Through-Space Amide Activation of C–H Bonds in Triangulanes

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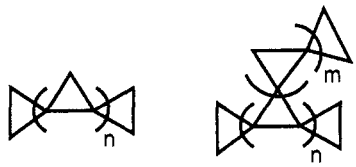
Abstract: Amide activation for anion formation from properly located CH groups in triangulanes is shown to provide for stereospecific functionalization. Thus, treatment of exo amide **20a** with $(TMP)_2Mg$ followed by CO_2 carboxylation leads to syn substitution in the adjacent ring (**21**). The same treatment of endo amide **20b** gives endo (syn) substitution in the remote ring (**22**).

Introduction

Triangulanes are a class of strained hydrocarbons constructed exclusively from spiroannulated cyclopropane fragments.[1,2] There are linear (**1**) and branched (**2**) triangulanes. Extraordinary spatial relationships develop in these systems as a function of the oligomerization terms "*n*" and "*m*". As the synthesis of complex



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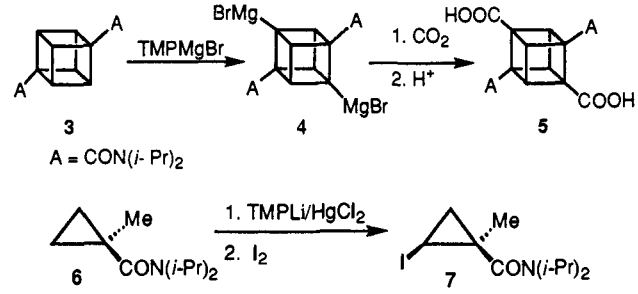
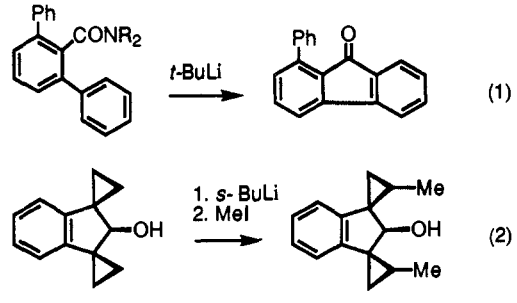
members is not yet simple, unfolding the full chemistry of these compounds requires first finding procedures for their effective elaboration, most particularly their stereospecific functionalization. Ultimately, this will allow preparation of triangulane networks with high C:H ratios and enormous energy content.

In earlier work from this laboratory it was shown that carboxamido substituents provide remarkably effective "activation"[3] of β C–H bonds in highly-strained, saturated hydrocarbons with s-rich C–H bonds.[4,5] For example, treatment of the 1,4-dicarboxamido cubane **3** with (2,2,6,6-tetramethylpiperidino)-magnesium bromide (TMPMgBr) in refluxing THF results in the ready formation of the bis-Grignard compound **4**; carboxylation gives the cubane tetraacid derivative **5** in 80% overall yield.[5] Similarly, metalation of the carboxamido cyclopropane **6** with $TMPLi/HgCl_2$ followed by treatment with iodine gives the 1,2-iodoamide **7**.[4b] Note that the reaction proceeds stereospecifically; the new substituent is introduced cis to the activating group.

The phenomenon of C–H activation by the carboxamido group is probably the result of several factors, including favorable organization of the transition state for proton removal by the



base and carbanion stabilization by complexation of the gegen cation with the carbonyl oxygen.[6] Conceptually, neither of these factors limits C–H activation to β C–H bonds. In compounds with appropriate geometry the effects might be transmitted through space to C–H bonds in other locations. The formation of fluorenones observed by Snieckus from reactions of carboxamido *m*-terphenyls with alkyllithium (eq 1) probably proceeds in this manner.[6] The directed metalations of cyclopropylcarbinyl alcohols and ethers reported by Klump[7] and later by Beak (eq 2)[8] are particularly relevant to the present work.



Molecular mechanics calculations (MM2) place the closest approach between the oxygen in the linear triangulane amide **8** and the *syn* hydrogen on C-7 *in the adjacent ring* at 2.535 Å, almost exactly equal to that (in another conformer) between the oxygen and the β-cis (exo) hydrogen on the same ring as the amide (2.531 Å). As the latter arrangement is known to suffice for activation in simple cyclopropanes,[4b] triangulane geometry might allow *transannular* functionalization *via* carboxamido

* Abstract published in *Advance ACS Abstracts*, November 1, 1993.

(1) For a discussion of triangulane nomenclature, see: Zefirov, N. S.; Kozhushkov, S. I.; Kuznetzova, T. S.; Kokoreva, O. V.; Lukin, K. A.; Ugrak, B. I.; Tratch, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 7702.

(2) (a) Lukin, K. A.; Kozhushkov, S. I.; Andrievski, A. A.; Ugrak, B. I.; Zefirov, N. S. *J. Org. Chem.* **1991**, *56*, 6176. (b) Zefirov, N. S.; Kozhushkov, S. I.; Ugrak, B. I.; Lukin, K. A.; Kokoreva, O. V.; Yufit, D. S.; Struchkov, Yu. T.; Zoelner, S.; Boese, R.; De Meijere, A. *J. Org. Chem.* **1992**, *57*, 701. (c) Kozhushkov, S. I.; Haumann, T.; Boese, R.; De Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 401–403 and references cited therein.

(3) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356–363.

(4) (a) Eaton, P. E.; Cunkle, G. T.; Marchioro, G.; Martin, R. M. *J. Am. Chem. Soc.* **1987**, *109*, 948–949. (b) Eaton, P. E.; Daniels, R. G.; Casucci, D.; Cunkel, G. T. *J. Org. Chem.* **1987**, *52*, 2100.

(5) Eaton, P. E.; Lee, C. H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8061.

(6) See the discussion and references in the following: Snieckus, V. *Chem. Rev.* **1990**, *90*, 928–929.

(7) Klump, C. W. *Recl. Trav. Chim. Pay-Bas* **1986**, *55*, 5454.

(8) Gallagher, D. J.; Garrett, C. G.; Lemieux, R. P.; Beak, P. *J. Org. Chem.* **1991**, *56*, 853.

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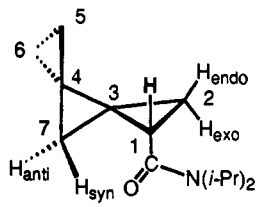
activation.[9] In the endo triangulane amide **9**, epimeric at position 1, there are no hydrogens in the middle ring close enough to the amide oxygen to be activated by it. However, on the *farthest* cyclopropane ring the endo (syn) hydrogen at C-5 is just 2.485 Å away from the amide oxygen and might be activated by the through-space mechanism.



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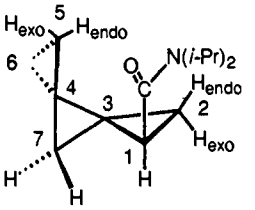

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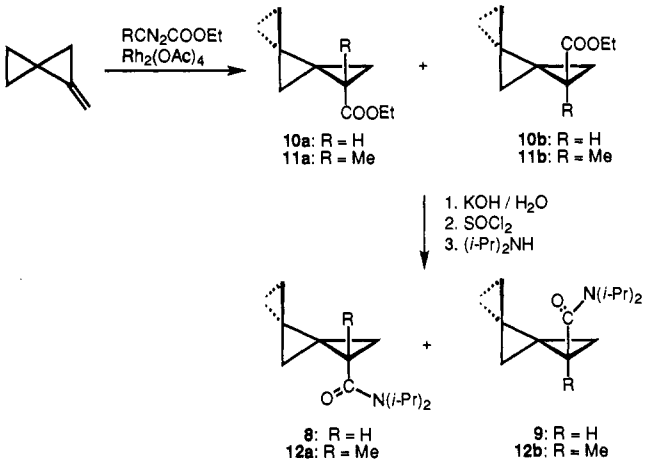
Results

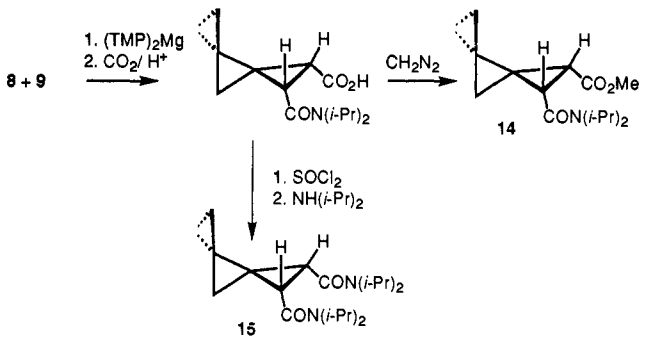
The spatially isomeric 1-carbethoxy[3]triangulanes (**10a,b**) were prepared by rhodium acetate-catalyzed cyclopropanation of methylenespiropentane with ethyl diazoacetate following the published procedure of Doyle.[10] Similarly, rhodium acetate-catalyzed cyclopropanation of methylenespiropentane with ethyl diazopropionate was used to obtain the 1-methyl-1-carbethoxy-[3]triangulanes (**11a,b**). Pure samples of each isomer were obtained by column chromatography and converted by standard manipulations (see Experimental Section) to the corresponding *N,N*-diisopropyl carboxamides **8** and **9** and the methylated analogs **12a** and **12b** (Scheme I).

Scheme I



As hydrolysis of ester **10a** (but not **10b**) gave the known exo acid **13a**, whose structure had already been established by X-ray crystallography,[9] the stereochemistry of the derivative **8** and its isomer **9** could be assigned unambiguously, as illustrated. In the ^{1}H-NMR spectra of each pair of compounds the resonances of the endo hydrogens on the functionalized three-membered ring were noted to be 0.12–0.25 ppm upfield from those of their exo counterparts, a result of shielding by the remote ring.[11a] Extending this, we assigned exo stereochemistry to the isomer with the higher field methyl group resonance ($\Delta\delta \sim 0.2$ ppm) in the sets **11a/11b** and **12a/12b**. It later proved useful to have noticed that the difference between the chemical shifts of the trans hydrogens in the carboxamido-substituted three-membered ring was much higher for endo isomers **9** and **10b** than for their exo isomers **8** and **10a** (examples: $\Delta\delta_{trans} = 0.8$ ppm for endo ester **10b**; $\Delta\delta_{trans} = 0.2$ ppm for exo ester **10a**).

Scheme II

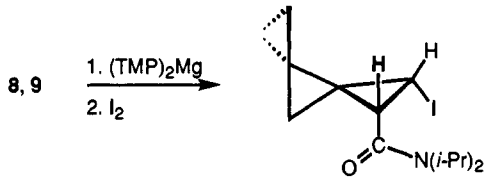


Treatment of a mixture of amides **8** and **9** with bis(2,2,6,6-tetramethylpiperidino)magnesium [(TMP)$_2$Mg] in THF followed by carboxylation and esterification with diazomethane (Scheme II) gave only one product, **14**. The ^{1}H-NMR spectrum of **14** made it clear that carboxylation had occurred on the already functionalized ring; the hydrogens (4H, δ 0.5–0.9 ppm) on the distant ring, as well as those on the central ring (2H, doublet pair, δ 1.46 and 1.97 ppm, $J = 5$ Hz), were intact. This was confirmed by the ^{13}C-DEPT spectrum,[12] which displayed a new methine resonance. The large coupling, $J = 8.4$ Hz, between the methine hydrogens thereof indicated their cis relationship on a cyclopropane ring.[11b] Complete proof of this was obtained when the amido–acid precursor of **14** was converted into bis(diisopropyl)-amide **15**; the number of signals in the ^{1}H- and ^{13}C-NMR spectra decreased in accord with the introduction of a plane of symmetry, an event possible only if **14** is cis. The notable downfield shift of the resonance of one C-7 proton from that of compound **8** ($\Delta\delta = 0.87$ ppm) is strongly indicative of exo geometry for the cis carbonyl substituents.

The mass balance in the conversion of the **8** and **9** mixture to **14** was high enough (>60%) to require that **14** derived from *both* **8** and **9**. Therefore, base-induced epimerization must have occurred at the α-carbon of one of them. Experiments with the pure isomers showed that endo triangulane **9** undergoes almost complete isomerization on treatment with (TMP)$_2$Mg to the exo isomer **8**. This must certainly proceed *via* metalation α to the carboxamido group. However, there was no indication of any formation of 1,1-dicarbonyl compounds when the reaction mixture was quenched with CO_2. It could be that such products would have decomposed (decarboxylation) or that the intermediate α-anion was protonated prior to carboxylation in favor of the β-anion. To probe this more deeply, the course of metalation was monitored by quenching aliquots from the reaction mixture [(TMP)$_2$Mg in THF] with methanol-*O-d*; deuteriation patterns were then analyzed by ^{1}H- and ^{2}H-NMR. We found that after 1-h reaction time at room temperature, 64% of the endo triangulane **9** was converted to the exo isomer **8** with 53% of the introduced deuterium α to the carbonyl group and 46% at the cis β position. A similar deuterium distribution was found in nonisomerized **9**. When the experiment was run starting with exo isomer **8**, 22% was converted to endo **9** after 15 min,[13] with more then 90% deuterium at the α position. Nonisomerized **8** contained 54% of the introduced deuterium at the α position and the rest at the β position. Finally, when reactions started with **8** *or* **9** were quenched with methanol-*O-d* after 1 h at reflux, *all* the product was the exo triangulane **8** and *all* the deuterium was found at the β position therein. In accord with these results, we found that treatment of the mixed triangulanes **8** and **9** with

(9) The calculated geometry of **8** fits well with the experimental data obtained from the X-ray structure of the corresponding triangulane carboxylic acid: Lukin, K. A.; Yufit, D. S. Unpublished results.
(10) Doyle, M. P.; Leusen, D.; Tamblyn, H. *Synthesis* **1981**, No. 10, 787.
(11) (a) Gunter, H. *NMR Spectroscopy*; Georg Thieme Verlag: Stuttgart, Germany, 1983; p 88. (b) *Ibid.* p 319.
(12) Derome, A. E. *Modern NMR Techniques for Chemistry and Research*; Pergamon: New York, 1987; pp 144–147.
(13) After 1 h reaction time the concentration of **9** was too low to obtain the deuterium content/distribution.

$(TMP)_2Mg$ followed by iodination gave iodide **16** as the only product. The structure of **16** followed from a comparison of aspects of its ^{1}H-NMR spectrum to those of **14**, noting in particular the large 8-Hz coupling constant in the CHI–$CH_{(amide)}$ doublet and the considerable 0.96 ppm downfield shift of the anti C-7 hydrogen resonance from that in **8**.



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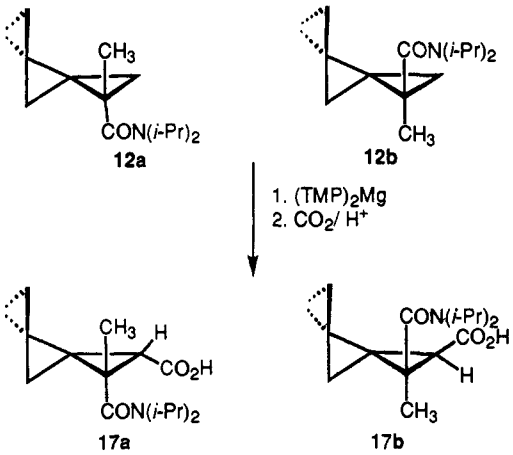
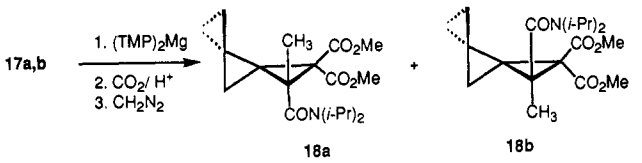
Clearly, the α-anion must be formed and reprotonated during the course of these reactions. The α-proton is more labile kinetically than the β-proton, but the equilibrium mixture of the various α- and β-anions that can be formed by $(TMP)_2Mg$ metalation of amides **8** and **9** favors decisively the intramolecularly chelated β-anion derived from **8**. Beak *et al.* demonstrated earlier that proximity effects can overcome inductive and conjugative effects so that β-anion formation in activated metalation of certain carbonyl compounds is favored *kinetically* over α-enolate formation.[14] *Now we can extend the extraordinary effects of remote activation to include a thermodynamic preference for a β-anion over an α-enolate.* In the case at hand, this is probably due not only to the favorable intramolecular complexation of the β-metal but also to the unfavorable high energy of the double bond exocyclic to a three-membered ring in the mesomeric structure of the α-enolate.[15]

In order to avoid the complications due to isomerizations α to the carboxamido group, we turned to the methyl-substituted triangulanes **12a** and **12b** for our further studies (see Scheme I). Experiments were carried out with the pure endo isomer **12b** or with a mixture of the exo and endo isomers, **12a/b**. (Getting **12a** pure was difficult and proved unnecessary as sufficient data about its behavior could be obtained using NMR subtraction procedures.) We found, as expected from our earlier results with their desmethyl counterparts, that metalation with $(TMP)_2Mg$ of amides **12a** and **12b** followed by carboxylation gave respectively **17a** and **17b**, the result of magnesiation on the same ring as the activating group. Comparison of the ^{1}H-NMR spectra of isomers **17a** and **17b** showed that in **17a** the CH_3 and $CHCO_2H$ resonances were both upfield shifted, indicating that the amide and acid functionalities are cis and exo in this isomer.



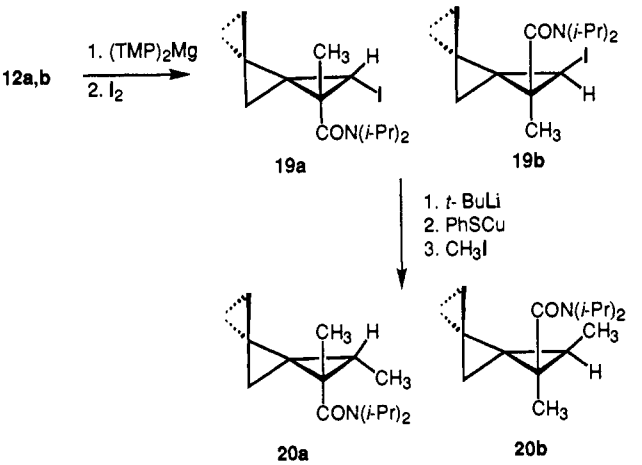
Treatment of the amide–acids **17a** and **17b** with $(TMP)_2Mg$ followed by carboxylation and esterification with diazomethane resulted in formation of the 1,1-diesters **18a** and **18b**, a product of anion formation α to the acid substituent rather than metalation in either unfunctionalized three-membered ring.



18a **18b**

To prevent this kind of same-ring metalation (and thus hopefully to observe remote-ring metalation), we introduced a methyl group cis and β to the activating carboxamido group in **12a,b**. Conveniently, we were able to use exactly the kind of reaction we were trying to prevent to achieve synthesis of these methylated compounds (Scheme III). Carboxamides **12a/12b** (and separately **12b** alone) were β-metalated and iodinated to give iodoamides **19a/19b**. These were converted to the corresponding (phenylthio)cuprates.[16] Methylation with iodomethane gave the *cis*-β-methyl compounds **20a** and **20b**. A comparison of their ^{1}H-NMR spectra showed that the doublet from the introduced methyl group is upfield in **20b** from that in **20a**, while the singlet from the other methyl group is upfield in **20a** from that in **20b**. As per the earlier discussion of shift versus stereochemistry, this is reasonable evidence for the assigned trans relationship of these methyls, as expected for intramolecular carboxamido stabilization of the intermediate metalated species.

Scheme III



Treatment of the triangulane amide mixture **20a/20b** with $(TMP)_2Mg$ followed by carboxylation and esterification with diazomethane gave **21** from **20a** and **22** from **20b** in 35–40% yield overall (Scheme IV).[17] These structural assignments are fully consistent with the ^{1}H-, ^{13}C-, and ^{13}C-DEPT-NMR data. The ^{1}H-NMR spectrum of compound **21** shows four undisturbed protons on the terminal three-membered ring and one on the amido-substituted three-membered ring. On the other hand, the doublet pair from the hydrogens at C-7 in starting amide **20a** was replaced with one singlet at 2.09 ppm in **21**. As no reaction was observed at C-7 with endo isomer **20b** (confirming the necessity of carboxamido group participation), we assign the syn configuration to the carboxyl group introduced onto **20a**. (Electrophilic substitution of stabilized cyclopropyl anions is known to proceed with retention of configuration.[8]) The ^{13}C- and ^{1}H-NMR spectra

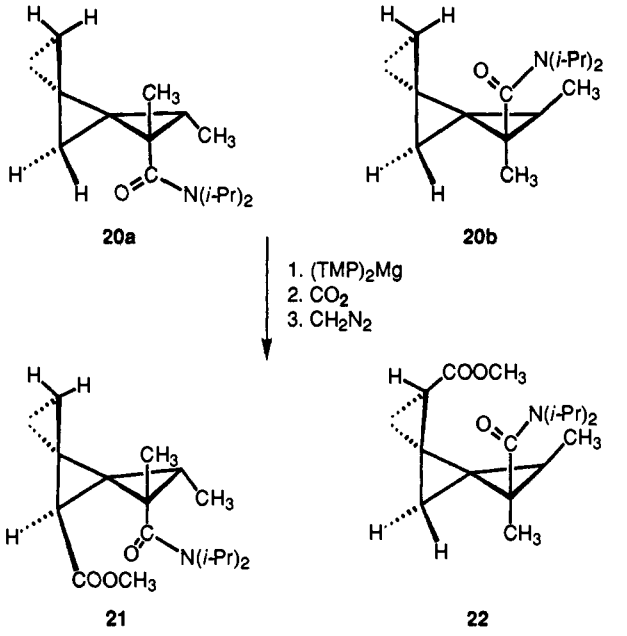
(14) Beak, P.; Hunter, J. E.; Young, M. J.; Wallin, A. *J. Am. Chem. Soc.* **1987**, *109*, 5403.

(15) Brickhouse, M. D.; Squires, R. R. *J. Phys. Org. Chem.* **1989**, *2*, 389–409.

(16) Piers, E.; Lau, C. K.; Nagakura, I. *Tetrahedron Lett.* **1976**, 3233–3236.

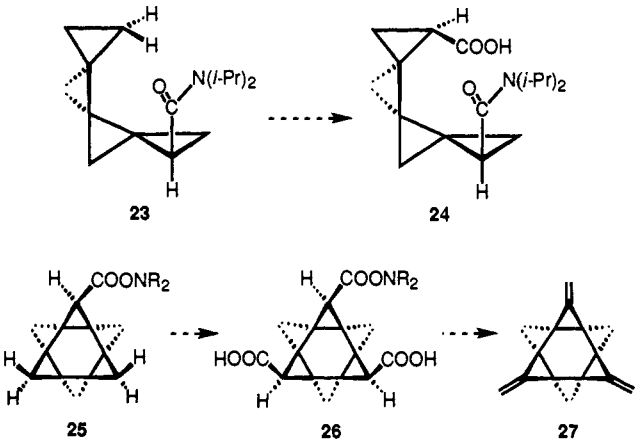
(17) Much of the starting materials remained unreacted under the conditions employed. As we only had a little material to work with, we did not look to optimize conditions. The results were sufficient to demonstrate the looked-for transannular activation.

Scheme IV



of **22** both reflected the loss of a high-field signal from an unfunctionalized three-membered ring. New signals characteristic of an AMX system and very similar to those in compounds **9** and **10b** appeared in the proton spectrum of **22**. Moreover, the large difference in chemical shifts of the trans hydrogens in this monosubstituted three-membered ring ($\Delta\delta_{trans}$ = 0.74 ppm) corresponds (*vide supra*) to endo positioning of the methoxycarbonyl group.

The formation of compounds **21** and **22** nicely proves stereospecific metalation of remote three-membered rings in carboxamido triangulanes as a result of carboxamido-directed activation of remote C–H bonds, *quod erat demonstrandum*. We are currently investigating new possibilities in triangulane synthesis associated with this discovery. We predict at this point that metalation of the [4]triangulane **23** would occur specifically to give, after carboxylation, **24**, a potential precursor of cyclic triangulanes, *e.g.* **25**. Looking further ahead, we predict polyfunctionalization of **25** to **26**, a suitable precursor for the tris(methylene)[6]triangulane **27**, a plausible parent of yet higher triangulane "networks".[2c]



Experimental Section

General. NMR spectra were run in $CDCl_3$: ^{1}H-NMR spectra at 400 MHz and referenced to chloroform (δ 7.24 ppm); ^{13}C-NMR spectra at 100.6 MHz and referenced to the central line of $CDCl_3$. Proton chemical shifts are reported to a precision of ±0.01 ppm; coupling constants, to a precision of 0.2 Hz. Carbon chemical shifts are given to a precision of ±0.1 ppm. EI low-resolution mass spectra were obtained at 70 eV using samples vaporized from a direct insertion probe. Merck silica gel 60 (230–400 mesh) was used for column chromatography. THF was distilled from sodium benzophenone ketyl. All metalations were carried out under argon in vacuum oven-dried glassware. "Evaporation of solvent under reduced pressure" and similar phrases refer to use of a rotary evaporator operated at house vacuum (*ca.* 50 Torr) unless otherwise specified. The evaporator bath was not heated above room temperature. Methylenespiropentane was obtained by the procedure of Arora and Binger.[18] $(TMP)_2Mg$ was prepared as previously described.[5]

General Procedure for Cyclopropanation of Methylenespiropentane with Ethyl Diazoacetate and Ethyl Diazopropionate. The procedure is derived from that of Doyle.[10] A solution of the appropriate diazo ester (35 mmol) in ether (15 mL) was added dropwise to a stirred solution of methylenespiropentane (2.4 g, 30 mmol) and dirhodium tetraacetate (0.1 g, 0.3 mmol) in ether (20 mL) at 20 °C. The first half was added at a rate of 6 mL/h; the second half, at 3 mL/h. After 10 min additional reaction time, the mixture was filtered through a small pad of silica gel. Simple vacuum distillation gave the triangulanes. A mixture of isomers **10a**/**10b** was obtained in 69% yield: bp 59–61 °C (2 mm). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found C, 72.47; H, 8.63. Pure endo and exo isomers were separated by column chromatography, eluting with ether/pentane (30:70). The endo isomer **10b** was eluted first.

***exo*-1-(Ethoxycarbonyl)dispiro[2.0.2.1]heptane (10a)**: ^{1}H-NMR δ 0.7 (m, 2 H), 0.88 (m, 2 H), 1.20 (dd, J = 4.3, 7.5 Hz, 1 H), 1.22 (t, J = 7.0 Hz, 3 H), 1.23 (d, J = 4.5 Hz, 1 H), 1.33 (d, J = 4.5 Hz, 1 H), 1.51 (t, J = 4.3 Hz, 1 H), 1.76 (dd J = 4.3, 7.5 Hz, 1 H), 4.20 ppm (m, 2 H); ^{13}C-NMR δ 5.7 (CH_2), 5.8 (CH_2), 12.1 (CH_2), 14.4 (2C, CH_2, CH_3) 15.0 (C), 19.8 (CH), 24.3 (C), 60.3 (CH_2), 173.6 ppm (CO).

***endo*-1-(Ethoxycarbonyl)dispiro[2.0.2.1]heptane (10b)**: ^{1}H-NMR δ 0.7–0.9 (m, 4 H), 1.19 (d, J = 4 Hz, 1 H), 1.20 (t, J = 7.0 Hz, 3 H), 1.27 (d, J = 4 Hz, 1 H), 1.36 (dd, J = 5, 6.5 Hz, 2 H), 2.03 (dd, J = 5, 6.5 Hz, 2 H), 4.2 ppm (m, 2 H); ^{13}C-NMR δ 4.0 (CH_2), 5.4 (CH_2), 12.2 (CH_2), 13.9 (C), 14.0 (CH_2), 14.2 (CH_3), 20.9 (CH), 22.72 (C), 60.1 (CH_2), 173.5 ppm (CO). A mixture of isomers **11a**/**11b** was obtained in 53% yield: bp 65–70 °C (2 mm). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.54; H, 8.59. The pure endo and exo isomers were separated by column chromatography, eluting with ether/pentane (30:70). The endo isomer **11b** was eluted first.

***exo*-1-(Ethoxycarbonyl)-*endo*-1-methyldispiro[2.0.2.1]heptane (11a)**: ^{1}H-NMR δ 0.65 (m, 1 H), 0.85 (m, 2 H), 0.89 (d, J = 3.8 Hz, 1 H), 0.96 (m, 1 H), 1.19 (s, 3 H) and superimposed a doublet (J = 4.5 Hz, 1 H), 1.24 (t, J = 7.0 Hz, 3 H), 1.30 (d, J = 4.5 Hz, 1 H), 1.74 (d, J = 3.8 Hz, 1 H), 4.13 ppm (m, 2 H); ^{13}C-NMR δ 4.4 (CH_2), 5.4 (CH_2), 13.2 (CH_2), 14.7 (CH_3), 15.0 (C), 17.0 (CH_2), 21.3 (CH_3), 25.9 (C), 28.5 (C), 60.6 (CH_2), 175.0 ppm (CO).

***endo*-1-(Ethoxycarbonyl)-*exo*-1-methyldispiro[2.0.2.1]heptane (11b)**: ^{1}H-NMR δ 0.7–0.9 (m, 4 H), 1.07 (d, J = 3.8 Hz, 1 H), 1.09 (d, J = 3.8 Hz, 1 H), 1.19 (d, J = 3.2 Hz, 1 H), 1.20 (t, J = 7 Hz, 3 H), 1.35 (s, 3 H), 1.61 (d, J = 3.2 Hz, 1 H), 4.02 ppm (m, 2 H); ^{13}C-NMR δ 4.6 (CH_2), 5.6 (CH_2), 10.9 (CH_2), 14.4 (CH_3), 15.6 (C), 17.9 (CH_2), 21.5 (CH_3), 24.8 (C), 29.4 (C), 60.5 (CH_2), 175.3 ppm (CO).

General Procedure for Conversion of Triangulane Esters into *N,N*-Diisopropyl Carboxamides. A solution of triangulane ester(s) (19 mmol) and KOH (1.14 g, 20 mmol) in water (9.6 mL) and ethanol (40 mL) was refluxed for 4–6 h. Most of the ethanol was then removed *in vacuo*. The remaining aqueous solution was extracted with ether (3 × 10 mL); the extract was discarded. The aqueous layer was cooled to 5 °C, acidified with 2 N HCl to pH 1–2, and extracted with ether (3 × 20 mL). The extract was dried ($MgSO_4$). Removal of the solvent *in vacuo* left the triangulane carboxylic acid(s) (~85%), which was (without purification) dissolved in thionyl chloride (5.9 g, 50 mmol) and CH_2Cl_2 (50 mL). The mixture was stirred for 3 h, and then the solvent and unreacted thionyl chloride were removed *in vacuo*. The crude triangulane acid chloride so obtained was dissolved in anhydrous 1,3-dioxane (12 mL). Diisopropylamine (4 mL) in dioxane (12 mL) was added. This mixture was stirred for 2 h and then poured into chilled water (75 mL). This was acidified to pH 1–2 with 1 N hydrochloric acid and extracted with ether. The extract was dried ($MgSO_4$). Removal of the solvent *in vacuo* left the triangulane diisopropyl carboxamides pure enough for further chemical transformations. Analytical samples were obtained using column chromatography, eluting with ether/pentane (30:70). A mixture of isomers **8**/**9** was obtained from esters **10a**/**10b**. Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47. Found: C, 75.59; H, 10.44.

(18) Arora, S.; Binger, P. *Synthesis* **1974**, 801.

***exo*-1-[(Diisopropylamino)carbonyl]dispiro[2.0.2.1]heptane (8)** was obtained from ester **10a** in 71% yield as a colorless oil: ^{1}H-NMR δ 0.63 (m, 1 H), 0.7 (m, 1 H), 0.88 (m, 2 H), 1.02 (dd, J = 7.4, 4.2 Hz, 1 H), 1.10 (d, J = 4.3 Hz, 1 H), 1.2 (d, J = 6.6 Hz, 6 H), 1.28 (d, J = 4.3 Hz, 1 H), 1.32 (m, 6 H), 1.72 (t, J = 4.3 Hz, 1 H), 1.87 (dd, J = 7.4, 4.3 Hz, 1 H), 3.7 (m, 1 H), 4.07 ppm (m, 1 H); ^{13}C-NMR δ 5.4 (2 C, CH_2), 11.1 (CH_2), 11.3 (CH_2), 14.1 (C), 20.8 (CH_3), 21.0 (CH_3), 21.3 (CH_3), 21.6 (CH), 21.9 (CH_3), 22.8 (C), 45.5 (CH), 47.4 (CH), 170.6 ppm (CO). ***endo*-1-[(Diisopropylamino)carbonyl]dispiro[2.0.2.1]heptane (9)** was obtained from ester **10b** in 73% yield as a colorless oil: ^{1}H-NMR δ 0.65–0.85 (m, 4 H), 1.16 (dd, J = 7.3, 4.1 Hz, 1 H), 1.18 (s, 2 H), 1.19–1.35 (m, 12 H), 1.56 (t, J = 4.1 Hz, 1 H), 2.17 (dd, J = 7.3, 4.1 Hz, 1 H), 3.7 (m, 1 H), 4.09 ppm (m, 1 H); ^{13}C-NMR δ 3.8 (CH_2), 5.3 (CH_2), 10.8 (CH_2), 12.0 (CH_2), 14.3 (C), 20.6 (br, CH_3), 20.7 (br, CH_3), 21.4 (br, CH_3), 21.5 (br, CH_3), 22.1 (CH), 29.7 (C), 45.6 (br, CH), 47.4 (br, CH), 170.2 ppm (CO). A mixture of isomers **12a/12b** was obtained from esters **11a/11b**. Anal. Calcd for $C_{15}H_{25}NO$: C, 76.54; H, 10.71. Found: C, 76.32; H, 10.64.

***exo*-1-[(Diisopropylamino)carbonyl]-*endo*-1-methyldispiro[2.0.2.1]-heptane (12a)** was obtained from ester **11a** in 69% yield as a colorless oil: ^{1}H-NMR δ 0.6 (m, 1 H), 0.61 (d, J = 4.4 Hz, 1 H), 0.79–0.92 (m, 3 H), 1.12 (d, J = 3.8 Hz, 1 H), 1.14 (s, 3 H) with 1.13–1.20 multiplet (6 H) superimposed, 1.31 (d, J = 4.1 Hz, 1 H) with 1.30–1.40 multiplet (6 H) superimposed, 1.45 (d, J = 3.8 Hz, 1 H), 3.24 (m, 1 H), 4.10 ppm (m, 1 H); ^{13}C-NMR δ 3.6 (CH_2), 4.6 (CH_2), 12.1 (CH_2), 13.0 (C), 18.1 (CH_2), 20.2 (CH_3), 20.8 (br, CH_3), 20.9 (br, CH_3), 21.0 (br, CH_3), 22.1 (br, CH_3), 24.3 (C), 27.7 (C), 45.5 (br, CH), 48.2 (br, CH), 172.3 ppm (CO).

***endo*-1-[(Diisopropylamino)carbonyl]-*exo*-1-methyldispiro[2.0.2.1]-heptane (12b)** was obtained from ester **11b** in 70% yield as a colorless oil: ^{1}H-NMR δ 0.6 (m, 2 H), 0.75 (m, 2 H), 0.79 (d, J = 4.2 Hz, 1 H), 0.94 (m, 2 H), 1.05 (d, J = 4.2 Hz, 1 H), 1.12–1.37 (m, 14 H), 1.38 (s, 3 H), 3.27 (m, 1 H), 4.09 ppm (m, 1 H); ^{13}C-NMR δ 5.3 (CH_2), 6.1 (CH_2), 10.7 (CH_2), 14.8 (C), 18.5 (CH), 19.5–21.3 (br, 5 C, CH_3), 26.0 (C), 27.1 (C), 45.7 (br, CH), 48.2 (br, CH), 171.9 ppm (CO).

General Procedure for Carboxylation of Carboxamido Triangulanes. Neat carboxamido triangulane (0.5 mmol) was added by syringe to 10 mL of a 0.33 M solution of $(TMP)_2Mg$ in THF under argon. The mixture was gently refluxed for 2 h and then cooled to −78 °C. CO_2 was bubbled through the solution for 20 min. The mixture was allowed to warm to room temperature, and the addition of CO_2 was discontinued. The solution was acidified to pH 1–2 with 0.2 N hydrochloric acid and extracted with ethyl acetate (3 × 15 mL). The extract was washed with 10% aqueous Na_2CO_3 (3 × 15 mL). The wash was collected and acidified with concentrated hydrochloric acid to pH 1–2 and extracted with ethyl acetate (3 × 15 mL). This extract was dried (Na_2SO_4), and the solvent was removed *in vacuo*. The crude acid(s) so obtained was purified by crystallization or converted directly into the methyl ester(s) by treatment with ethereal diazomethane.

***exo*-1-[(Diisopropylamino)carbonyl]-*exo*-2-(methoxycarbonyl)dispiro-[2.0.2.1]heptane (14)** was obtained from amides **8/9** in 61% yield as a colorless oil: ^{1}H-NMR δ 0.6–0.69 (m, 2 H), 0.84–0.91 (m, 2 H), 1.07 (d, J = 6.6 Hz, 3 H), 1.14 (d, J = 6.6 Hz, 3 H), 1.34 (d, J = 6.6 Hz, 3 H), 1.37 (d, J = 6.6 Hz, 3 H), 1.46 (d, J = 5.1 Hz, 1 H), 1.97 (d, J = 5.1 Hz, 1 H), 2.09 (d, J = 8.4 Hz, 1 H), 2.12 (d, J = 8.4 Hz, 1 H), 3.35 (m, 1 H), 3.64 (s, 3 H), 4.23 ppm (m, 1 H); ^{13}C-NMR δ 5.3 (CH_2), 5.6 (CH_2), 10.8 (CH_2), 14.08 (C), 20.4 (CH_3), 20.5 (2 C, CH_3), 21.2 (CH_3), 25.2 (CH), 26.3 (C), 27.6 (CH), 45.6 (CH), 48.4 (CH), 51.5 (CH_3), 166.1 (CO), 171.0 ppm (CO); MS m/e 279 (M^+).

A mixture of isomers **17a/17b** was obtained from amides **12a/12b** in 60% yield. Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.78; H, 9.02; N, 5.01. Found: C, 68.68; H, 8.72; N, 4.82.

***exo*-1-[(Diisopropylamino)carbonyl]-*endo*-1-methyldispiro[2.0.2.1]-heptane-*exo*-2-carboxylic acid (17a)**: ^{1}H-NMR δ 0.68 (m, 1 H), 0.88–0.97 (m, 3 H), 1.14 (d, J = 6.7 Hz, 3 H), 1.20–1.30 (m, 1 H) with 1.21 doublet (J = 6.7 Hz, 6 H) and 1.24 singlet (3 H) superimposed, 1.36 (br d, J = 6.7 Hz, 6 H), 1.80 (s, 1 H), 1.81 (d, J = 4.6 Hz, 1 H), 3.28 (m, 1 H), 4.05 ppm (m, 1 H); ^{13}C-NMR δ 4.3 (CH_2), 5.1 (CH_2), 11.8 (CH_2), 14.2 (C), 20.1 (CH_3), 20.2 (CH_3), 20.3 (CH_3), 20.3 (CH_3), 21.0 (CH_3), 32.0 (CH), 32.2 (C), 36.1 (CH), 46.0 (CH), 48.7 (CH), 169.3 (CO), 175.8 ppm (CO); MS m/e 279 (M^+).

***endo*-1-[(Diisopropylamino)carbonyl]-*exo*-1-methyldispiro[2.0.2.1]-heptane-*endo*-2-carboxylic acid (17b)** was obtained from amide **12b** in 58% yield: mp 148 °C; ^{1}H-NMR δ 0.62 (m, 1 H), 0.93 (m, 1 H), 1.04 (m, 1 H), 1.08 (d, J = 6.7 Hz, 3 H), 1.12 (d, J = 4.1 Hz, 1 H), 1.20 (d, J = 6.7 Hz, 3 H), 1.22–1.30 (m, 1 H) with 1.22 doublet (J = 4.1 Hz, 1 H) and 1.26 doublet (J = 6.7 Hz, 3 H) superimposed, 1.43 (s, 3 H), 2.0 (s, 1 H), 3.23 (m, 1 H), 4.08 ppm (m, 1 H); ^{13}C-NMR δ 3.5 (CH_2), 6.6 (CH_2), 10.8 (CH_2), 15.1 (C), 19.7 (CH_3), 20.3 (CH_3), 20.8 (CH_3), 21.5 (CH_3), 21.6 (CH_3), 32.4 (C), 33.9 (CH), 35.1 (C), 45.9 (CH), 48.7 (CH), 168.2 (CO), 176.8 ppm (CO); MS m/e 279 (M^+).

A mixture of isomers **18a/18b** was obtained from acids **17a/17b** in 69% yield. Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.32; N, 3.99. Found: C, 65.26; H, 8.25; N, 3.63.

2,2-Bis(methoxycarbonyl)-*exo*-1-[(diisopropylamino)carbonyl]-*endo*-1-methyldispiro[2.2.1]heptane (18a): ^{1}H-NMR δ 0.81–0.99 (m, 4 H), 1.07 (d, J = 6.6 Hz, 3 H), 1.18–1.22 (m, 4 H) with 1.19 singlet (3 H) superimposed, 1.38 (d, J = 6.6 Hz, 3 H), 1.40 (d, J = 6.6 Hz, 3 H), 2.10 (d, J = 4.9 Hz, 1 H), 3.38 (m, 1 H), 3.68 (s, 3 H), 3.73 (s, 3 H), 4.31 ppm (m, 1 H); ^{13}C-NMR δ 4.0 (CH_2), 5.3 (CH_2), 11.7 (CH_2), 14.7 (C), 17.3 (CH_3), 20.1 (CH_3), 20.2 (CH_3), 20.3 (CH_3), 21.6 (CH_3), 34.6 (C), 38.0 (C), 42.5 (C), 45.8 (CH), 48.2 (CH), 52.1 (CH_3), 52.3 (CH_3), 167.2 (CO), 168.1 (CO), 168.5 ppm (CO). MS m/e 351 (M^+).

2,2-Bis(methoxycarbonyl)-*endo*-1-[(diisopropylamino)carbonyl]-*exo*-1-methyldispiro[2.0.2.1]heptane (18b) was obtained from acid **17b** in 66% yield: mp 127–128 °C; ^{1}H-NMR δ 0.68 (m, 2 H), 1.02 (d, J = 6.6 Hz, 3 H), 1.08 (m, 1 H), 1.20 (d, J = 6.6 Hz, 3 H), 1.23 (d, J = 4.4 Hz, 1 H), 1.32 (d, J = 6.6 Hz, 3 H), 1.36 (d, J = 6.6 Hz, 3 H), 1.37 (s, 3 H), 1.4 (m, 1 H), 1.49 (d, J = 4.4 Hz, 1 H), 3.23 (m, 1 H), 3.61 (s, 3 H), 3.78 (s, 3 H), 4.42 ppm (m, 1 H); ^{13}C-NMR δ 3.7 (CH_2), 7.0 (CH_2), 10.3 (CH_2), 15.2 (C), 19.3 (CH_3), 19.8 (CH_3), 20.1 (CH_3), 20.2 (CH_3), 21.4 (CH_3), 35.6 (C), 38.0 (C), 42.1 (C), 45.6 (CH), 48.4 (CH), 51.9 (CH_3), 52.4 (CH_3), 167.1 (CO), 167.5 (CO), 168.3 ppm (CO); MS m/e 351 (M^+).

A mixture of isomers **21/22** was obtained from the mixture of isomeric amides **20a/20b** in 41% yield. Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51. Found: C, 70.39; H, 9.10.

***exo*-1-[(Diisopropylamino)carbonyl]-*endo*-1-*exo*-2-dimethyl-*syn*-7-(methoxycarbonyl)dispiro[2.0.2.1]heptane (21)**: ^{1}H-NMR δ 0.58 (m, 1 H), 0.9 (m, 2 H), 0.95 (q, J = 6.2 Hz, 1 H), 1.09 (d, J = 6.2 Hz, 3 H), 1.13 (m, 1 H), 1.19 (s, 3 H), 1.20–1.35 (m, 12 H), 2.09 (s, 1 H), 3.23 (m, 1 H), 3.68 (s, 3 H), 4.23 ppm (m, 1 H); ^{13}C-NMR δ 4.1 (CH_2), 5.1 (CH_2), 13.0 (CH_3), 19.4 (C), 19.6 (CH_3), 20.0 (CH_3), 20.2 (CH_3), 20.6 (CH_3), 21.4 (CH_3), 24.0 (CH), 24.1 (CH), 31.5 (C), 34.9 (C), 45.7 (CH), 48.5 (CH), 51.4 (CH_3), 169.4 (CO), 173.5 ppm (CO); MS m/e 307 (M^+).

***endo*-1-[(Diisopropylamino)carbonyl]-*exo*-1-*endo*-2-dimethyl-*endo*-5-(methoxycarbonyl)dispiro[2.0.2.1]heptane (22)** was obtained from amide **20b** in 35% yield: mp 87–88 °C; ^{1}H-NMR δ 0.87 (d, J = 3.9 Hz, 1 H), 1.12 (dd, J = 7.4, 3.9 Hz, 1 H), 1.14 (d, J = 6.2 Hz, 3 H), 1.20 (d, J = 6.6 Hz, 3 H), 1.21 (d, J = 6.6 Hz, 3 H), 1.21–1.29 (m, 1 H) with 1.26 (d, J = 3.9 Hz, 1 H), 1.31 (s, 3 H), 1.33 (d, J = 6.6 Hz, 3 H), 1.34 (d, J = 6.6 Hz, 1 H), 1.58 (t, J = 4.2 Hz, 1 H), 2.32 (dd, J = 4.5, 7.4 Hz, 1 H), 3.23 (m, 1 H), 3.73 (s, 3 H), 4.32 ppm (m, 1 H); ^{13}C-NMR δ 11.9 (CH_2), 12.0 (CH_2), 13.1 (CH_3), 20.4 (CH_3), 20.9 (CH_3), 21.2 (CH), 21.7 (CH_3), 22.1 (CH_3), 22.6 (CH_3), 23.7 (C), 26.5 (CH), 28.4 (C), 30.42 (C), 45.3 (CH), 48.3 (CH), 51.4 (CH_3), 169.8 (CO), 172.9 ppm (CO); MS m/e 307 (M^+).

***exo,exo*-1,2-Bis[(diisopropylamino)carbonyl]dispiro[2.0.2.1]heptane (15)** was prepared from acid **14a** in 64% yield according to the procedure described above for the preparation of **8**, **9**, and **12**: mp 135 °C; ^{1}H-NMR δ 0.64 (m, 2 H), 0.89 (m, 2 H), 1.18 (d, J = 6.6 Hz, 12 H), 1.33 (d, J = 6.6 Hz, 6 H), 1.36 (d, J = 6.6 Hz, 6 H), 1.69 (br s, 2 H), 2.04 (br s, 2 H), 3.58 (m, 2 H), 4.11 ppm (m, 2 H); ^{13}C-NMR δ 5.4 s (2 C, CH_2), 10.3 (CH_2), 13.7 (C), 20.5 (4 C, CH_3), 20.9 (2 C, CH_3), 20.9 (2 C, CH_3), 21.7 (C), 26.2 (2 C, CH), 45.4 (2 C, CH), 47.6 (2 C, CH), 167.7 ppm (2 C, CO); MS m/e 349 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{36}N_2O_2$: C, 72.36; H, 10.41; N, 8.04. Found: C, 72.36; H, 10.13; N, 7.90.

General Procedure for Iodination of Carboxamido Triangulanes 8, 9, and 12. Neat carboxamido triangulane (0.5 mmol) was added via syringe to 10 mL of a 0.33 M solution of $(TMP)_2Mg$ in THF under argon. The mixture was refluxed gently for 2 h, cooled to −10 °C, and slowly cannulated into a solution of iodine (0.9 g, 7.1 mmol) in THF (3 mL) cooled to −50 °C. The mixture was allowed to warm to room temperature, and then poured into water (30 mL). The whole was extracted with $CHCl_3$ (3 × 15 mL). The extract was washed with saturated aqueous Na_2SO_3 (3 × 15 mL) and dried (Na_2SO_4). Removal of the solvent *in vacuo*, followed by column chromatography, eluting with ether/pentane (25:75) gave the iodides.

***exo*-1-[(Diisopropylamino)carbonyl]-*exo*-2-iododispiro[2.0.2.1]-heptane (16)** was obtained from **8/9** in 48% yield as a colorless oil: ^{1}H-

NMR δ 0.52–0.63 (m, 2 H), 0.75–0.81 (m, 1 H), 0.85–0.91 (m, 1 H), 1.11 (d, J = 6.6 Hz, 3 H), 1.12 (d, J = 4.8 Hz, 1 H), 1.30 (d, J = 6.6 Hz, 3 H), 1.35 (d, J = 6.6 Hz, 3 H), 1.38 (d, J = 6.6 Hz, 3 H), 1.98 (d, J = 7.7 Hz, 1 H), 2.06 (d, J = 4.8 Hz, 1 H), 3.04 (d, J = 7.7 Hz, 1 H), 3.40 (m, 1 H), 4.21 ppm (m, 1 H); ^{13}C-NMR δ –2.8 (CHI), 5.4 (CH_2), 6.0 (CH_2), 15.7 (CH_2), 17.9 (C), 20.7 (CH_3), 21.0 (CH_3), 21.2 (CH_3), 21.3 (CH_3), 24.3 (CH), 27.2 (C), 45.9 (CH), 48.4 (CH), 167.7 ppm (CO); MS m/e 347 (M^+).

A mixture of isomers **19a/19b** was obtained from amides **12a/12b** in 67% yield. Anal. Calcd for $C_{15}H_{24}INO$: C, 49.87; H, 6.70; N, 3.87. Found: C, 50.17; H, 6.83; N, 3.79.

***exo*-1-[(Diisopropylamino)carbonyl]-*exo*-2-iodo-*endo*-1-methyldispiro-[2.0.2.1]heptane (19a)**: ^{1}H-NMR δ 0.45 (m, 1 H), 0.73–0.92 (m, 3 H), 0.96 (d, J = 4.3 Hz, 1 H), 1.19 (d, J = 6.6 Hz, 3 H), 1.20 (s, 3 H), 1.35 (d, J = 6.6 Hz, 3 H), 1.38 (d, J = 6.6 Hz, 6 H), 2.02 (br d, J = 4.3 Hz, 1 H), 2.76 (s, 1 H), 3.28 (m, 1 H), 4.09 ppm (m, 1 H); ^{13}C-NMR δ 4.26 (CH), 4.62 (CH_2), 4.96 (CH_2), 17.21 (CH_2), 17.74 (C), 19.71 (CH_3), 20.37 (CH_3), 21.81 (CH_3), 21.95 (CH_3), 22.07 (CH_3), 31.53 (C), 32.23 (C), 45.98 (CH), 48.73 (CH), 170.51 (CO); MS m/e 361 (M^+).

***endo*-1-[(Diisopropylamino)carbonyl]-*endo*-2-iodo-*exo*-1-methyldispiro-[2.0.2.1]heptane (19b)** was obtained from amide **12b** in 71% yield: mp 99–100 °C; ^{1}H-NMR δ 0.54 (m, 1 H), 1.15 (m, 1 H), 1.18 (d, J = 3.7 Hz, 1 H), 1.25–1.29 (m, 3 H), 1.31 (d, J = 3.7 Hz, 1 H), 1.35–1.49 (m, 12 H), 1.50 (s, 3 H), 3.10 (s, 1 H), 3.34 (m, 1 H), 4.20 ppm (m, 1 H); ^{13}C-NMR δ 0.99 (CH_2), 6.98 (CH), 6.99 (CH_2), 13.12 (CH_2), 19.93 (C), 20.32 (br, CH_3), 20.52 (br, CH_3), 21.83 (CH_3), 21.91 (br, CH_3), 22.25 (br, CH_3), 29.13 (C), 31.62 (C), 45.87 (br, CH), 49.05 (br, CH), 169.61 ppm (CO); MS m/e 361 (M^+).

1-[(Diisopropylamino)carbonyl]-1,2-dimethyldispiro[2.0.2.1]heptanes (20a/20b). *tert*-Butyllithium (1.25 mmol, 17 N solution in pentane) was added dropwise to a solution of iodides **19a/19b** (184 mg, 0.5 mmol) in THF (5 mL) cooled to –78 °C. The reaction mixture was stirred for 5 min and cannulated into a slurry of (phenylthio)copper (100 mg, 0.55 mmol) in THF (5 mL) cooled to –78 °C. Iodomethane (0.5 mL) was added after 15 min of stirring. The mixture was allowed to warm to room temperature, poured into water (25 mL), and extracted with $CHCl_3$ (3 × 15 mL). The extract was dried (Na_2SO_4). The solvent was evaporated *in vacuo*. Compounds **20a/20b** were purified by column chromatography, eluting with ether/pentane (30:70).

***exo*-1-[(Diisopropylamino)carbonyl]-*endo*-1-*exo*-2-dimethyldispiro-[2.0.2.1]heptane (20a)**: ^{1}H-NMR δ 0.52 (m, 1 H), 0.74–0.82 (m, 3 H), 1.09 (d, J = 6.2 Hz, 3 H), 1.12 (s, 3 H), 1.15–1.25 (m, 8 H), 1.28–1.4 (m, 7 H), 3.25 (m, 1 H), 4.25 ppm (m, 1 H); ^{13}C-NMR δ 3.8 (CH_2), 4.6 (CH_2), 9.6 (CH_2), 13.6 (C), 14.1 (CH_3), 20.2 (CH_3), 20.4 (br, CH_3), 20.8 (br, CH_3), 21.9 (br, CH_3), 22.1 (br, CH_3), 23.5 (CH), 28.0 (C), 30.4 (C), 45.6 (CH), 48.1 (CH), 171.6 ppm (CO); MS m/e 249 (M^+).

***endo*-1-[(Diisopropylamino)carbonyl]-*exo*-1-*endo*-2-dimethyldispiro-[2.0.2.1]heptane (20b)** was obtained from iodide **19b** in 64% yield: ^{1}H-NMR δ 0.63 (m, 1 H), 0.81 (m, 1 H), 0.87 (d, J = 3.4 Hz, 1 H), 0.97 (d, J = 6.3 Hz, 3 H), 1.02 (m, 1 H), 1.13 (d, J = 3.8 Hz, 1 H), 1.18–1.25 (m, 8 H), 1.29–1.39 (m, 6 H) with 1.33 singlet (3 H) superimposed, 3.24 (m, 1 H), 4.28 ppm (m, 1 H); ^{13}C-NMR δ 3.3 (CH_2), 6.4 (CH_2), 11.5 (CH_2), 12.9 (CH_3), 14.3 (C), 20.4 (br, CH_3), 20.6 (br, CH_3), 21.7 (br, CH_3), 21.75 (CH_3), 22.1 (br, CH_3), 26.5 (CH), 28.1 (C), 29.7 (C), 45.4 (br, CH), 48.4 (br, CH), 170.9 ppm (CO); MS m/e 249 (M^+).

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