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A Tandem Cycloaddition Protocol for the Controlled Synthesis of [*n*]Ladderanes: New Rods and Spacers

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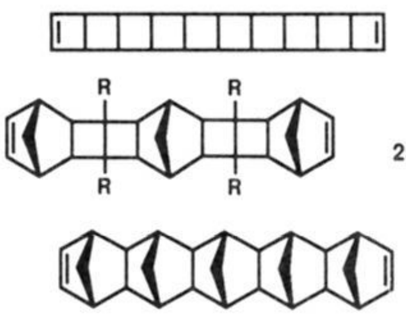
As the complexity and specificity of supramolecular structures continue to grow, so the need for new structural elements in molecular design becomes more acute. In the arena of spacer molecules, there are now a number of alternative types available,[1,2] including the binane class which we described some years ago.[2a] These and related polyalicyclic systems form rigid molecular racks (molracs)[3] which have proved to be versatile spacer molecules, finding wide application in the study of energy transfer[4] and also as templates for the control of polymerization.[5] As a further extension of the molrac concept, we now report on the synthesis of a new range of rigid rods based on the [*n*]ladderanes.[6]

The individual topology of *exo,exo*-fused [*n*]ladderanes is revealed by molecular modeling, where the straightness of their alicyclic framework sets them aside from the curved binanes and [*n*]polynorbornanes. This is apparent in Figure 1, which shows minimum energy configurations[11] for the three protype molracs: [10]ladderane (**1**), the 10σ binane **2a**, and [5]polynorbornane (**3**). The curved nature of binane spacers is well illustrated in the recently reported X-ray structure for a "ball and chain" Buckminsterfullerene[12] and is completely in agreement with X-ray data obtained from the 10σ binane **2b**.[13] X-ray structures for [4]ladderane **10**[13] and [5]ladderane **16** (Figure 2) confirm the rodlike corrugated backbone which fully accords with the modeling predictions for [*n*]ladderanes.



[10]ladderane
1

10σ binane
2a R=H; **2b** R=CO_2Me

[5]polynorbornane
3

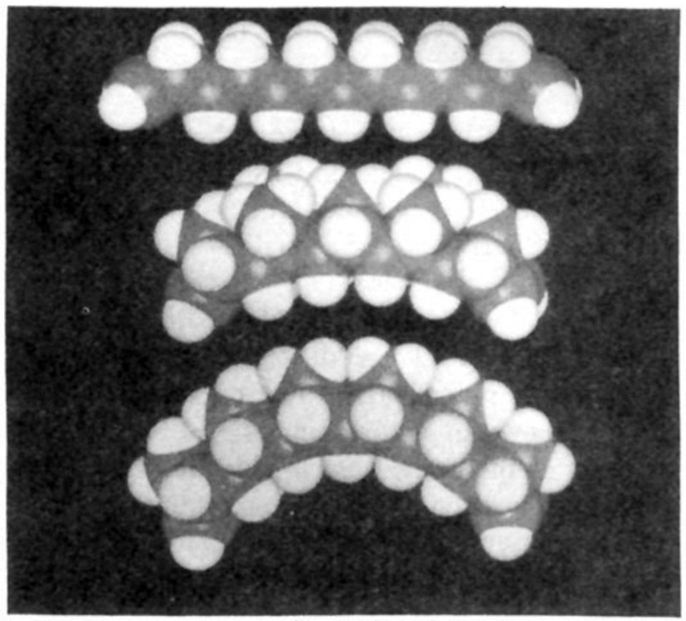
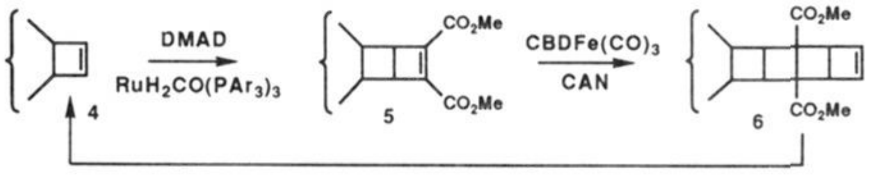


Figure 1. Minimum energy configurations for spacer molecules (a, top) [10]ladderane (**1**), (b, middle) 10σbinane (**2a**), and (c, bottom) [5]-polynorbornene (**3**).

Our approach to the synthesis of these rodlike [*n*]ladderanes required a stereocontrolled assembly which ensured *exo,exo*-fusion of the cyclobutane framework. This was achieved using the tandem cycloaddition protocol shown below, whereby archetype [*n*]ladderane **4** is extended by one cyclobutane ring in the [$2\pi + 2\pi$] cycloaddition step to form **5** and by two cyclobutane rings by [$4\pi + 2\pi$] cycloaddition of cyclobutadiene (CBD) to form **6**.[14]



This protocol provides a complete range of rods differing in length by 1.30 ± 0.01 Å (cf. [2]staffanes, 4.28 Å),[1b] which allows fine tuning in the construction of bifunctionalized spacer molecules.

Thus the norbornane-fused cyclobutene 3,4-diester **7**[16] (Scheme 1) is reacted (0 °C, THF) with CBD, generated *in situ* by CAN oxidation of the CBDFe(CO)$_3$ complex.[18] This reaction is both facially specific and highly stereoselective in yielding a 9:1 mixture of adducts **8** and **9**.[19] The major Alder adduct **8** has the olefinic resonances at δ 6.23 owing to shielding by the juxtaposed ester carbonyls; the minor isomer **9** lacking this shielding occurs at δ

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(1) Staffanes and rodanes: (a) Kaszynski, P.; McMurdie, N. D.; Michl, J. *J. Am. Chem. Soc.* **1992**, *114*, 601–620. (b) Zimmerman, H. E.; King, R. K.; Meinhardt, M. B. *J. Org. Chem.* **1992**, *57*, 5484–5492. (c) Butterfield, K.; Thomas, E. J. *Synlett* **1993**, 411–412. Aromatics and heteroaromatics: (d) Cozzi, F.; Cinquini, M.; Annuziata, R.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 5330–5331. (e) Rebek, J.; Marshall, L.; Wolak, R.; Parris, K.; Killoran, M.; Askew, B.; Nemeth, D.; Islam, N. *J. Am. Chem. Soc.* **1985**, *107*, 7476–7481. Porphyrins: (f) Giraudeau, A.; Gisselbrecht, J. P.; Gross, M.; Weiss, J. *J. Chem. Soc., Chem. Commun.* **1993**, 1103–1105.

(2) Molracs: (a) Warrener, R. N.; Pitt, I. G.; Butler, D. N. *J. Chem. Soc., Chem. Commun.* **1983**, 1340–1342; (b) Warrener, R. N.; Groundwater, P.; Pitt, I. G.; Butler, D. N.; Russell, R. A. *Tetrahedron* Lett. **1991**, *32*, 1885–1888.

(3) Warrener, R. N. *Chem. Aust.* **1992**, *59*, 578–581.

(4) (a) Paddon-Row, M. N.; Verhoeven, J. W. *New J. Chem.* **1991**, *15*, 107–116. (b) Golka, A.; Keyte, P. J.; Paddon-Row, M. N. *Tetrahedron* **1992**, *48*, 7663–7678.

(5) Feldman, K. S.; Bobo, J. S.; Tewalt, G. L. *J. Org. Chem.* **1992**, *57*, 4573–4574.

(6) Smaller [*n*]ladderanes ($n \leq 4$) have been prepared by cycloadditions involving cyclobutadiene cycloaddition;[7] higher order [*n*]ladderanes ($n \leq 7$) have been obtained by oligomerization of cyclobutadiene 1,2-diester.[8] Fusion of ladderanes to norboranes has also been reported.[9,10] Almost without exception, these products do not possess the *exo,exo*-stereochemistry required in rod formation.

(7) Criegee, R. *Angnew. Chem., Int. Ed. Engl.* **1962**, *1*, 519–527. Askana, R.; Wieduwilt, M. *Chem. Ber.* **1976**, *109*, 1887–1897.

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(9) Mehta, G.; Viswanath, M. B.; Nethaji, M.; Venkatesan, K. *J. Chem. Soc., Chem. Commun.* **1992**, 82–84.

(10) *Inter alia*: Sket, B.; Zupan, M. *Tetrahedron* **1989**, *45*, 6741–6748. Sket, B.; Zupancic, N.; Zupan, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1287–1291. Bryce-Smith, D.; Gilbert, A.; Orger, B. H.; Twitchert, P. J. *J. Chem. Soc., Perkin Trans. 1* **1978**, 232–243.

(11) Biosym, Insight II, Discover. This force field treatment tends to overestimate the curvature.

(12) Khan, S. I.; Oliver, A. M.; Paddon-Row, M. N.; Rubin, Y. *J. Am. Chem. Soc.* **1993**, *115*, 4919–4920.

(13) The X-ray structure of the 10 σ binane tetraester **2b** and [4]ladderane **10** are included in the supplementary material.

(14) This synthetic protocol is based directly on our acetylene stacking algorithm.[15]

(15) Warrener, R. N.; Pitt, I. G.; Weerasuria, K. D. V.; Russell, R. A. *Aust.J. Chem.* **1992**, *45*, 155–178. Warrener, R. N. In *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI Press Inc.: Greenwich, CT, 1992; Vol. 2, pp 143–205.

(16) Prepared by selective hydrogenation (10% Pd/C, EtAc; 10–15 °C) of Smith's diester.[17]

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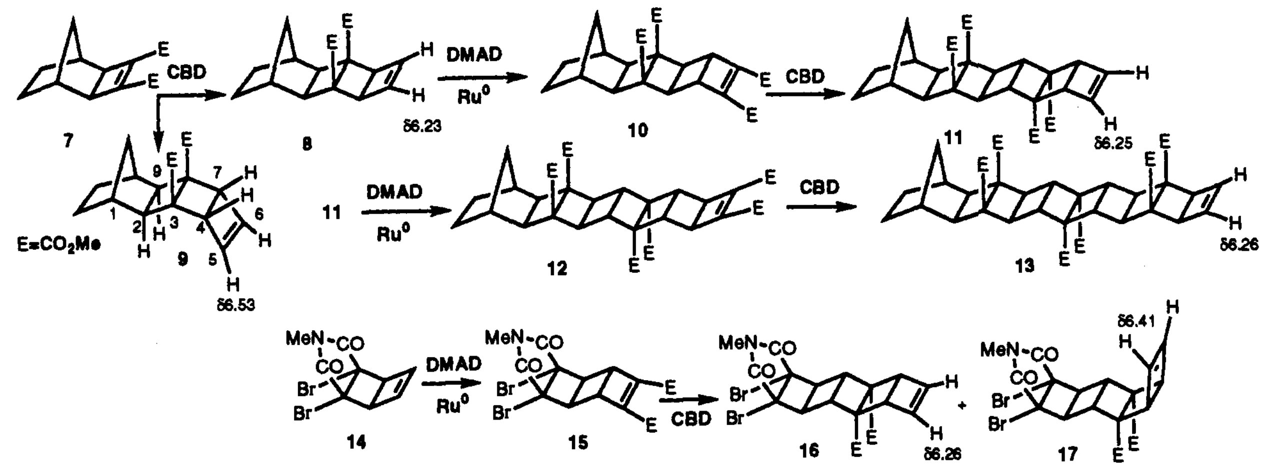
Scheme 1



6.53. This chemical shift difference is used as an NMR probe for stereochemical assignment in this series.

The major isomer **8** is reacted with excess DMAD (5 equiv) in the presence of $RuH_2CO(PAr_3)_3$ (Ar = *p*-fluorophenyl) (0.25 equiv) at 50 °C in benzene for 5 days to produce the [$\pi2 + \pi2$] cycloaddition product **10**, mp 162–163 °C, in 52% yield. This Ru^0-catalyzed [$2\pi + 2\pi$] cycloaddition of DMAD to a cyclobutene π-bond is without precedent.[20] The crystal structure of [5]-ladderane **16**, shown in Figure 2, indicates that *exo*-specificity occurs in each of the tandem cycloaddition processes.

Continued application of the tandem sequence to cyclobutene diester **10** yields in turn: [6]ladderane **11**, mp 164–165 °C, 50% yield; [7]ladderane **12**, mp 176–177 °C, 61% yield; [9]ladderane **13**, mp 180–182 °C, 77% yield. Essentially none of the anti-Alder isomer (ratio > 10:1) was detected in the reactions leading to **11** or **13**. The *exo*-stereochemistry was supported by vinylic proton chemical shifts in **11** of δ 6.25 and in **13** of δ 6.26.

As part of a program to prepare key spacer units as building blocks,[3] the dibromo compound **16** was identified as a target [5]ladderane.[22] It was produced by subjecting the known bicyclo-[2.2.0]hexene **14**[23] to a single tandem cycle. The cyclobutene **15**, mp 162–163 °C, was produced from **14** by treatment with DMAD/Ru^0 (benzene, 50 °C, 4 days) in 52% yield. Cycloaddition of CBD onto **15** yields a 5:1 mixture of 1:1 adducts:major isomer **16**, mp 163–164 °C, 38% yield, vinylic proton resonance at δ 6.26; minor isomer **17**, 8% yield, vinylic proton resonance at δ 6.41. The X-ray crystal structure of [5]ladderane **16** not only confirms the *exo*-stereochemistry of the products **15** and **16** but also allows the stereochemistry of the starting material **14** to be deduced.

End-functionalization of the [*n*]ladderane can be achieved at any stage of the elongation procedure. This is illustrated both by the conversion of [3]ladderane **8** to the pyridazine **18** (mp 184–185 °C, 50% yield) by treatment with 3,6-di(2′-pyridyl)-*s*-tetrazine[24] followed by dehydrogenation (DDQ) and by the conversion of the [4]ladderane **10** to an 8:1 mixture of cycloadducts **19** (mp 160–161 °C) and **20** (mp 165–167 °C)[25] by treatment with cyclopentadiene ($CDCl_3$, 60 °C, 3 h, 79% yield).

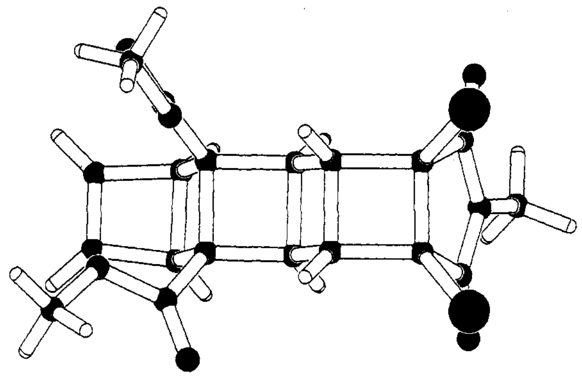
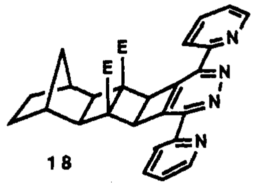
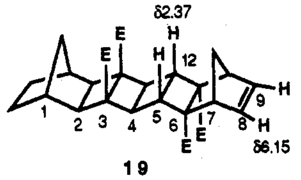


Figure 2. Pluton diagrams based on X-ray structure analysis of [5]-ladderane (**16**).



18



19

In conclusion, it has been shown that serial application of CBD and DMAD/Ru^0 cycloadditions can form *exo,exo*-fused polycyclobutanes with a range of cyclobutenoid starting materials.

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Supplementary Material Available: Tables of bond lengths and bond angles and X-ray structure data for **2b**, **10**, and **16**; ^1H NMR and ^{13}C NMR spectra for all new compounds (38 pages) listing of observed and calculated structure factors (25 pages). This material is contained in many 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.

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(19) The mixture was separated by radial chromatography (silica, 10% EtAc in hexane). Compound **8** was recrystallized from hexane (−196 °C) and isolated as colorless plate, mp 75–76 °C; compound **9** remained oily. All new compounds were characterized by CH analysis (±0.4%) or accurate mass.

(20) This reaction has been applied previously only to norbornenyl π-bonds.[2a,b,21]

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(22) Debromination (Zn/Ag couple) yields cyclobutenomaleimides; these are active dienophiles which can be trapped by a variety of dienes.[23]

(23) (a) Pitt, I. G.; Warrener, R. N.; Russell, R. A. *Aust. J. Chem.* **1991**, *44*, 1275–1292. (b) Pitt, I. G.; Russell, R. A.; Warrener, R. N. *J. Am. Chem. Soc.* **1985**, *107*, 7176–7178.

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(25) Butler, D. N.; Russell, R. A.; Waring, R. B.; Warrener, R. N. *Aust. J. Chem.* **1984**, *37*, 1293–1302.