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Construction of Bicyclic Ring Systems via a Transannular SmI_2-Mediated Ketone−Olefin Cyclization Strategy

Gary A. Molander,* Barbara Czakó, and Michael Rheam

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323

gmolandr@sas.upenn.edu

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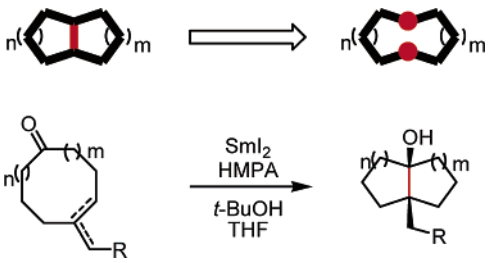

The development of novel methods and strategies for the formation of polycyclic ring structures is of utmost importance in organic synthesis. The present study describes the investigation of a transannular cyclization strategy for constructing bicyclic ring systems. To test the viability of the approach, the SmI_2-mediated ketone−olefin coupling reaction, a method previously developed in this laboratory, was examined. Investigation of the transannular cyclization of cyclooctene, cyclodecene, and cycloundecene derivatives revealed that the process proceeds with high yield and diastereoselectivity, and in the case of larger ring-sized compounds, with excellent regioselectivity. The regioselectivity of the annulation process could be rationalized based on examining the low energy conformations of the keto alkene starting materials. These results demonstrate the efficiency and the potential of the transannular cyclization tactic for the creation of bicyclic ring systems.

Introduction

The development of efficient methods for constructing polycyclic compounds has been a longstanding objective of synthetic organic chemists. Traditionally, bicyclic ring systems are created via two approaches: (1) annulation of a side chain onto a preexisting ring[1] and (2) cycloaddition reactions (such as the Diels−Alder reaction, [3 + 2] cycloaddition, etc.) (Figure 1).[2−17]

In addition to these strategies, a third possible approach is the formation of bicycles via transannular cyclizations (Figure 2).

A thorough examination of the literature reveals that besides the transannular Diels−Alder reaction, this strategy has not been systematically studied.[18,19] Transannular transformations appear in the chemical literature rather sporadically, mainly in connection with method development as isolated examples of a general, nontransannular process.[20−32] A small number of

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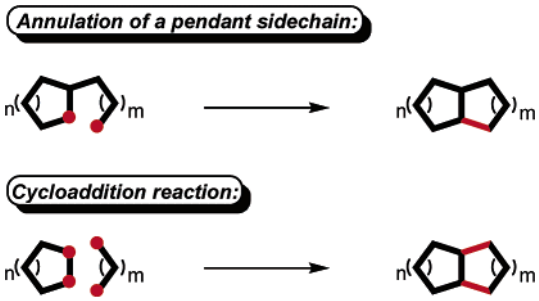


FIGURE 1. Traditional cyclization approaches.

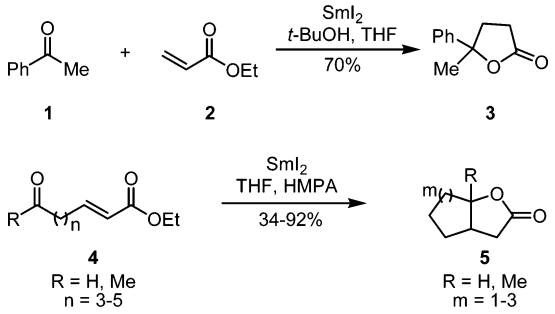
FIGURE 2. Transannular cyclization.

examples were also found in which transannular transformations were utilized in natural product synthesis.[33−40]

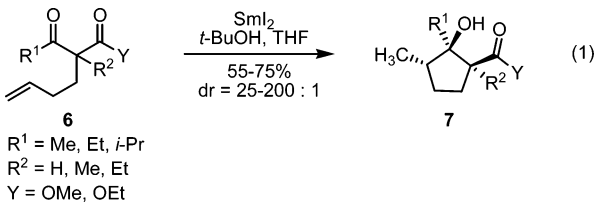
Because of the scarcity of data regarding the transannular ring formation tactic, we initiated a study that focused on investigating the synthetic utility of this strategy. The importance of the systematic investigation of the transannular ring formation strategy is twofold: (1) Polycyclic compounds with immense skeletal and functional group diversity are abundant in nature, and the development of novel methods and strategies enabling the synthesis of structures of increasing complexity is essential. (2) Examination of the factors influencing the inherent regio- and diastereoselectivity of transannular processes would contribute to the general understanding of these transformations.

To test the viability of the strategy, the SmI_2-mediated ketone−olefin coupling reaction, a method that was previously developed in this laboratory, was examined. Since its introduction to organic synthesis, SmI_2 has proven to be an extraordinary

SCHEME 1



reagent that is capable of promoting of a wide variety of processes ranging from functional group interconversions to carbon−carbon bond formations.[41−54] One of the most interesting and unique processes induced by SmI_2 is the reductive coupling of carbonyls with alkenes via ketyl radical anion intermediates. The first example of this transformation was reported by Fukuzawa et al. in 1986.[55] They described the SmI_2-mediated coupling of acetophenone **1** with ethyl acrylate **2** in THF in the presence of *t*-BuOH, affording the lactone product **3** in 70% yield. Later it was demonstrated by the same group that the reaction can be performed in an intramolecular fashion, producing the corresponding bicyclic lactones **5** in moderate to good yields (Scheme 1).[56]



Shortly after the first report, Molander and co-workers published an extensive study of SmI_2-mediated intramolecular ketone−olefin cyclizations in which the coupling of β-keto esters and amides with unactivated olefins was described.[57−61]

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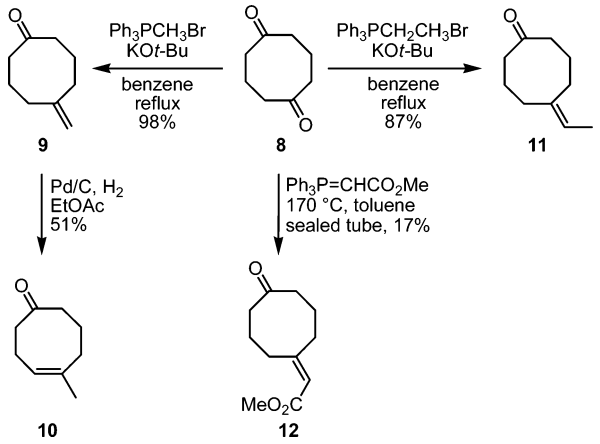
SCHEME 2



This process was successfully utilized for the synthesis of monocyclic and bicyclic ring systems in high yield and excellent diastereoselectivity (eq 1).

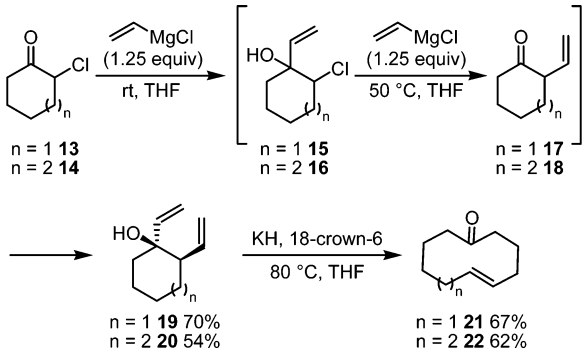
In the same publication, the intramolecular cyclization of alkynes and nitriles with β-keto esters was also described. During the following two decades, the reductive coupling of carbonyls promoted by SmI_2 was extensively investigated, and the substrate scope of the reaction was extended to unactivated ketones[59,60] and allenes.[62] The ketone−olefin cyclization was further exploited in sequential processes, leading to more densely functionalized and highly complex carbocyclic and heterocyclic products. Representative examples for sequenced reactions are the tandem nucleophilic acyl substitution/ketone−olefin coupling, radical cyclization/intermolecular nucleophilic addition, and the ketone−olefin coupling/β-elimination sequence.[63,64]

Results and Discussion

Synthesis of Substrates. To test the viability of the transannular cyclization strategy, the SmI_2-mediated ketone−olefin coupling reaction of cyclooctenone, cyclodecenone, and cycloundecenone derivatives was studied, focusing on the efficiency, functional group tolerance, and diastereoselectivity of the process. A key element to the success of this strategy was the rapid construction of the medium-sized ring starting materials.

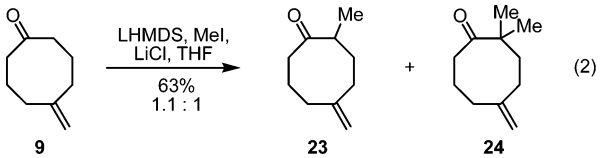
A common precursor to several substrates was cyclooctane-1,5-dione **8**. The first substrate, 5-methylenecyclooctanone **9**, was easily prepared from cyclooctane-1,5-dione **8** via Wittig reaction utilizing $Ph_3P{=}CH_2$, providing the product in excellent yield.[65−67] To examine the difference between the transannular ketone−olefin cyclization of endocyclic and exocyclic alkenes, the endocyclic variant of **9**, (*Z*)-5-methylcyclooct-4-enone **10**, was prepared. This compound was synthesized from 5-methylenecyclooctanone **9** by exposing it to 10% Pd/C and H_2 in EtOAc at room temperature overnight.[68] 5-Ethylidenecyclooctanone **11** was prepared starting from cyclooctane-1,5-dione **8** via a Wittig reaction.[33,67] To investigate the feasibility of the transannular ketone−olefin cyclization of activated alkene substrates, (5-oxo-cyclooctylidene)acetic acid methyl ester **12** was also prepared (Scheme 2).

SCHEME 3



The next objective was to synthesize larger ring-sized cyclic keto alkene derivatives. An efficient synthesis of (*E*)-cyclodec-5-enone **21** was achieved following the procedure developed by Kato and co-workers (Scheme 3).[69] According to this route, 2-chlorocyclohexanone **13** was reacted with vinylmagnesium bromide at room temperature over 1 h, producing the corresponding 2-chloro-1-vinylcyclohexanol **15**. This product was exposed to another 1.25 equiv of vinylmagnesium chloride in the same pot at 50 °C and kept at this temperature overnight, affording a separable 7:1 mixture of diastereomeric 1,2-divinylcyclohexanols. According to the literature procedure, (1*R**,2*S**)-1,2-divinylcyclohexanol **19** was warmed to 220 °C to effect the oxy-Cope rearrangement, leading to (*E*)-cyclodec-5-enone **21**.[70,71] However, under the above conditions, the starting material was recovered intact from the reaction. Further optimization revealed that the transformation can be realized under anionic oxy-Cope conditions using KH and 18-crown-6 in THF at 80 °C.[72] The synthesis of (*E*)-cycloundec-5-enone **22** was accomplished in a similar fashion. 2-Chlorocycloheptanone **14** was exposed to 2.5 equiv of vinylmagnesium chloride in two portions, affording (1*R**,2*S**)-1,2-divinylcycloheptanol **20** in 54% yield. Subsequent anionic oxy-Cope rearrangement delivered the requisite (*E*)-cycloundec-5-enone **22** in 62% yield.

To examine the diastereoselectivity of the ketone−olefin coupling, the synthesis of substituted 5-methylenecyclooctanones and (*E*)-cyclodec-5-enones was targeted. 2-Methyl-5-methylenecyclooctanone **23** was obtained along with 2,2-dimethyl-5-methylenecyclooctanone (**24**) by the methylation of 5-methylenecyclooctanone **9** using LHMDS and methyl iodide (eq 2).



2-Phenyl-5-methylenecyclooctanone **25** was prepared from 5-methylenecyclooctanone **9** using the Buchwald−Hartwig

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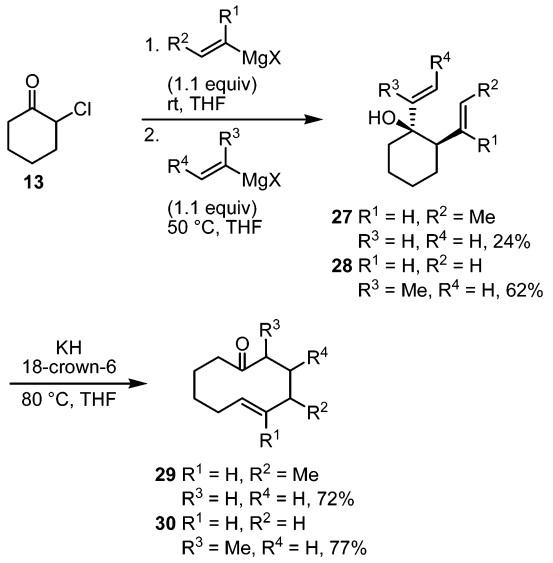
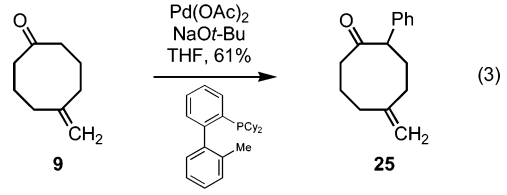
SCHEME 4

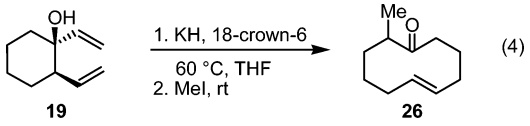


ketone arylation procedure.[73,74] To achieve this transformation, various conditions were tested including changing the Pd source [Pd_2dba_3, $Pd(OAc)_2$], the base (NaO*t*-Bu, K_3PO_4), and the solvent (THF, toluene) (eq 3). The best results were obtained when dicyclohexyl(2′-methylbiphenyl-2-yl)phosphine was used as a ligand and NaO*t*-Bu was used as base in THF at reflux, affording the product in 61% based on recovered starting material.



(3)

(*E*)-10-Methylcyclodec-5-enone **26** could be accessed from 1,2-divinylcyclohexanol **19** via an oxy-Cope rearrangement and subsequent quenching of the resulting enolate with methyl iodide (eq 4).[75]

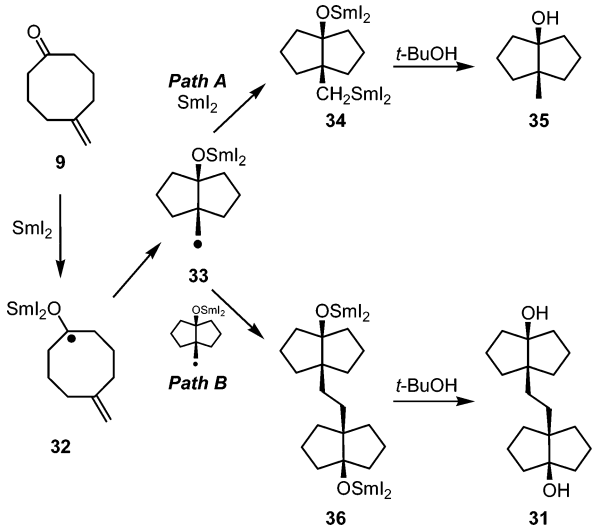


(4)

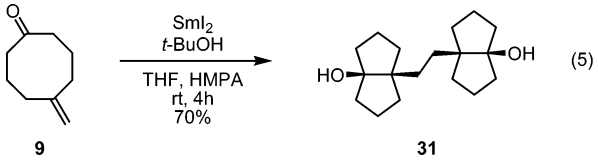
The requisite 2- and 4-methyl-substituted cyclodec-5-enone derivatives were synthesized by a general sequence according to which 2-chlorocyclohexanone was reacted with the appropriate Grignard reagent followed by oxy-Cope rearrangement as depicted in Scheme 4.[75−77]

Optimization of the Transannular Cyclization. Having prepared the requisite substrates, attention was turned to the exploration of the transannular SmI_2-mediated ketone−olefin

SCHEME 5



cyclization. The first reaction examined was the annulation of the simplest substrate, 5-methylenecyclooctanone **9** (eq 5). Surprisingly, under standard ketone−olefin coupling conditions, according to which the THF solution of the substrate ($c = 0.03$ M) and *t*-BuOH was added to a SmI_2/HMPA solution ($c = 0.13$ M) at room temperature over 15 min, the dimerized product **31** was formed exclusively.



(5)

The structure of compound **31** was established by X-ray crystallography. This outcome can be explained by the rapid reduction of the ketone to the corresponding ketyl radical anion, which results in the local depletion of the SmI_2 concentration (Scheme 5). The ketyl radical **32** undergoes an intramolecular addition onto the alkene, producing methyl radical **33**. Subsequent reduction of this radical to the corresponding organosamarium species **34** is disfavored because of the low SmI_2 concentration (Path A). On the other hand, the high concentration of radical **33** creates ideal conditions for the dimerization, leading to product **31** (Path B).

To avoid dimerization, extensive optimization studies were conducted. The obvious first experiment was to perform the reaction under more dilute conditions, employing a 0.004 M substrate concentration and increasing the addition time to 4 h. Although under these conditions the monomer/dimer ratio increased to 1.8:1, still a substantial amount of dimer formed (entry 2, Table 1). Further reduction of the concentration of the substrate to 0.002 M did not lead to significant improvement, resulting in a 3.2:1 monomer/dimer ratio (entry 3, Table 1).[78]

Next, the effect of radical scavengers was examined. Unfortunately, addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT) did not change the outcome.[79] Performing the reaction under high dilution conditions in the presence of BHT afforded high yields, but as a 3.1:1 mixture of the monomer and dimer (entry 4, Table

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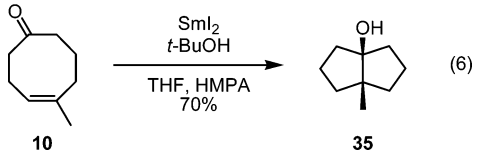
TABLE 1. Optimization of the Ketone−Olefin Coupling

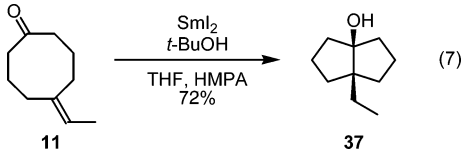
entry	substrate concn (M)	additive	addition time	**35**: **31** yield (%)
1	0.03	−	15 min	**31** (70%)
2	0.004	−	4 h	1.8:1 (59%, 33%)
3	0.002	−	4 h	3.2:1 (75%, 23%)
4	0.002	2,6-di-*tert*-butyl-4-methylphenol	4 h	3.1:1 (72%, 23%)
5	0.05	$(EtO)_2P(O)H$ (5 equiv)	20 min	2:1 (56%, 28%)
6	0.05	$Ph_2P(O)H$ (5 equiv)	20 min	5.3:1 (64%, 12%)
7	0.05	PhSH (5 equiv)	20 min	35 (80%)
8	0.05	PhSH (1.4 equiv)	20 min	35 (80%)

1). Carrying out the reaction in the presence of 5 equiv of diethyl phosphonite under standard conditions, employing a substrate concentration of 0.05 M and a 20 min addition time, furnished a 2:1 mixture of the monomer and dimer (entry 5, Table 1).[80] Utilizing diphenylphosphine oxide under the standard conditions led to further improvement, providing a 5.3:1 ratio of the monomer and dimer (entry 6, Table 1).[81] Finally, thiophenol was tested.[82] Performing the reaction under standard conditions in the presence of five equivalents of thiophenol led to the exclusive formation of the monomeric product (entry 7, Table 1). Gratifyingly, identical results were obtained when the reaction was performed in the presence of 1.4 equiv of thiophenol (entry 8, Table 1).

Exploring Substrate Scope. Next, the effect of changing the position of the double bond from exocyclic to endocyclic was examined. To this end, the transannular ketone−olefin coupling of (*Z*)-5-methylcyclooct-4-enone **10** was performed (eq 6). Under standard conditions, in the absence of a radical scavenger, the reaction led to the clean formation of the expected bicyclic alcohol **35**.

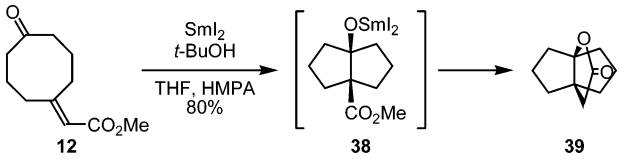


To determine whether dimerization occurs when the reaction proceeds through an exocyclic secondary radical intermediate, the annulation of 5-ethylidenecyclooctanone **11** was examined. Performing the reaction under standard conditions furnished the expected bicycle **37** as the single product, and no dimer could be detected (eq 7).

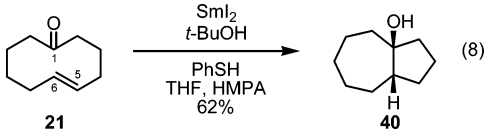


The outcome of these experiments indicated that dimerization occurs only in the case of substrates when the reaction proceeds through the sterically accessible primary radical. When the reaction proceeds through the sterically more hindered, kinetically stable secondary radical, dimer formation is inhibited.

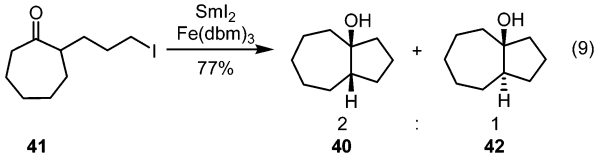
SCHEME 6



These examples demonstrated that the transannular SmI_2-mediated ketone−olefin coupling of substrates containing an unactivated alkene occurs readily. As expected, activated alkenes also undergo the transformation. The transannular cyclization of methyl (5-oxo-cyclooctylidene)acetic acid methyl ester **12** proceeded with ease; however, the reaction did not stop after the first transannular bond formation, but the resulting samarium alkoxide **38** reacted further with the ester moiety, producing the tricyclic lactone product **39** (Scheme 6).[83,84]



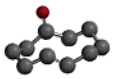
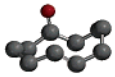
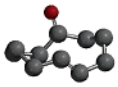
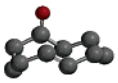
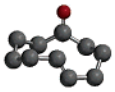
Extension of the Method to Larger Ring-Sized Compounds. Successful application of the transannular ketyl−olefin cyclization to the synthesis of [3.3.0] bicyclic ring systems prompted the investigation of the cyclization reaction of compounds with a larger ring size. First, the transannular cyclization of (*E*)-cyclodec-5-enone **21** was examined. Depending on the regio- and diastereoselectivity of the process, this cyclization could lead to the formation of four different products. Addition of the ketyl radical to the C-5 position of the double bond could potentially produce the *cis*- or *trans*-bicyclo[5.3.0]-decan-1-ol products, while annulation onto the C-6 position of the alkene would result in the formation of the *cis*- or *trans*-bicyclo[4.4.0]decan-1-ol products. Performing the reaction under standard conditions, in the presence of the radical scavanger, revealed that the transformation proceeds with high regio- and diastereoselectivity, furnishing *cis*-bicyclo[5.3.0]decan-1-ol **40** in 62% yield (eq 8). In the absence of thiophenol, the formation of a small amount of dimeric product could be observed. The structure of the bicyclic product was established by comparison to literature data.[1,85]



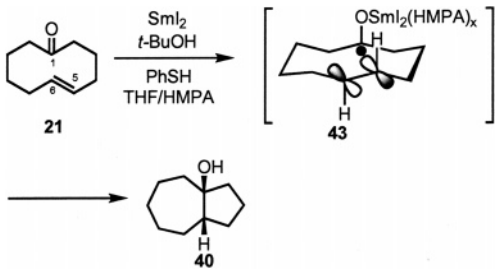
It is important to note that a synthesis of the same compound employing an intramolecular Barbier strategy delivered the product in a much lower 2:1 diastereoselectivity (eq 9).[1,86] In this instance, the transannular cyclization approach was clearly superior to the traditional annulation strategy.

(80) Barton, D. H. R. J., D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1992**, *33*, 2311−2314.
(81) Barks, J. M. G., B. C.; Parsons, A. F.; Upeandran, B. *Tetrahedron Lett.* **2001**, *42*, 3137−3140.
(82) Banwell, M. G. H., David, C. R.; McLeod, Malcolm, D. *New J. Chem.* **2003**, *27*, 50−59.
(83) Kakiuchi, K.; Masaki, U.; Takeda, M.; Tadaki, T.; Kato, Y.; Nagashima, T.; Tobe, Y.; Koike, H.; Ida, N.; Odaira, Y. *Chem. Pharm. Bull.* **1987**, *35*, 617−631.
(84) Tobe, Y.; Hayauchi, Y.; Odaira, Y. *J. Org. Chem.* **1981**, *46*, 5219−5221.
(85) Li, J.; Gallardo, T.; White, J. B. *J. Org. Chem.* **1990**, *55*, 5426−5428.
(86) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1986**, *51*, 1778−1786.

TABLE 2. Minimum Energy Conformations of (*E*)-Cyclodec-5-enone 21

entry	conformer	relative energy (kcal/mol)	distance to C-5 (Å)	distance to C-6 (Å)
1		0	2.979	3.239
2		1.29	3.006	3.316
3		2.85	3.217	3.071
4		2.96	2.935	3.273
5		2.96	3.186	3.012

SCHEME 7

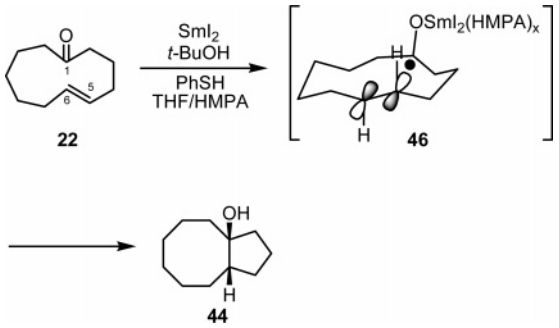


The high regio- and diastereoselectivity of the transannular process can be rationalized based on the reaction mechanism (Scheme 7). Examining the structure of the ketyl radical anion intermediate **43** reveals that the LUMO orbital of the alkene is lined up in a fashion that is perfect for the addition of the ketyl radical to the C-5 position of the double bond. This alignment also accounts for the cis diastereoselectivity of the process. Addition of the radical to the C-6 position of the double bond is less favored. This position is more distant to the ketyl radical, and the orbital alignment is not ideal for the bond formation.

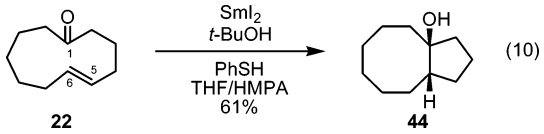
The conformation of the ketyl radical anion intermediate **43** was based on the minimum energy conformation of (*E*)-cyclodec-5-enone **21** that was obtained from MMFF calculations using the Spartan modeling program. Examining the five lowest energy conformers of **21** demonstrates that transition structures based on the conformers shown in entries 1, 2, and 4 would favor the formation of *cis*-bicyclo[5.3.0]decan-1-ol **40** (Table 2).

Next, attention was turned to the transannular cyclization of (*E*)-cycloundec-5-enone **22** (eq 10). Theoretically, this reaction also could provide four different products: *cis*- or *trans*-bicyclo-[6.3.0]undecan-1-ol and *cis*- or *trans*-bicyclo[5.4.0]undecan-1-

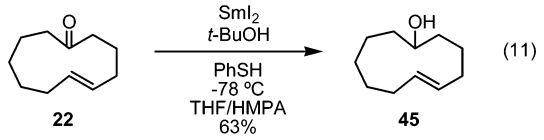
SCHEME 8



ol systems. However, the only detectable product that formed in this reaction was *cis*-bicyclo[6.3.0]undecan-1-ol **44**.[87,88] The structure of this compound was established based on X-ray crystallography analysis.



When the reaction was carried out under identical conditions but at −78 °C, the only product that formed was the reduced alcohol **45** (eq 11). This result suggests that at low temperatures, the reduction of the radical becomes faster than the annulation process.



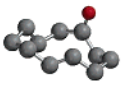
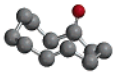
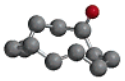
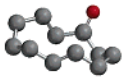
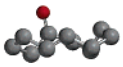
To rationalize the high regio- and stereochemical outcome of the transannular transformation, a similar analysis as described above was used. In the ketyl radical anion intermediate **46**, the alignment of the molecular orbitals is ideal for bond formation between the ketyl radical and the C-5 position of the alkene functionality. However, bond formation between the radical and the C-6 position of the alkene appears to be unfavorable (Scheme 8). This alignment also accounts for the cis diastereoselectivity of the transformation.

The conformation of the ketyl radical anion intermediate was based on the minimum energy conformation of (*E*)-cycloundec-5-enone **22** (entry 1, Table 3). Examining the next four conformers also predicts the formation of the *cis*-bicyclo[6.3.0]-undecane ring system (entries 2−5, Table 3).

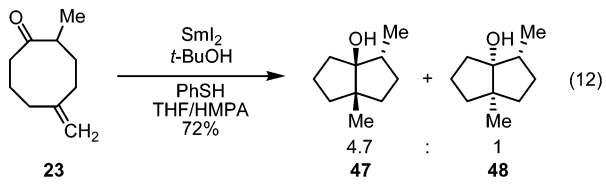
Examining the Diastereoselectivity. To investigate the diastereoselectivity of the SmI_2-mediated transannular ketone−olefin coupling, the cyclization of substituted 5-methylenecyclooctanone and (*E*)-cyclodec-5-enone derivatives was exam-

(87) Crandall, J. K.; Magaha, H. S.; Henderson, M. A.; Widener, R. K.; Tharp, G. A. *J. Org. Chem.* **1982**, *47*, 5372−5380.
(88) Suginome, H.; Kondoh, T.; Gogonea, C.; Singh, V.; Goto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 69−71.
(89) Bessiere, J. M.; Christol, H. *Bull. Soc. Chim. Fr.* **1969**, 4063−4068.
(90) Colclough, D.; White, J. B.; Smith, W. B.; Chu, Y. *J. Org. Chem.* **1993**, *58*, 6303−6313.
(91) Crandall, J. K.; Magaha, H. S. *J. Org. Chem.* **1982**, *47*, 5368−5371.
(92) Hiyama, T.; Fujita, S.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2797−2801.
(93) Shono, T.; Kise, N.; Fujimoto, T.; Tominaga, N.; Morita, H. *J. Org. Chem.* **1992**, *57*, 7175−7187.
(94) Stuedemann, T.; Ibrahim-Ouali, M.; Cahiez, G.; Knochel, P. *Synlett* **1998**, 143−144.

TABLE 3. Minimum Energy Conformations of (*E*)-Cycloundec-5-enone 22

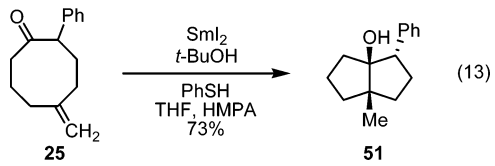
entry	conformer	relative energy (kcal/mol)	distance to C-5 (Å)	distance to C-6 (Å)
1		0	2.222	3.779
2		0.06	3.145	3.512
3		1.57	3.166	3.812
4		1.67	3.266	3.752
5		2.27	3.115	3.501

ined. Performing the SmI_2-mediated cyclization of 2-methyl-5-methylenecyclooctanone **23** afforded a 4.7:1 mixture of diastereomers (eq 12), the stereochemical assignment of which was conducted by NOESY experiments (see Supporting Information). This ratio was determined based on the ^1H NMR analysis of the reaction mixture.



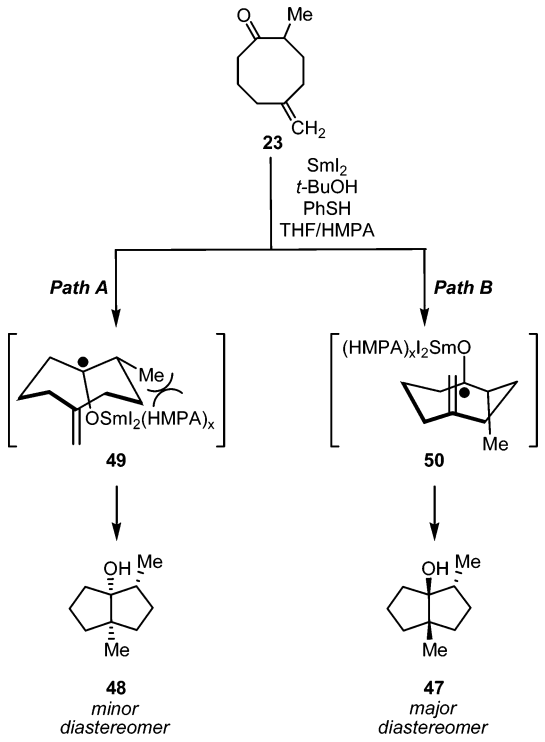
The outcome of this transformation can be explained by examining the ketyl radical anion intermediates leading to the two diastereomeric products (Scheme 9). When the reaction follows path A, the methyl group at the C-2 position is situated in a seemingly favorable quasi-equatorial orientation. However, further examination of intermediate **49** reveals that in this case, an unfavorable gauche interaction develops between the methyl group at the C-2 position and the samarium alkoxide, rendering this pathway less favored. On the other hand, when the reaction proceeds through transition structure **50**, although the methyl group is in a quasi-axial orientation, the unfavorable steric interaction between the C-2 methyl and the samarium alkoxide is avoided, thus rendering this pathway the major route.

When the methyl group was exchanged to the bulkier phenyl substituent, the transannular cyclization proceeded with complete diastereoselection furnishing bicycle **51** as a single product (eq 13).

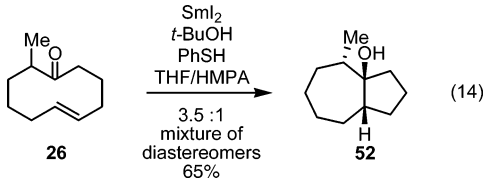


The stereochemical outcome of the reaction can be explained based on similar arguments to those that were presented in the case of the transannular cyclization of 5-methyl-2-methylenecyclooctanone **23**.

SCHEME 9



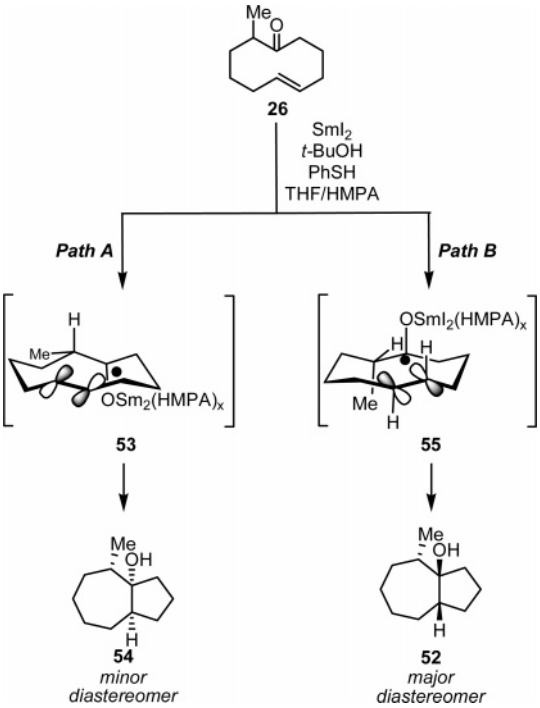
Subsequently, the transannular cyclization of methyl substituted cyclodec-5-enone derivatives was investigated. Treatment of (*E*)-10-methylcyclodec-5-enone **26** with SmI_2 under standard conditions led to the formation of a 3.5:1 mixture of diastereomers (eq 14).



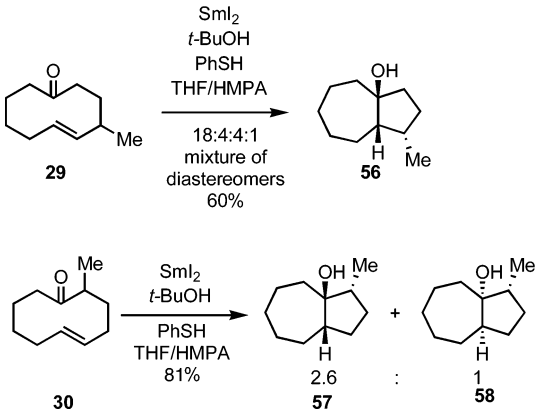
The stereochemical outcome of the transformation can be rationalized based on conformational analysis of the ketyl radical anion intermediate. The regioselectivity of the annulation as well as the diastereoselectivity at the ring juncture can be well explained by using the same analysis that was employed in the case of the annulation of (*E*)-cyclodec-5-enone **21** (Scheme 10). When the methyl group in the ketyl radical anion intermediate in the minimum energy conformation of the cyclodec-5-enone ring is situated in a quasi-equatorial orientation, there is an unfavorable steric interaction between the samarium alkoxide and the methyl group (Path A). On the other hand, when the methyl group is positioned quasi-axially (Path B), this gauche interaction is avoided, thus rendering this route the major pathway of the transformation.

Transannular cyclization of (*E*)-4-methylcyclodec-5-enone **29** and (*E*)-2-methylcyclodec-5-enone **30** proceeded with comparable yield and diastereoselectivity. Treatment of (*E*)-4-methylcyclodec-5-enone **29** with SmI_2 under standard conditions provided an 18:4:4:1 mixture of isomers in 60% yield, and the reaction of (*E*)-2-methylcyclodec-5-enone **30** furnished a 2.6:1 separable mixture of diastereomers in 72% yield (Scheme 11).

SCHEME 10



SCHEME 11



The stereochemical outcome of these transformations can be rationalized based on a similar analysis to that employed in the case of the transannular cyclization of (*E*)-10-methylcyclodec-5-enone **26**.

Conclusion

The goal of this study was to investigate the efficiency of the transannular cyclization tactic for creating bicyclic ring structures. To test the strategy, the SmI_2-mediated ketone−olefin cyclization was selected. The transannular cyclization of cyclooctanone derivatives revealed that this is a powerful approach to construct bicyclo[3.3.0]octane ring systems. Although initially the annulation of 5-methylenecyclooctanone **9** led to dimer formation exclusively, this side reaction could be completely avoided by employing thiophenol as a radical scavenger. (*Z*)-5-Methylcyclooct-4-enone **10** also underwent the transformation demonstrating that compounds containing an endocyclic double bond were viable substrates in the annulation. Reaction of 5-ethylidenecyclooctanone **11** afforded the bicycle without the need to employ a radical scavenger. Activated alkene **12** underwent the transformation equally well. The strategy was extended to larger ring-sized compounds. Subjecting (*E*)-cyclodec-5-enone **21** to the reaction conditions proceeded with very high regio- and diastereoselectivity, affording bicycle **40** as the major product. The cyclization of (*E*)-cycloundec-5-enone **22** also proved to be efficient, providing bicyclic compound **44** as the only product. The excellent regio- and diastereoselectivity of these processes could be rationalized by examining the orbital alignment of the ketyl radical anion intermediates that were based on the lowest energy conformation of the keto alkene starting materials. Investigation of the transannular cyclization of 2-methyl- and 2-phenylcyclooctanone as well as the cyclization of substituted cyclodecenone derivatives revealed that the annulation proceeds with high diastereoselectivity. The stereochemical outcome of these processes was governed by the substituents occupying the sterically more favorable quasi-axial position in the transition state.

The above results demonstrate that the SmI_2-mediated transannular ketone−olefin coupling provides efficient access to bicyclic alcohols. Extension of the transannular cyclization strategy to other methods holds enormous potential as it can become a novel disconnection for the creation of polycyclic ring structures.

Experimental Section

Tetrahydrofuran (THF) was distilled prior to use from sodium/benzophenone under nitrogen. Samarium metal (99.9%) was purchased from Strem Chemical, Inc. and stored under nitrogen. Diiodomethane was purified via distillation, stored over copper beads and protected from light. HMPA was distilled from sodium. Air-sensitive materials were handled using standard benchtop techniques. For purification, standard flash chromatography methods were employed using 32−63 μm silica gel purchased from Sorbent Technologies.

General Procedure for the Transannular SmI_2-Mediated Ketyl−Olefin Cyclization: Preparation of SmI_2 Solution in THF and HMPA. A flame-dried round-bottom flask was charged with Sm metal (135 mg, 0.9 mmol) (Strem) and THF (4.1 mL) under Ar. This was followed by the addition of CH_2I_2 (216 mg, 0.81 mmol) in two portions over 30 min. The reaction mixture was stirred at room temperature for 4 h. HMPA was added (1.3 g, 1.3 mL, 7.3 mmol), and the solution was stirred for 15 min at room temperature.

Method A. The substrate (0.18 mmol) was dissolved in THF (3.6 mL), and *t*-BuOH (26 mg, 0.36 mmol) was added. This solution was added dropwise to the SmI_2/THF/HMPA solution (5.4 mL) under Ar at room temperature over 15 min. The reaction was stirred for 2−4 h. Upon consumption of the starting material, saturated $NaHCO_3$ solution (3 mL) was added and stirring was continued for another 10 min. This was followed by the addition of Et_2O. The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic phases were dried (Na_2SO_4) and filtered, and the solvent was evaporated.

Method B. The substrate (0.18 mmol) was dissolved in THF (3.6 mL) and *t*-BuOH (26 mg, 0.36 mmol), and PhSH (27 mg, 0.25 mmol) was added. This solution was added dropwise to the SmI_2/THF/HMPA solution (5.4 mL) under Ar at room temperature over 15 min. The reaction was stirred for 2−4 h. Upon consumption of the starting material, saturated $NaHCO_3$ solution (3 mL) was added and stirring was continued for another 10 min. This was followed by the addition of Et_2O. The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic phases were dried (Na_2SO_4) and filtered, and the solvent was evaporated.

Preparation of the Dimer of 5-Methylbicyclo[3.3.0]octan-1-ol 31. Prepared from 5-methylenecyclooctanone **9** (10 mg, 0.072 mmol) according to the general procedure described in Method A,

to afford the product after flash chromatography on Florisil, using Et_2O−pentane (10%) as eluent (7 mg, 70%). ^1H NMR (500 MHz, $CDCl_3$): 1.87−1.82 (m, 4H), 1.72−1.67 (m, 4H), 1.64−1.58 (m, 8H), 1.57−1.56 (m, 2H), 1.48−1.43 (m, 8H), 1.29 (s, 4H). ^{13}C NMR: (125 MHz, $CDCl_3$): δ 90.4, 53.2, 42.1, 38.3, 31.9, 22.7. IR (film): 3325, 2947, 2860, 1458, 1445, 1395, 1309, 1289, 1230, 1139, 1106, 1080, 1035 cm^{-1}. HRMS: calcd for $C_{18}H_{30}O_2$ $[M]^+$ 261.2245, found 261.2233.

Preparation of 5-Methylbicyclo[3.3.0]octan-1-ol 35.[78] Prepared from 5-methylenecyclooctanone **9** (10 mg, 0.072 mmol) according to the general procedure described in Method B, to afford the product after flash chromatography on Florisil, using Et_2O−pentane (10%) as eluent (8 mg, 80%). 5-Methylbicyclo[3.3.0]octan-1-ol **35** was also prepared from (*Z*)-5-methylcyclooct-4-enone **10** (50 mg, 0.38 mmol) according to the general procedure described in Method A, to afford the product after flash chromatography on Florisil, using Et_2O−pentane (10%) as eluent (37 mg, 70%). ^1H NMR (500 MHz, $CDCl_3$): 1.81−1.77 (m, 2H), 1.71−1.60 (m, 2H), 1.60−1.57 (m, 2H), 1.53−1.45 (series of multiplets, 6H), 1.32 (s, 1H), 0.98 (s, 3H). ^{13}C NMR: (125 MHz, $CDCl_3$): δ 89.5, 50.2, 41.7, 41.0, 23.1, 22.4. IR (film): 3389, 2935, 2857, 1462, 1451, 1376, 1116, 993 cm^{-1}. HRMS: calcd for C_9H_{15} $[M - OH]^+$ 123.1173, found 123.1165.

Preparation of 5-Ethylbicyclo[3.3.0]octan-1-ol 37. Prepared from methyl 5-ethylenecyclooctanone **11** (25 mg, 0.16 mmol) according to the general procedure described in Method A, to afford the product after flash chromatography on Florisil, using Et_2O−pentane (10%) as eluent (20 mg, 72%). ^1H NMR (500 MHz, $CDCl_3$): 1.84−1.81 (m, 2H), 1.69−1.63 (m, 2H) 1.60−1.55 (series of multiplets 4H), 1.45−1.41 (series of multiplets, 4H), 1.41 (s, 1H), 1.30 (q, J = 7.3 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H). ^{13}C NMR: (125 MHz, $CDCl_3$): δ 90.2, 42.0, 39.5, 37.6, 28.4, 22.6, 9.9. IR (film): 3422, 2935, 2857, 1689, 1460, 1451, 1376, 1309, 1295, 1258, 1233, 1127, 1076, 1032 cm^{-1}. HRMS: calcd for $C_{10}H_{17}$ $[M - OH]^+$ 137.1330, found 137.1333.

Preparation of Compound 39.[83,84] Prepared from (5-oxocyclooctylidene)acetic acid methyl ester **12** (44 mg, 0.22 mmol) according to the general procedure described in Method A, to afford the product after flash chromatography on Florisil, using Et_2O−pentane (10%) as eluent (29 mg, 80%). ^1H NMR (500 MHz, $CDCl_3$): 2.57 (s, 2H), 2.01 (m, 2H), 1.75−1.68 (series of multiplets, 10H). ^{13}C NMR: (125 MHz, $CDCl_3$): δ 177.8, 104.7, 55.3, 43.9, 40.6, 38.7, 25.2. IR (film): 2946, 2857, 1767, 1462, 1451, 1412, 1323, 1297, 1253, 1211, 1180, 1146, 976 cm^{-1}. HRMS: calcd for $C_{10}H_{14}O_2$ $[M]^+$ 166.0993, found 166.0994.

Preparation of Bicyclo[3.3.0]decan-1-ol 40.[1,85,87,89−94] Prepared from (*E*)-cyclodec-5-one **21** (50 mg, 0.32 mmol) according to the general procedure described in Method B, to afford the product after flash chromatography on Florisil, using Et_2O−pentane (10%) as eluent (32 mg, 62%). Characterization data are in agreement with the reported literature data.

Preparation of Bicyclo[3.3.0]undecan-1-ol 44. Prepared from (*E*)-cycloundec-5-one **22** (60 mg, 0.36 mmol) according to the general procedure described in Method B, to afford the product after flash chromatography on Florosil, using Et_2O−pentane (10%) as eluent (37 mg, 61%). ^1H NMR (500 MHz, $CDCl_3$): 2.22 (m, 1H), 1.82−1.28 (series of multiplets, 18H), 1.15 (s, 1H). ^{13}C NMR: (125 MHz, $CDCl_3$): δ 83.9, 49.6, 42.1, 36.6, 33.9, 33.4, 31.0, 25.7, 25.6, 23.6, 21.0. IR (film): 3375, 2919, 2853, 2708, 1463, 1443, 1369, 1323, 1287, 1229, 1202, 1170, 1117, 1069 cm^{-1}. HRMS: calcd for $C_{11}H_{18}$ $[M - H_2O]^+$ 150.1408, found 150.1399.

Preparation of (*E*)-Cycloundec-5-ol 45. Prepared from (*E*)-cycloundec-5-one **22** (60 mg, 0.36 mmol) according to the general procedure described in Method B, with the exception of performing the reaction at −78 °C, to afford the product after flash chromatography on Florisil, using Et_2O−pentane (20%) as eluent (39 mg, 63%). ^1H NMR (500 MHz, $CDCl_3$): 5.39 (m, 2H), 3.77 (m, 1H), 2.20 (m, 2H), 1.96 (m, 1H), 1.87 (m, 1H), 1.67−1.40 (series of multiplets, 8H), 1.30−1.12 (series of multiplets, 5H). ^{13}C NMR: (125 MHz, $CDCl_3$): δ 132.1, 130.8, 71.3, 36.0, 35.1, 34.1, 34.1, 26.7, 26.2, 24.7, 24.0. IR (film): 3341, 2927, 2845, 1457, 1438, 1348, 1233, 1164, 1065, 1034, 976 cm^{-1}. HRMS: calcd for $C_{11}H_{20}O$ $[M]^+$ 168.1514, found 168.1523.

Preparation of 2,5-Dimethylbicyclo[3.3.0]octan-1-ol 47. Prepared from 2,5-dimethylcyclooctanone **23** (110 mg, 0.72 mmol) according to the general procedure described in Method B, to afford a 4.7:1 mixture of diastereomers after flash chromatography on Florisil, using Et_2O−pentane (10%) as eluent (80 mg, 72%). ^1H NMR (500 MHz, $CDCl_3$): 1.75 (m, 1H), 1.62 (m, 1H), 1.60 (m, 2H), 1.50 (m, 2H), 1.50−1.43 (series of multiplets, 4H), 1.16 (s, 1H), 1.10 (m, 1H), 0.98 (d, J = 6.6 Hz, 3H), 0.98 (s, 3H). ^{13}C NMR: (125 MHz, $CDCl_3$): δ 90.9, 50.2, 44.5, 42.2, 38.8, 36.2, 29.5, 23.8, 23.3, 13.6. IR (film): 3417, 2941, 2868, 1636, 1454, 1379, 1289, 1258, 1211, 1130, 1088, 1071, 1034, 1001, 984 cm^{-1}. HRMS: calcd for $C_{10}H_{17}$ $[M - OH]^+$ 137.1330, found 137.1321.

Preparation of 2-Phenyl-5-methylbicyclo[3.3.0]octan-1-ol 51. Prepared from 2-phenyl-5-methylcyclooctanone **25** (50 mg, 0.234 mmol) according to the general procedure described in Method B, to afford the product after flash chromatography on Florisil, using Et_2O−pentane (10%) as eluent (36 mg, 73%). ^1H NMR (500 MHz, $CDCl_3$): 7.36−7.29 (series of multiplets, 4H), 7.24 (m, 1H), 3.04 (t J = 9.6 Hz, 1H), 1.85−1.83 (series of multiplets, 2H), 1.74−1.68 (series of multiplets, 2H), 1.61−1.49 (series of multiplets, 5H), 1.43 (s, 1H), 1.14 (m, 1H), 1.10 (s, 3H). ^{13}C NMR: (125 MHz, $CDCl_3$):δ 141.1, 127.9, 127.8, 126.2, 91.2, 54.7, 50.6, 42.6, 38.7, 38.6, 25.6, 24.1, 23.4. IR (film): 3473, 3086, 3058, 3030, 2941, 2862, 1949, 1876, 1801, 1600, 1496, 1446, 1373, 1269, 1208, 1130, 1071, 1034, 1001 cm^{-1}. HRMS: calcd for $C_{15}H_{20}O$ $[M]^+$ 216.1514, found 216.1501.

Preparation of 2-Methylbicyclo[3.3.0]decan-1-ol 52. Prepared from 10-methyl-(*E*)-cyclodec-5-one **26** (20 mg, 0.12 mmol) according to the general procedure described in Method B, to afford the product after flash chromatography on Florisil, using Et_2O−pentane (10%) as eluent (13 mg, 65%). ^1H NMR (500 MHz, $CDCl_3$): 2.15−2.12 (m, 1H), 1.82−1.72 (series of multiplets, 3H), 1.71−1.58 (series of multiplets, 6H), 1.53−1.49 (m, 1H), 1.32−1.26 (series of multiplets, 4H), 1.26−1.03 (series of multiplets, 2H), 0.96 (d, J = 5.95 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 86.2, 53.5, 41.8, 41.4, 35.3, 34.0, 32.6, 30.6, 30.4, 23.7, 18.7. IR: 3550−3050 (bs), 2918, 2857, 1451, 1376, 1320, 1261, 1205, 1090, 1020, 959, 925. HRMS: calcd for $C_{11}H_{20}O$ $[M^+]$ 168.1514, found. 168.1515.

Preparation of 8-Methylbicyclo[3.3.0]decan-1-ol 56. Prepared from 4-methyl-(*E*)-cyclodec-5-one **29** (88 mg, 0.52 mmol) according to the general procedure described in Method B, to afford an 18:4:4:1 mixture of isomeric products after flash chromatography on Florisil, using Et_2O−pentane (10%) as eluent (54 mg, 60%). ^1H NMR (500 MHz, $CDCl_3$): δ 1.01 (d, J = 6.0 Hz, 3H), 1.13 (m, 1H), 1.24−1.32 (series of m, 4H), 1.33−1.50 (series of m, 3H), 1.51−1.72 (series of m, 6 H), 1.73−1.87 (series of m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.5, 23.6, 29.5, 31.5, 32.2, 33.0, 40.2, 43.2, 43.3, 61.4, 84.8. IR(film): 3378, 2857, 1451, 1376, 1345, 1323, 1289, 1275, 1211, 1158, 1121, 1104, 1012, 984, 962, 914 cm^{-1}. HRMS: Calculated for $C_{11}H_{20}O$ $[M^+]$ 168.1514 found 168.1506.

Preparation of 10-Methylbicyclo[3.3.0]decan-1-ol 57 and 58. Prepared from 2-methyl-(*E*)-cyclodec-5-one **30** (88 mg, 0.52 mmol) according to the general procedure described in Method B, to afford a 2.6:1 mixture of isomeric products after flash chromatography on Florisil, using Et_2O−pentane (10%) as eluent (72 mg, 81%). ^1H NMR (500 MHz, $CDCl_3$): Major diastereomer: δ 0.89 (d, J = 5.95 Hz, 3H), 0.95−1.06 (series of m, 2H), 1.22 (m, 2H), 1.26−1.43 (series of m, 3H), 1.50 (m, 1H), 1.54−1.64 (series of m, 4H), 1.75−1.83 (series of m, 3 H), 1.88 (m, 1 H), 1.96 (m, 1H). Minor diastereomer: δ 0.88 (d, J = 5.65 Hz, 3H), 1.20−1.38 (series of m, 6H), 1.70−1.86 (series of m, 5 H), 1.87−1.91 (series of m,

4H), 1.92−2.02 (series of m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): Major diastereomer: δ 12.0, 23.3, 30.2, 31.6, 32.2, 32.5, 35.0, 38.1, 45.1, 53.6, 84.0. Minor diastereomer: δ 15.6, 23.1, 29.8, 31.2, 31.9, 32.0, 34.6, 35.0, 48.3, 53.1, 85.7. IR(film): Major diastereomer: 3602, 3468, 2919, 2857, 2689, 2364, 1457, 1385, 1323, 1276, 1259, 1208, 1169, 1150, 1105, 1066, 1035, 999, 979, 929, 864, 822, 792 cm^{-1}. Minor diastereomer: 3384, 2919, 2852, 2695, 2359, 1457, 1376, 1345, 1329, 1278, 1258, 1128, 1203, 1164, 1133, 1105, 1074, 1046, 1013, 976, 959, 929, 912, 867, 842, 822, 792, 738 cm^{-1}. HRMS: Major diastereomer: Calculated for $C_{11}H_{20}O$ 168.1514 [M^+], found 168.1516. Minor diastereomer: Calculated for $C_{11}H_{18}$ [$M^+ - H_2O$] 150.1409, found 150.1403.

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Supporting Information Available: Experimental details and structural data for all new compounds not described within this text. This material is available free of charge via the Internet at http://pubs.acs.org.

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