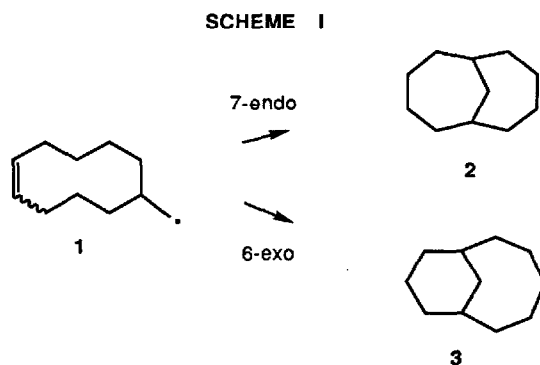# TEN-MEMBERED RING TEMPLATES FOR STEREOSELECTIVE RADICAL CYCLIZATIONS

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Abstract. Transannular cyclization of the radicals derived from cis- and trans-6-iodomethylcyclodecene both lead to the regio- and stereoselective formation of cis-bicyclo[5.3.1]undecane, an important structural feature of the taxane diterpenes. The ratio of cyclization to reduction of the cyclodec-6-enylmethyl radical depends critically on the alkene geometry.
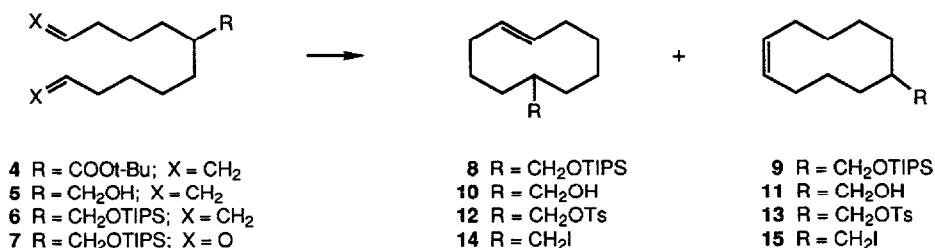
The conformational biases of medium rings can lead to valuable templates for stereoselective carbon-carbon bond formation.[3] We have recently demonstrated that the cyclization of suitably substituted mono- and di-substituted cyclooctadienes leads to the stereoselective formation of cis-syn-cis triquinanes and trans-bicyclo[6.3.0]undecane ring systems, respectively.[4] Transannular addition of a 6-cyclodecenylmethyl radical, 1 (Scheme I), could in principle lead to the formation of either bicyclo[4.4.1]undecane, 2, or bicyclo[5.3.1]undecane, 3, which are integral structural features of the ingenane[5] and taxane[6] diterpenes, respectively. We report herein that the transannular cyclization of the radicals derived from cis- and trans-6-iodomethylcyclodecene both lead to the regio- and stereoselective formation of cis-bicyclo[5.3.1]undecane,[7] and that the ratio of cyclization to reduction, i.e., formation of 6-methyl-cyclodecene, observed in the reaction depends critically on the alkene geometry.


SCHEME I

To determine the effect of the ten-membered ring template and the alkene geometry on the regiochemical and stereochemical (cis or trans intrabridgehead stereochemistry) outcome of the transannular reaction, the cis- and trans- 6-iodomethyl-cyclodecenes were prepared as outlined in Scheme II. Alkylation of tert-butyl acetate[8] with 4-pentenyl iodide (LDA, THF, -78°C, 62%) led to the formation of t-butyl 6-heptenoate, which, on alkylation with 5-hexenyl iodide (LDA, THF, -78°C, 46%), gave 4. Reduction (LAH, Et$_2$O, 25°C), followed by protection as the tri-isopropylsilyl ether (tri-isopropylsilyl triflate, Et$_3$N, CH$_2$Cl$_2$,

25°C)[9] gave **6** in 91% yield from **4**. Reaction of **6** with ozone (-78°C, 1:1 CH$_2$Cl$_2$:MeOH, Me$_2$S workup) provided the dialdehyde **7** in 78% yield, which was added slowly (0.03 mmol/hour) to a solution of Mc-Murry's reagent (Zn-Cu, TiCl$_3$, dimethoxyethane, 86%)[10] at reflux, to give the desired alkenes **8** and **9** in a ratio of 1.7:1, which could be separated by flash chromatography using silver nitrate-impregnated silica gel. Desilylation (nBu$_4$NF, THF, 78% for both isomers),[11] followed by tosylation [TsCl, DMAP, Et$_3$N, CH$_2$Cl$_2$, 76% (cis), 60% (trans)] and displacement with iodide [NaI, acetone reflux, 59% (cis), 88% (trans)] resulted in the formation of radical cyclization substrates **14** and **15,** from **8** and **9**, respectively.

<div align="center">

SCHEME   II

</div>

4 R = COOt-Bu; X = CH$_2$	**8** R = CH$_2$OTIPS	**9** R = CH$_2$OTIPS
5 R = CH$_2$OH; X = CH$_2$	**10** R = CH$_2$OH	**11** R = CH$_2$OH
6 R = CH$_2$OTIPS; X = CH$_2$	**12** R = CH$_2$OTs	**13** R = CH$_2$OTs
7 R = CH$_2$OTIPS; X = O	**14** R = CH$_2$I	**15** R = CH$_2$I

Treatment of the isomeric cyclodecenyl methyl iodides with tributyltin hydride[12] [1.1 equiv (n-Bu)$_3$SnH, 6 mM in benzene] led to the results which are summarized in the Table. While the ratio of cyclization to reduction with **14** was 2.4:1 at 80°C, the ratio at 145°C increased to 4.1:1, presumably a consequence of the greater population of the conformation which leads to cyclization at elevated temperatures.[13] The cyclization/reduction ratios were very different for the trans-alkene **15**, although analogous temperature dependence was observed. The ratio of cyclization to reduction increased from 0.2:1 at 80°C to 0.8:1 at 145°C. These results indicate that the rate of transannular cyclization for cis-**14** is comparable to that reported for the acyclic 7-heptenyl radical.[14] The cyclization of trans-**15** is ca. 12 times slower than that of

14 (cis), **15** (trans)   **1 6**   **17** (cis), **18** (trans)
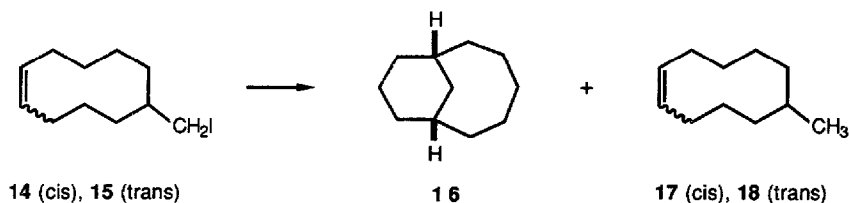
SUBSTRATE	TEMP (oC)	R-H	YIELD	RATIO (16:17,18)
14	80	(Bu)$_3$SnH	99%	2.4:1
	80	(TMS)$_3$SiH	100%	4.0:1
	145	(Bu)$_3$SnH	100%	4.1:1
15				
	80	(Bu)$_3$SnH	82%	0.2:1
	145	(Bu)$_3$SnH	94%	0.8:1

the cis isomer (vide infra). Chatgilialoglu has recently reported that the rate constant for hydrogen atom abstraction from tris-(trimethylsilyl)silyl hydride[15] is ca. 4 times slower than the corresponding reaction with tributyltin hydride, so that replacing the stannane with $(TMS)_3SiH$ should result in a decrease in the reduction rate relative to the desired transannular cyclization. In the event, reaction of **14** with $(TMS)_3SiH$ at 80°C led to the same ratio of cyclization to reduction that was obtained with $(n-Bu)_3SnH$ at 145°C.

The different reactivities of the cis- and trans-alkenes with respect to cyclization vs. reduction can be explained by examination of the energy-minimized conformations shown below.[16] Only the pseudo-axial conformation of the iodomethyl cyclodecene can lead to transannular cyclization, and while the difference in energy between axial (shown below) and equatorial is 3-4 kcal/mole in trans-**15**, the iodomethyl group occupies a nodal position in cis-**14**, i.e., MM2 calcluations indicate an energy difference of <0.5 kcal/mol between the equatorially and axially substituted conformations of **14**. In addition, while the plane of the π system is orthogonal to the plane of the cyclodecene in trans-**15**, the π plane of cis-**14** is tilted relative to the ring plane by ca. 20°, making the π system more accessible for transannular addition in **14**.

14 (cis)   15 (trans)
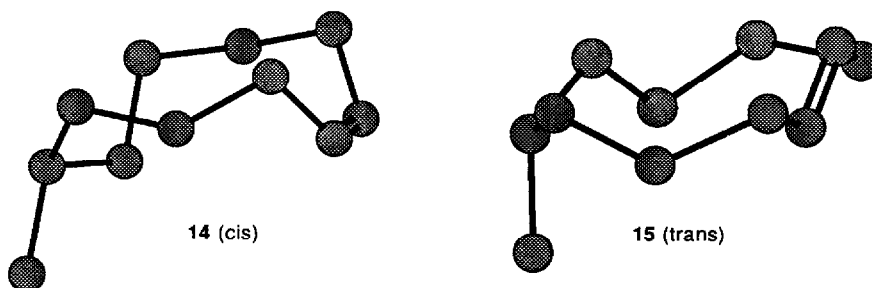
The stereoselective synthesis of the cis-bicyclo[5.3.1]undecane described herein attests to the potential of transannular radical cyclizations for the synthesis of structurally complex bicyclic ring systems. Further studies in the application of this methodology to the construction of other ring systems are currently in progress and will be reported in due course.

References

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