2), 32.69 (CHBr). MS: *m/e* 292, 294, 296 (1, M^+), 213 (20), 133 (77), 119 (21), 105 (27), 91 (85), 79 (61), 67 (100), 53 (34).

Bromide **23** (7.4 g, 37 mmol) was converted into 1.9 g (35%) of **24**, identical to those described above.

10-Bromotricyclo[7.1.0.0^{4,6}]decane (27). A diazomethane solution obtained from 7 g of *N*-nitroso-*N*-methylurea in ether (40 mL) was added dropwise at −4 °C to the suspension of 1.7 g (8.4 mmol) of bromide **23** and palladium(II) acetate (50 mg) in ether (5 mL). The reaction mixture was stirred for 15 min and filtered through silica gel (5 cm). After evaporation of the solvent, 1.45 g (80%) of bromide **27** (mixture of isomers) was isolated, bp 92–93 °C/2 mm. ^{1}H NMR (300 MHz, CD_2Cl_2): δ −0.20 to −0.08 and 0.5–0.75 (2m, 2H), 0.80–0.97 (m, 4H), 1.20–1.44 and 1.90–2.32 (2m, 8H), 3.22 and 3.35 (2t, 1H, J = 6.6 Hz). ^{13}C NMR (CD_2Cl_2): δ 13.06 (CH_2), 13.40 (CH_2), 14.46 (CH), 18.20 (CH), 18.56 (CH), 22.07 (CH), 23.53 (CH_2), 25.66 (CH_2), 26.45 (CH_2), 28.18 (CH_2), 30.28 (CH_2), 31.43 (CHBr), 33.91 (CHBr). MS: *m/e* 214, 216 (3, M^+), 135 (56), 120 (42), 105 (41), 91 (77), 79 (43), 67 (100), 53 (30).

General Procedure for Preparation of Hydrocarbons 18, 21, 26, and 30. Bromide or dibromide (1 equiv) was added under Ar at 20 °C to potassium *tert*-butoxide (5 equiv) in dry DMSO. The reaction mixture was stirred for 6 h (15 h for dibromide **24**) and then quenched with cold water. Pentane was added, and the organic layer was separated, washed with water, and dried. The pentane solution was carefully concentrated. Olefins **17**, **20**, and **28** were isolated by flash distillation; olefins **25** and **29** were used withour purification. The formation of the C=CH bond was always proven by ^{1}H NMR.

A diazomethane solution obtained from 4 g of *N*-nitroso-*N*-methylurea in ether (25 mL) was added dropwise at −4 to 0 °C to the mixture of an olefin (5 mmol; 2.5 mmol in the case of **25**) and palladium(II) acetate (30 mg) in ether (3 mL). The reaction mixture was allowed to warm to rt over 30 min and then filtered through silica gel (3 cm). After evaporation of the solvent the hydrocarbons **18**, **21**, **26**, and **30** were isolated by preparative GLC (3000 × 5 mm; 150 °C/235 °C, 80 mL of He/min).

Tricyclo[7.1.0.0^{1,3}]decane (18). Bromide **16** (1.7 g, 8 mmol) was converted into 0.78 g (80%) of olefin **17**, bp 30 °C/2 mm. Spectral data are identical to those reported.[10,11] Cyclopropanation of **17** (0.3 g, 2.5 mmol) resulted in 0.27 g (80%) of **18**. ^{1}H NMR (300 MHz, CD_2Cl_2): δ 0.39 (t, 2H, J = 4.3 Hz), 0.71–0.77 (m, 2H), 1.14–1.28 (m, 2H), 1.28–1.38 and 1.42–1.56 (2m, 6H), 1.8–1.95 (m, 2H). ^{13}C NMR (CD_2Cl_2): δ 10.72 (C^2, C^{10}), 17.70 (C^3, C^9), 17.88 (C^1), 24.13 (C^5, C^7), 30.76 (C^4, C^8), 32.47 (C^6). MS: *m/e* 136 (20, M^+), 121 (17), 107 (20), 93 (50), 79 (43), 67 (100), 53 (15). Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 87.95; H, 11.71.

Tetracyclo[8.1.0.0^{1,3}.0^{3,5}]undecane (21). Bromide **19** (23 g, 100 mmol) was converted into 8.6 g (64%) of **20**, bp 45 °C/2 mm. ^{1}H NMR (60 MHz, CCl_4): δ 0.4–0.9 (m, 1H), 1.0–2.5 (m, 12H), 5.6–5.9 (m, 1H). Cyclopropanation of **20** (0.4 g, 3 mmol) resulted in 0.3 g (80%) of **21**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.45 (t, 2H, J = 5.8 Hz), 0.6–0.83 (m, 2H), 1.0–1.24 (m, 6H), 1.3–1.46 (m, 2H), 1.48–1.69 (m, 2H), 1.96–2.14 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 13.62 (C^4, C^{11}), 14.32 (C^2), 18.44 (C^1, C^3), 18.92 (C^5, C^{10}), 26.10 (C^7, C^8), 28.34 (C^6, C^9). MS: *m/e* 148 (14, M^+), 133 (31), 119 (39), 105 (84), 91 (100), 79 (98), 67 (36), 53 (15). Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 88.89; H, 10.87.

Tetracyclo[8.1.0.0^{1,3}.0^{5,7}]undecane (26). Bromide **27** (1.5 g, 7 mmol) was converted into 0.65 g (70%) of **28**, bp 50 °C/2 mm. ^{1}H NMR (60 MHz, CD_2Cl_2): δ −0.20 to 0.25 (m, 1H), 0.5–1.31 (m, 12H), 5.8–6.1 (m, 1H). Cyclopropanation of **28** (0.26 g, 2 mmol) gave 0.23 g (80%) of **26** which is a 4:1 mixture of isomers. They were separated by preparative GLC. (a) ^{1}H NMR (300 MHz, CD_2Cl_2): major isomer δ −0.24 to −0.18 (m, 1H), 0.24–0.34 (m, 1H), 0.50 (t, 1H, J = 3.75 Hz), 0.6–1.0 (m, 8H), 1.21–1.32 (m, 1H), 1.33–1.43 (m, 1H), 1.95–2.10 (m, 1H), 2.36–2.47 (m, 1H), 2.58–2.66 (dt, 1H, J_1 = 3.4 Hz, J_2 = 3.4 Hz). ^{13}C NMR (CD_2Cl_2): δ 12.41 (CH_2), 14.69 (CH_2), 17.03 (CH), 17.77 (CH_2), 19.13 (CH), 19.22 (CH), 19.55 (C), 19.78 (CH), 28.62 (CH), 33.83 (CH_2), 36.18 (CH). (b) ^{1}H NMR (300 MHz, CD_2Cl_2): minor isomer δ −0.30 to −0.25 (m, 1H), 0.32–0.36 (m, 1H), 0.45–0.83 (m, 4H), 0.88–0.95 (m, 3H), 1.28–1.43 (m, 5H), 1.85–1.96 (m, 1H), 2.07–2.23 (m, 1H), 2.31–2.41 (dm, 1H). ^{13}C NMR (CD_2Cl_2): δ 9.18 (CH_2), 10.72 (CH_2), 10.98 (CH), 14.76 (CH), 15.22 (CH_2), 15.87 (CH), 17.60 (CH), 22.94 (C), 22.14 (CH_2), 28.73 (CH_2), 30.15 (CH_2). MS: *m/e* 148 (5, M^+), 133 (27), 119 (34), 105 (76), 91 (100), 67 (44), 53 (13). Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 88.90; H, 10.90.

Cyclopropanation of **25** (0.32 g, 2.7 mmol) obtained by dehydrobromination of bromide **23** (0.8 g, 3 mmol) gave 0.3 g (76%) of **26**. Spectral parameters were identical to those described above.

Pentacyclo[9.1.0.0^{1,3}.0^{4,6}.0^{6,8}]dodecane (30). Cyclopropanation of the mixture of olefins, obtained by dehydrobromination of dibromide **24** (1 g, 3.4 mmol) with an excess of diazomethane, resulted in 0.15 g of a mixture of hydrocarbons separated by preparative GLC (three fractions). The first major fraction is 0.1 g (25%) of **30**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.23 (t, 2H, J = 3.9 Hz), 0.58–0.64 (m, 2H), 0.73–0.78 (m, 4H), 0.98–1.08 (m, 2H), 1.15–1.3 (m, 4H), 2.46–2.50 (m, 1H), 2.51–2.55 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 7.84 (C^7, C^{12}), 10.56 (C^2, C^5), 12.49 (C^8, C^{11}), 16.90 (C^1, C^6), 17.39 (C^3, C^4), 31.43 (C^9, C^{10}). MS: *m/e* 160 (10, M^+), 145 (28), 131 (33), 119 (41), 105 (77), 91 (100), 79 (80), 67 (45), 53 (27). Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.73; H, 10.00.

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Supplementary Material Available: Copies of ^{1}H NMR and ^{13}C NMR spectra (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(15) Baird, M. S.; Reese, C. B. *J. Chem. Soc. C* **1969**, 1803.
(16) The signal of the quaternary carbon of minor isomer has low intensity and has not been observed.
(17) Baird, M. S.; Reese, C. B. *J. Chem. Soc. C* **1969**, 1808.