the positions of hydrogen atoms were located on a difference Fourier map, except for methyl hydrogens, which were calculated. Hydrogen atoms were included in the refinement with isotropic thermal parameters. Refinement proceeded to convergence by minimizing the function $\sum w(|F_o| - |F_c|)^2$, where the weight, w, is $\sigma(F)^{-2}$. The discrepancy indices $R = \sum||F_o| - |F_c||/\sum|F_o|$ and $R_w = |\sum w(|F_o| - |F_c|)^2/\sum w(|F_o|)|^{1/2}$ are presented below.

Crystallographic Data. A. Compound 6: $C_8H_9N_5$, space group $C2/c$, a = 23.32 (12) Å, b = 3.870 (2) Å, c = 18.235 (9) Å, β = 91.68 (2)°, V = 1645.3 (9) Å^3, Z = 8, D_{calcd} = 1.41 g cm^{-3}, μ (Mo Kα) = 0.09 mm^{-1}. Number of unique reflections = 1082, reflections with $1 \geq 3\sigma(1)$ = 783; R = 0.054, R_w = 0.059.

B. Compound 8·CF$_3$CO$_2$H: $C_{10}H_{10}N_5O_2F_3$, space group $P2_1/n$, a = 4.615 (2) Å, b = 26.328 (9) Å, c = 10.224 (5) Å, β = 90.59 (4)°, V = 1242 (1) Å^3, Z = 4, D_{calcd} = 1.55 g cm^{-3}, μ (Mo Kα) = 0.13 mm^{-1}. Number of unique reflections = 1611, reflections with $1 \geq 3\sigma(1)$ = 1192; R = 0.054, R_w = 0.060.

C. Compound 14b: $C_7H_{10}N_6$, space group $P2_1/c$, a = 7.495 (5) Å, b = 16.456 (9) Å, c = 7.427 (3) Å, β = 108.85 (4)°, V = 866.9 (8) Å^3, Z = 4, D_{calcd} = 1.37 g cm^{-3}, μ (Mo Kα) = 0.58 cm^{-1}. Number of unique reflections = 1129, reflections with $1 \geq 3\sigma(1)$ = 962; R = 0.046, R_w = 0.062.

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Supplementary Material Available: Tables of bond lengths, bond angles, torsional angles, and positional parameters for compounds **6**, **8**·TFA, and **14b** (9 pages). Ordering information is given on any current masthead page.

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Synthesis of Amino-Substituted Dodecahedranes, Secododecahedranes, and Homododecahedranes and Their Antiviral Relationship to 1-Aminoadamantane

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Several spherically shaped molecules carrying an amino head group have been prepared and assayed for antiviral activity against influenza A virus. The secododecahedrane derivatives **4** and **5** have been arrived at through suitable chemical manipulation of intermediates utilized in the synthesis of dodecahedrane itself. The important relay precursor to dodecahedranes **6** and **7** is amide **16**, available by reaction of ester **15** with dimethylaluminum amide. Dehydration to nitrile **19** and subsequent catalytic hydrogenation gave **6**. In order to bypass complications often brought on by the steric bulk of the dodecahedrane framework and insolubility factors, Hoffmann rearrangement of **16** was effected with the highly reactive [bis(trifluoroacetoxy)iodo]benzene reagent. Treatment of bromododecahedrane **12** with trimethylsilyl azide and stannic chloride gave rise to the azahomododecahedrane derivative **22**, the immediate precursor of **23**. Finally, the results of the bioassays are presented.

There has been considerable recent interest in the synthesis of dodecahedrane (**1**),[1-3] the structurally most complex and aesthetically appealing member of the C_nH_n convex polyhedra (n = 20). Derivatives of **1**, although necessarily of symmetry lower than the unrivaled I_h level of the parent hydrocarbon, hold high interest in their own right. Knowledge of the magnitude of structural distortion incurred by replacing methine hydrogen by larger substituents of divergent electronic character is one aspect that has received some attention.[4-7] During the course of our successful efforts to prepare **1**,[8] it proved feasible to incorporate pendant alkyl groups early in the scheme and to access by this means the monomethyl derivative,[9] several dimethyl isomers,[10,11] and the 1,4,16-trimethyl-substituted hydrocarbon.[11] For the purpose of introducing a greater array of functional groups, recourse has since been made to engaging dodecahedrane itself directly into chemical reaction.[12] More recently, controlled 1,16-disubstitution of **1** has also become possible via its D_{3d} symmetric dication **2**,[13] and direct annulation of a cyclopropane ring to the sphere as in **3** has been realized.[14,15]

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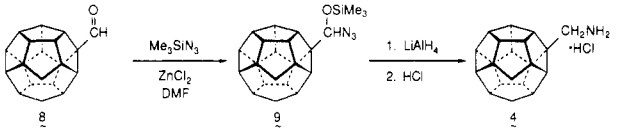
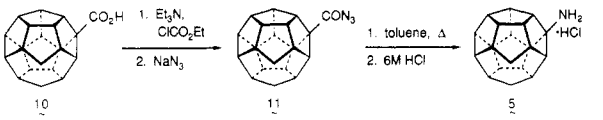
0022-3263/88/1953-5315$01.50/0

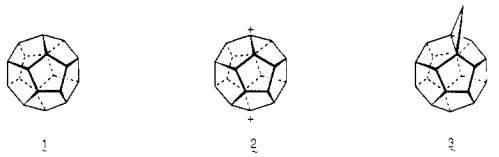
Scheme I



Scheme II



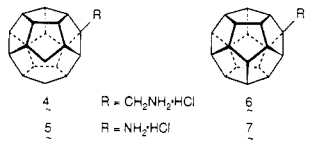
The gas-phase basicities of selected dodecahedranes are beginning to make their appearance.[16]



To date, no amino derivative of 1 or of a closely related compound has been reported. Interest in the acquisition of such substances stems from possible enhancement of the efficacious antiviral[17] and anti-Parkinsonian properties[18] of 1-aminoadamantane. Should the capacity of this pharmaceutical to penetrate body tissues as well as brain and cerebrospinal fluids[19] evolve from a high degree of lipid solubility, low extent of ionization,[20] and lack of plasma-protein binding, then the molecules targeted herein could represent candidates where more rapid passage through these media might be facilitated. To the extent that a heightened level of symmetry is conducive to antiviral activity,[21] monosubstituted dodecahedranes have an advantage unattainable by any other structural type.

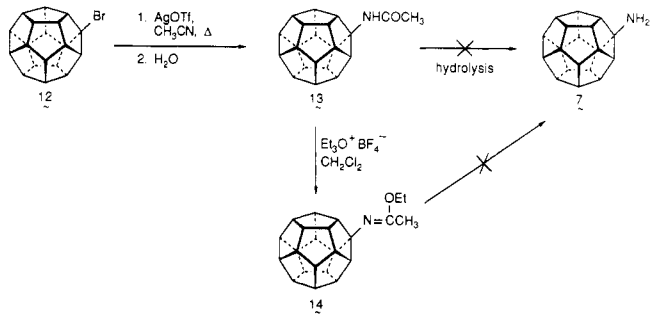
Results and Discussion

Synthetic Considerations. The primary focus of the present study was the synthesis and in vitro antiviral evaluation of hydrochlorides **4–7**. For secododecahedranes

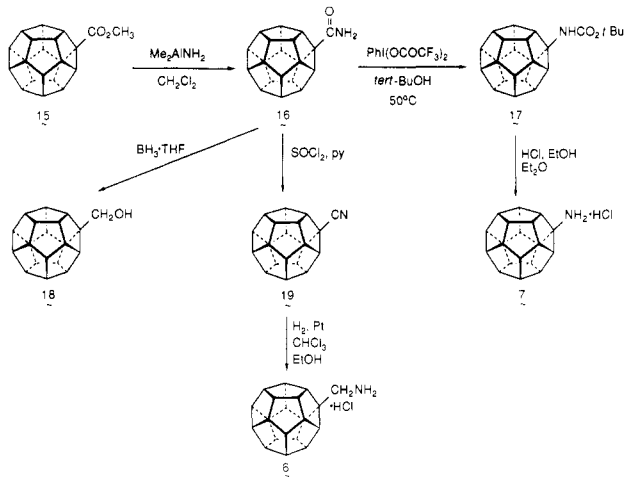


4 and **5**, the intent was to utilize, if possible, intermediates currently employed in our improved dodecahedrane synthesis.[12b] As matters turned out, aldehyde **8** and carboxylic acid **10** proved to be viable precursors to **4** and **5**, respectively (Schemes I and II).

Scheme III



Scheme IV



Addition of azidotrimethylsilane[22] to **8** furnished siloxy azide **9**, which was directly reduced with lithium aluminum hydride[23] to give the free amine. Following treatment with ethanolic hydrogen chloride, **4** was acquired in 65% yield after purification (Scheme I).

10 was transformed via its mixed anhydride with ethyl chloroformate to acyl azide **11** to arrive at **5**. This compound was not isolated but directly dissolved in toluene and heated at the reflux temperature overnight to give the isocyanate. Warming this intermediate with 6 M hydrochloric acid delivered **5** in an overall yield of 70% (Scheme II).

Although many conceivable routes to **6** and **7** exist, we were already well aware that dodecahedrane does not exhibit reactivity comparable to adamantane. The reasons underlying this dichotomy are discussed elsewhere.[12] Consequently, it came as no surprise to find that attempted direct chloramination of **1** with NCl_3 and $AlCl_3$[24] failed completely. Similarly, certain solvolyses of bromododecahedrane under conditions previously shown to be effective in the adamantane series ($HCONH_2$, Δ;[25] AgOTf, NH_3; Me_2AlNH_2; $HN(TMS)_2$, Δ) proved unsuccessful.

At this point, exploits of a less direct nature were undertaken. Indeed, conversion of bromide **12** to acetamide **13** could be accomplished quantitatively[12] (Scheme III). However, **13** proved to be unusually resistant to alkaline and acidic hydrolysis. Whereas recourse to other con-

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ventional methodology (Li, NH_3;[26] H_2NNH_2, Δ;[27] Dibal-H;[28] CH_3Li) failed to remove the acetyl group, harsher conditions (e.g., potassium hydroxide, ethylene glycol, reflux)[29] did cause a chemical change to occur, but failed to give **7**. The highly touted method involving O-alkylation to generate **14** followed by aqueous hydrolysis[30] was equally unrewarding.

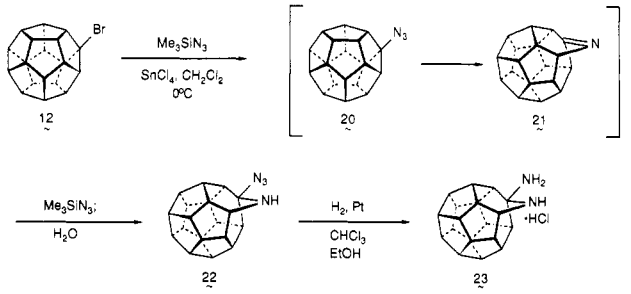
Somewhat surprisingly, dodecahedranecarboxylic acid proved unreactive when subjected to the protocol earlier found to proceed satisfactorily with the related seco derivative (Scheme II). A two-step procedure aimed at direct conversion of the acid to **7** by means of diphenyl phosphorazidate[31] also proved unworkable.

The successful route began with ester **15**[21] (Scheme IV). Although ammonia and cyanide ion in methanol solution[32] was ineffective at transforming **15** to **16**, Weinreb's aluminum amide reagent[33] was well suited to the task. In fact, formation of amide **16** approached near quantitative levels when reaction was allowed to proceed for 2–3 days at room temperature in the presence of a large excess of the reagent. Gentle warming accelerated the process without disadvantageous side effects.

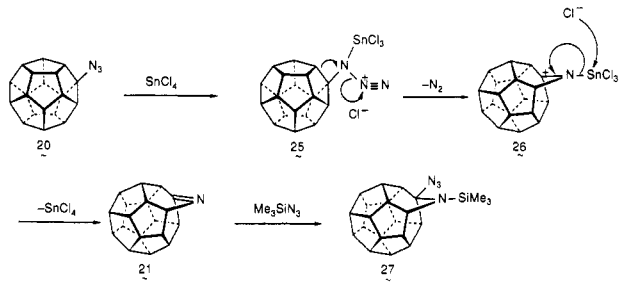
As matters turned out, amide **16** was the key precursor to both **6** and **7**. Our choice of conditions for implementation of the Hoffmann rearrangement was guided by recent reports[34] indicating derivatives of iodobenzene to give superior yields of carbamate products. The most promising of these new methods consists of amide addition to [bis(trifluoroacetoxy)iodo]benzene in aqueous acetonitrile; C → N migration and hydrolysis to the amine take place sequentially in situ. However, when this procedure was applied to **16**, the only identifiable product proved to be the isocyanate. Mainly for solubility reasons, hydrolysis of this intermediate proved troublesome. Consequently, the solvent was changed to *tert*-butyl alcohol. Gratifyingly, carbamate **17** was now obtained. Its exposure to hydrogen chloride eventuated in smooth hydrolysis and decarboxylation to deliver **7**.

Some time ago, H. C. Brown and his associates discovered that primary amides experience ready reduction in the presence of diborane to give the corresponding aminomethyl derivatives in high yield.[35] In these reports, comment is made that a major benefit of diborane relative to lithium aluminum hydride derives from the fact that no C–N bond heterolysis had ever been observed. Apparently, sterically hindered examples were not accorded adequate attention. In the case of **16**, steric crowding causes cleavage of the C–N bond to be the only reaction pathway operative, (hydroxymethyl)dodecahedrane (**18**) being isolated in 73% yield. Reduction occurred relatively

Scheme V



Scheme VI



rapidly at room temperature (complete in less than 1 h) and more slowly on warming from −78 to 0 °C. In either case, **18** was formed exclusively. Interestingly, treatment of amide **16** with lithium aluminum hydride resulted in loss of the acyl residue and return of the parent hydrocarbon **1** (capillary GC analysis). All other attempted reductions were similarly unsuccessful.

Accordingly, **16** was dehydrated to give nitrile **19**. Hydrogenation of **19** over platinum in ethanol containing a small amount of chloroform led directly to **6**. The role of the $CHCl_3$ was to provide low levels of hydrogen chloride through hydrogenolysis, thereby permitting in situ formation of the hydrochloride salt.

Along different lines, an interesting transformation materialized during attempts to prepare azidododecahedrane (**20**) from the bromide according to an established procedure.[36] We envisioned that the azide might serve as an alternative precursor to **7**. However, treatment of **12** with stannic chloride in the presence of azidotrimethylsilane led rapidly not to **20** but to the ring-expanded azahomododecahedrane derivative **22** (78%, Scheme V). The infrared spectrum of **22** displays a strong absorption at 2100 cm^{-1} in line with the presence of an azide group. Its ^1H NMR features were clearly inconsistent with retention of the intact, axially symmetric dodecahedryl framework. The appearance of **12** ^{13}C signals indicated further that the new compound had, however, retained a plane of symmetry. These data in combination with the mass spectrum indicated **22** to possess an unusual α-azido amine part structure.

Rationalization of the formation of **22** is based chiefly on prior demonstration that trialkylboranes coordinate to azido groups to initiate loss of nitrogen by migration of an alkyl group from boron to nitrogen (see **24**).[37] Since **20**

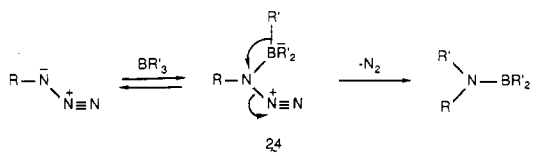


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Table I. Influenza A Virus Plaque Reduction Tests

test series	compd	percent inhibition of plaques, mcg/mL[a] 25	12.5	6.25	3.12	1.56	0.78	0.39	0.19	IC_{50}
A	AA·HCl[b]	94	89	85 ST	70	71	33	28	9	1.13
	5	T	T	71	13	0	0	0	0	5.13
	4	T	T	T	42	15	0	0	0	>3.12
B	AA·HCl[b]	85	83	87 ST	85	86	78	56	42	0.31
	5	T	T	77	45	9	5	0	0	3.62
	4	T	T	T	78	32	1	0	0	2.18
C	AA·HCl[b]	100	90	74	64	54	40	26		
	7	T	34	0	0	0	0	0		
D	AA·HCl[b]	100	91	81	72	68	52	40		
	7	T	0	0	0	0	0	0		
E	AA·HCl[b]	100	90	80	83	72	67	45	41	0.40
	6	T ST	25	5	0	0	0	0		>12.5
	23	98	50	0	0	0	0	0		12.5
F	AA·HCl[b]	100 ST	92	84	75	64	57	44		0.57
	23	100	61	27	0	0	0	0		10.4

[a] T = toxic; ST = slightly toxic. [b] AA·HCl = 1-aminoadamantane hydrochloride serving as the standard.

is produced in the presence of an excess of stannic chloride, it is possible that coordination of the Lewis acid sets the stage for comparably facile ejection of nitrogen (see **25**, Scheme VI). In this instance, the event is accompanied by ring enlargement and eventual passage via **26** to imine **21**. This intermediate is assumed to be adequately strained.[38] to allow rapid 1,2-addition of trimethylsilyl azide. All efforts to reconvert **22** to **21**, with particular attention to in situ reduction as a route to the unsubstituted azahomododecahedrane, have gone unrewarded, presumably owing to this strain factor.[38,39] On the other hand, it proved possible to transform **22** into the 1,1-diamine salt **23** by hydrogenation as before over Adams catalyst in the presence of chloroform. This aminal showed no obvious tendency to exist as an open-chain tautomer.

Antiviral Evaluation. 1-Aminoadamantane hydrochloride (AA·HCl) was approved in 1966 by the FDA for use against Asian influenza and became the first antiviral agent available for systemic use.[40-42] From the large number of saturated polycyclic amino compounds that have been prepared for antiviral evaluation,[21,43] only a very few select (highly symmetric) compounds exhibit useful activity.[21,44] For these reasons, we sought to establish if suitably derivatized condensed spherical alicyclics of dimension larger than adamantane would exhibit antiviral effects.

The plaque reduction assay employed to screen efficacy versus influenza A virus is described in the Experimental Section.[45] The test results are compiled in Table I. The minor differences seen between assays arise from the varying number of plaque-forming units (virus) that replicated on the control plates. The striking characteristic of all five amino compounds is their toxicity, with a maximum appearing in **7**. The data indicate **4** and **5** to be the most active antiviral agents of the set, their capacity for inhibition being 5- to 10-fold less than that of AA·HCl. Toxicity to the cell line sets in early, at about one dilution up from antiviral activity. Homoaza derivative **23** exhibits quite good activity at high doses, although slight toxicity is manifested concurrently. However, the dropoff in its efficacy is precipitous when compared to the bioactivity range of the adamantane derivative.

On a more positive note, **4**–**7** have shown very good levels of cytotoxicity when evaluated in vitro against CEM cells (a T-cell line). The relevant IC_{50} values are **4**, 1.1 μg/mL; **5**, 0.4 μg/mL; **6**, 1.7 μg/mL; and **7**, 0.6 μg/mL. The selectivity of these agents is not yet known. A future goal is the design of additional spherical molecules where the partitioning between cytotoxicity and viral inhibition is more clearly defined and activity in either assay is appreciably heightened.

Experimental Section

7-[α-[(Trimethylsilyl)oxy]azidomethyl]secododecahedrane (9). Aldehyde **8** (12.8 mg, 0.627 mmol) was dissolved in dimethylformamide (1 mL) under an argon atmosphere and trimethylsilyl azide (0.5 mL) was added along with zinc chloride (2 crystals). The mixture was stirred at room temperature for 4 h and diluted with ether (50 mL). The ether layer was washed with water and saturated sodium bicarbonate solution followed by drying. Filtration and solvent removal gave **9** as a colorless oil, which was used without further purification: IR ($CHCl_3$, cm^{-1}) 2940, 2860, 2100, 1255, 1135, 1110, 1100, 895, 880, 850; ^1H NMR (300 MHz, $CDCl_3$) δ 4.68 (s, 1 H), 3.55–2.91 (series of m, 19 H), 1.56–1.50 (m, 2 H), 0.21 (s, 9 H): MS, m/z ($M^+ - N_2$) calcd 377.2175, obsd 377.2197.

7-(Aminomethyl)secododecahedrane Hydrochloride (4). To lithium aluminum hydride (90 mg) suspended in dry ethyl ether (3 mL) under an argon atmosphere was added dropwise a solution of the unpurified **9** from above in ether (5 mL). The mixture was stirred at room temperature for 1 h and refluxed for 4 h. After cooling, the excess hydride was quenched by careful addition of saturated ammonium chloride solution. Aqueous sodium hydroxide solution (10 mL, 1 N) was next added until the mixture was stringly basic. The solution was extracted with

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ether (3 × 50 mL) and the combined organic extracts were washed with brine (30 mL) and dried. Filtration and solvent removal gave the free amine as a white solid, which was taken up in dry ether (20 mL), and ethanol saturated with gaseous hydrochloric acid (0.5 mL) was added. Amine hydrochloride **4** precipitated out of solution immediately and was collected after an additional hour of stirring. The white solid was taken up in methanol and reprecipitated by the addition of ether. This procedure was repeated three times, yielding 13.3 mg (64.5% from **8**) of **4**: mp >240 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 3.62–2.73 (series of m, 24 H), 1.65–1.55 (m, 2 H); ^{13}C NMR (75 MHz, CD_3OD) ppm 82.02, 70.42, 69.11, 67.29, 66.77, 66.48, 63.19, 55.33, 54.07, 53.72, 51.24, 51.08, 32.93; MS (FAB), m/z (M^+) calcd 292.2066, obsd 292.2081.

7-Aminosecododecahedrane Hydrochloride (5). Acid **10** (13.7 mg, 0.0447 mmol) was suspended in acetone (5 mL), and triethylamine was added until the acid completely dissolved. The solution was cooled to 0 °C and ethyl chloroformate (10 drops) was added along with water (2 mL). The solution was stirred for 1 h followed by the addition of an excess amount of sodium azide in water. After 1 h, a white solid appeared, which dissolved upon the addition of ether. The layers were separated and the aqueous layer was extracted with ether (2 × 30 mL). The combined extracts were washed with water and dried. Filtration and addition of toluene (15 mL) followed by concentration in vacuo to approximately 10 mL gave the acyl azide, which was slowly heated to 110 °C under argon and refluxed overnight. Concentration gave the isocyanate as a yellow oil: IR ($CHCl_3$, Cm^{-1}) 2940, 2260, 1700, 1380, 1330. This oil was taken up in tetrahydrofuran (3 mL), 6 M hydrochloric acid (2 mL) was added, and the mixture was heated at reflux for 2 h. The tetrahydrofuran was distilled out of the reaction vessel and the mixture was heated to 90 °C for 6 h. Evaporation in vacuo gave a grown semisolid, which was triturated with hot acetone and methanol to give the amine hydrochloride as an off-white solid. Purification by reprecipitation from methanol and ether (3×) yielded 10.3 mg (69.6%) of **5**: mp >240 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 3.65–2.99 (series of m, 22 H), 1.69–1.55 (m, 2 H); ^{13}C NMR (75 MHz, CD_3OD) ppm 98.15, 69.98, 68.35, 68.06, 66.86, 66.34, 62.76, 57.40, 53.77, 53.16, 50.58, 32.51; MS (FAB), m/z calcd 278.1909, obsd 278.1880.

Dodecahedranecarboxamide (16). Ester **15** (11.0 mg, 0.034 mmol) was taken up in dry dichloromethane (3 mL) and treated with a stock solution of dimethylaluminum amide (3 mL of 1 M in dichloromethane) at room temperature for 45 h. The mixture was quenched with methanol, diluted with saturated ammonium chloride solution, and stirred to dissolve the aluminum salts. The layers were separated and the aqueous phase was further extracted with methylene chloride (4 × 20 mL). The combined organic extracts were washed with brine and dried. Filtration and solvent removal yielded a white solid, which was triturated with hexane to give 9.1 mg (86.7%) of pure **16**: mp >250 °C; IR ($CHCl_3$, cm^{-1}) 3530, 3410, 2950, 1660, 1580, 1365; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.22 (br s), 3.77–3.67 (m, 3 H), 5.53 (m, 6 H), 3.42 (s, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 181.58, 85.61, 71.19, 66.98, 66.96, 66.75 (1 C not observed); MS, m/z (M^+) calcd 303.1623, obsd 303.1640.

[[(*tert*-Butyloxy)carbonyl]amino]dodecahedrane (17). Amide **16** (10.4 mg, 0.0343 mmol) was dissolved in *tert*-butyl alcohol (10 mL) and heated to 50 °C in the presence of [bis(trifluoroacetoxy)iodo]benzene (50 mg) under argon for 22 h. The mixture was diluted with water and extracted with ether (3 × 20 mL). The combined extracts were washed with water and brine prior to drying. Filtration and solvent removal yielded a white solid. The product was isolated from this solid by trituration with hexane (3 × 15 mL). Concentration of the triturates yielded 9.3 mg of **17**, which was used without further purification: IR ($CHCl_3$, cm^{-1}) 3440, 2950, 1700, 1480, 1370, 1170; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (br s, 1 H), 3.55 (br s, 6 H), 3.36 (s, 10 H), 3.25–3.21 (m, 3 H), 1.45 (s, 9 H); MS, m/z (M^+ – *t*-Bu) calcd 318.1515, obsd 318.1494.

Aminododecahedrane Hydrochloride (7). Unpurified carbamate **17** (9.3 mg, 0.0338 mmol) was taken up in ether (2 mL) and treated with ethanol saturated with hydrogen chloride (2 mL). The solution was stirred for 2 h and concentrated. The residue was triturated with ether (2×) and reprecipitated with methanol and ether to give 4.5 mg (42.1%) of **7** as a white solid: mp >250 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (br s, 6 H), 3.46 (s, 10 H), 3.35–3.31 (m, 3 H); ^{13}C NMR (75 MHz, CD_3OD) ppm 94.99, 73.14, 68.13, 67.99, 67.35, 67.26; MS (FAB), m/z (relative intensity) (M^+) calcd 276.29, obsd 276.29 (100).

(Hydroxymethyl)dodecahedrane (18). Carbomethoxydodecahedrane (**15**, 5.3 mg, 0.017 mmol) was dissolved in dry benzene (2 mL) and treated with diisobutylaluminum hydride (15 drops). The solution was stirred for 23 h under an argon atmosphere, after which time excess hydride was destroyed by the addition of methanol. The mixture was diluted with 1 N hydrochloric acid (5 mL) and extracted with methylene chloride (3 × 20 mL). The combined organic extracts were washed with brine and dried. Filtration and solvent removal afforded a white solid, which was triturated with hexane (2×), leaving 3.5 mg (72.9%) of pure **18**: mp >250 °C; IR ($CHCl_3$, cm^{-1}) 3500 (br), 2960, 1300; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.40 and 3.39 (two s, total 18 H), 3.09 (br s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 81.86, 71.06, 68.91, 67.10, 67.02, 66.56, 65.54; MS, m/z (M^+) calcd 290.1681, obsd 290.1659.

Cyanododecahedrane (19). To a solution of **16** (2.0 mg, 0.0067 mmol) in pyridine (3 mL) was added thionyl chloride (10 drops) and stirring was maintained at ambient temperature for 16 h. The solution was diluted with ether, water, and 1 N hydrochloric acid. The layers were separated and the aqueous layer was further extracted with ether (3 × 20 mL). The combined organic extracts were washed with 1 N hydrochloric acid, water, and brine prior to drying. The resulting solid was passed through a silica gel plug (elution with methylene chloride) to give the nitrile. Trituration with hexane gave 1.7 mg (90.4%) of pure **19**: mp >250 °C; IR ($CHCl_3$, cm^{-1}) 2940, 2220; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83–3.76 (m, 3 H), 3.59 (br s, 6 H), 3.42 (s, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 128.00, 73.91, 67.03, 66.87, 66.67 (2 C not observed); MS, m/z (M^+) calcd 285.1517, obsd 285.1520.

(Aminomethyl)dodecahedrane Hydrochloride (6). A solution of **19** (10.7 mg, 0.0375 mmol) in ethanol (4 mL) and chloroform (0.5 mL) was treated with a small amount of platinum oxide and hydrogenated at 50 psi for 24 h. The mixture was filtered through a Celite plug and concentrated. The resulting solid was triturated with ether (2×) and chloroform (2×). Reprecipitation using methanol and ether gave 5.5 mg (45%) of pure **6** as a white solid: mp >250 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 3.46 (m, 6 H), 3.42 (br s, 10 H), 3.12–3.10 (m, 3 H), 2.85 (s, 2 H); ^{13}C NMR (75 MHz, CD_3OD) ppm 79.11, 71.24, 68.30, 68.22, 67.72, 67.69, 50.47; MS (FAB), m/z (M^+ – HCl) calcd 290, obsd 290.

Homoazadodecahedryl Azide (22). Bromododecahedrane (**12**, 5.0 mg, 0.0118 mmol) was dissolved in deuteriated chloroform (0.5 mL) and trimethylsilyl azide (0.5 mL) was added under an argon atmosphere. The solution was cooled to 0 °C and treated with stannic chloride (3 drops). After 15 min, another aliquot of stannic chloride (3 drops) was added and stirring was continued for 45 min. The mixture was quenched by the addition of ice water and extracted with dichloromethane (3 × 20 mL). The combined extracts were washed with saturated sodium bicarbonate solution and dried. A total of 8.0 mg of **12** was treated in this manner (two reactions), giving 7.1 mg of a yellow solid. Twofold trituration with ether gave 5.8 mg (77.8%) of pure **22** was a colorless solid: mp >250 °C (from acetone); IR ($CHCl_3$, cm^{-1}) 2940, 2100, 1425, 1350, 900; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (t, J = 10.2 Hz, 1 H), 3.48–3.33 (series of m, 13 H), 3.02–2.60 (series of m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 87.76, 67.92, 66.88, 66.80, 64.37, 63.92, 63.28, 63.03, 59.43, 54.39, 49.90, 47.02; MS, m/z ($M^+ - N_2$) calcd 288.1626, obsd 288.1674; MS (FAB), m/z obsd for M + 1 317.27.

Catalytic Hydrogenation of 22. Azide **22** (9.8 mg, 0.0278 mmol) was dissolved in ethanol (4 mL) and chloroform (1 mL) and hydrogenated overnight (16 h) at 50 psi by using platinum oxide as catalyst. The mixture was filtered through a Celite plug and concentrated. The solid was triturated with ether (2×) and further purified by reprecipitation from methanol and ether. Drying afforded 4.7 mg (52%) of **23** as an off-white solid: mp >250 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 4.33–4.29 (m, 1 H), 3.70–3.64 (m, 3 H), 3.45 (br s, 10 H), 3.14–3.10 (m, 4 H), 2.93–2.88 (m, 2 H); ^{13}C NMR (75 MHz, CD_3OD) ppm 77.34, 69.79, 68.58, 68.39, 65.68, 65.11, 64.11, 64.97, 64.74, 58.41, 56.92, 47.93 (1 C not observed); MS (FAB), m/z (M^+ – HCl) calcd 291, obsd 291.

Procedure for Plaque Reduction Tests. Susceptible MDCK cells were grown in six-well costar cluster plates at 37 °C in

Medium 199 with 5% fetal bovine serum, penicillin (150 units/mL) and streptomycin (150 mcg/mL). When confluent monolayers were formed, the growth medium was removed and 250 mL of an appropriate dilution of virus was added to each well. Since the drugs must be present in this test during the adsorption phase, each aliquot of infectious virus was made up in the appropriate concentrations of drug before adding to the cell layer. After adsorption for 1 h at room temperature, the infected cell sheet was overlaid with equal parts of 1% agarose and 2X Medium 199 (2.5% FBS, penicillin, and streptomycin) containing varying concentrations of drug corresponding to those used during the adsorption phase. Cluster plates were incubated at 37 °C until the no drug control plates indicated optimum plaque size. A solution containing 10% formalin and 2% sodium acetate was added to each well to inactivate the virus and to fix the cell sheet to the plastic surface. The plaques were counted after staining the surrounding cell areas with crystal violet. Results from duplicate wells at each concentration were averaged and compared with control wells. The inhibition of plaque formation by 50% (IC_{50}) was estimated by plotting all results from 10 to 90% inhibition.

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Type III Intramolecular [2 + 2] Cycloadditions of Vinylketenes

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Treatment of trans α,β-unsaturated acid chlorides with Et_3N in benzene at reflux gives a ca. 1:1 mixture of cis and trans α,β-unsaturated ketenes in excellent yield. If there is a second double bond in the side chain, the cis isomer undergoes a type III intramolecular cycloaddition to produce a bicyclo[3.2.0]hept-3-en-6-one and/or a bicyclo[3.1.1]hept-2-en-6-one in 30–50% yield from the acid chloride. The effect of substituents on the stereochemistry and regiochemistry of the cycloaddition is described.

Introduction

We[1] and others[2] have recently recognized that the stereospecific intramolecular cycloaddition of ketenes to alkenes provides a general method for the synthesis of polycyclic cyclobutanones. Although simple ketenes do undergo intramolecular [2 + 2] cycloaddition with some alkenes, satisfactory yields are not generally obtained unless activated ketenes are used. Excellent success has been obtained with alkoxyketenes,[1a,e] chloroketenes,[1f,k] arylketenes,[1l] and most significantly α,β-unsaturated ketenes.[1b,c,g-j,2a,b] Intramolecular [2 + 2] cycloadditions with α,β-unsaturated ketenes can be classified as type I, type II, and type III, depending on whether the tether containing the second double bond which adds to the ketene is attached to the unsaturated ketene at the ketene carbon, the α-carbon, or the β-carbon, respectively. We have reported detailed studies on type I and type II reactions and used these reactions for the synthesis of several bicyclo[3.1.1]heptane-containing mono- and sesquiterpenoids.[1] We report here studies on the scope and limitations of type III intramolecular cycloadditions.[3]

The general form of a type III intramolecular cycloaddition is shown in eq 1. Attachment of the tether to the β-carbon of the unsaturated ketene requires that the conjugated double bond be cis, complicating the synthesis of the ketene. However, once the ketene is formed, cycloaddition should be very facile since the presence of a cis double bond in the tether will decrease rotational freedom, resulting in a less negative entropy of activation. Early examples of this class of reaction were reported by Schiess and co-workers who prepared the ketenes by pyrolysis of 8-oxabicyclo[5.1.0]octa-2,4-dienes.[4] Complex

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