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Enolization Regioselectivity Involving Stereoisomeric 4a-Methyl-5-methoxyperhydrobenzo[7]annulen-2-ones

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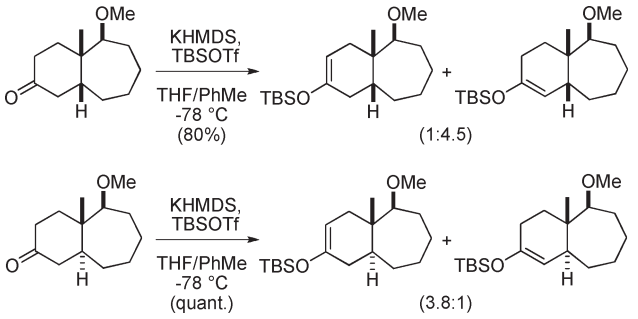
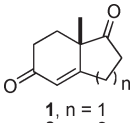


Efficient synthetic routes to the four isomers **17b**−**20b** of the title ketone are described. Entry begins from the Wieland−Miescher homologue **3** whose pair of carbonyl groups are amenable to regiochemical manipulation. The compositions of the reaction mixtures generated under kinetic or thermodynamic control were defined by ^{1}H NMR analysis subsequent to chromatographic purification. The regiochemical trends are correlated with B3LYP/6-31G* calculations, the results of which conform to the preferred introduction of a 1,2- or 2,3-double bond.

Introduction

Serving as important building blocks for many years,[1] the Hajos−Parrish (**1**) and Wieland−Miescher (**2**) ketones have been extensively utilized, especially in the context of natural product total synthesis.



1, n = 1
2, n = 2
3, n = 3

However, little attention has been paid to homologues thereof, such as those having a seven-membered ring (**3**), even though significant differences have already been documented in their reactivity profiles (Scheme 1).[2,3] For example, inversion of enantioselectivity operates in the L-phenylalanine-promoted Robinson annulations of triketones **4** and **7** to give predominantly (*S*)-**5** and (*R*)-**8**, respectively.[1] Equally striking is the chemoselectivity observed upon treatment of these products with sodium borohydride in ethanol. Whereas enedione **5**[4] favors α-attack at the isolated cyclohexanone carbonyl, **8** experiences instead kinetically favored hydride attack at the conjugated enone site.[1]

As a result of their close structural relationship to the A/B ring components of steroids, *cis*- and *trans*-2-decalones have drawn serious study with regard to their tendency to exhibit regiocontrolled enolization (Scheme 2).[5] As exemplified by the functionalization of **10**, the preference for introduction of

(1) For a collection of relevant references, consult: Nagamine, T.; Inomata, K.; Endo, Y.; Paquette, L. A. *J. Org. Chem.* **2007**, *72*, 123.

(2) (a) Selvarajan, R.; John, J. P.; Narayanan, K. V.; Swaminathan, S. *Tetrahedron* **1966**, *22*, 949. (b) Rajagopal, D.; Narayanan, R.; Swaminathan, S. *Proc. Indian Acad. Sci.* **2001**, *113*, 197. (c) Malathi, R.; Rajagopal, D.; Hajos, Z. G.; Swaminathan, S. *J. Chem. Sci.* **2004**, *116*, 159.

(3) (a) Inomata, K.; Barragué, M.; Paquette, L. A. *J. Org. Chem.* **2005**, *70*, 533. (b) The precursor to **3** is 2-methyl-1,3-cycloheptanedione, the preparation of which is described in: Lewicka-Piekut, S.; Okamura, W. H. *Synth. Commun.* **1980**, *10*, 415.

(4) (a) Dutcher, J. S. D.; Macmillan, J. G.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 2663. (b) Hagiwara, H.; Uda, H. *J. Org. Chem.* **1988**, *53*, 2308. (c) See also: Shigehisa, H.; Mizutani, T.; Tosaki, S.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **2005**, *61*, 5057.

(5) Some representative examples include: (a) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 1341. (b) Huffman, J. W.; Balke, W. H. *J. Org. Chem.* **1988**, *53*, 3828. (c) Paquette, L. A.; Sauer, D. R.; Cleary, D. G.; Kinsella, M. A.; Blackwell, C. M.; Anderson, L. G. *J. Am. Chem. Soc.* **1992**, *114*, 7375. (d) Nishitani, K.; Suzuki, J.; Ishibashi, H.; Saitoh, Y.; Kariya, S.; Yamakawa, K. *Heterocycles* **1994**, *39*, 43. (e) Bell, R. P. L.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **2001**, *66*, 2350.

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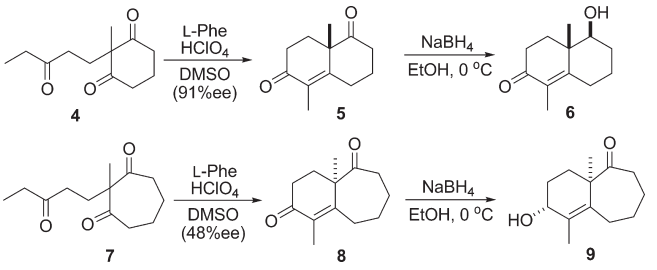
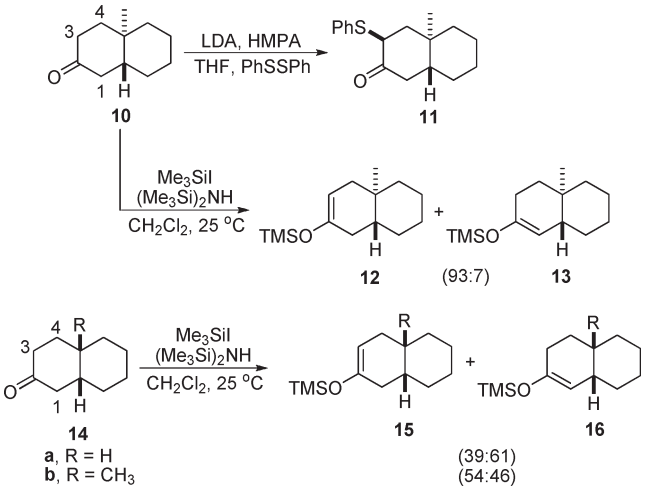
SCHEME 1. Differences in Chemoselectivity within [4.4.0]- and [5.4.0]-Bicyclic Systems



SCHEME 2. Regioselectivity Exhibited by [4.4.0]-Bicyclic Systems

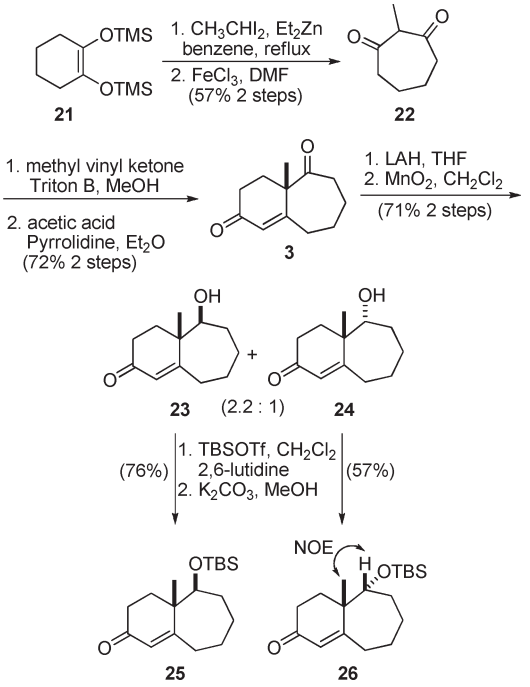


a 2,3-double bond under either kinetic or thermodynamic control is dominant in the trans series. In the case of **11**, the PhSSPh reagent was further found to approach from the β-face of the intermediate enolate anion. On the other hand, the cis isomers **14a** and **14b** gave rise to appreciable amounts of 1,2-enol-derived products as represented by **16a** and **16b**. Simple conformational arguments do not provide an adequate backdrop for explaining these experimental results, especially the attenuation effects often brought on when the angular methyl group is absent.[5b] Rather, these observations have been related to the stabilities of the corresponding olefins.[6]

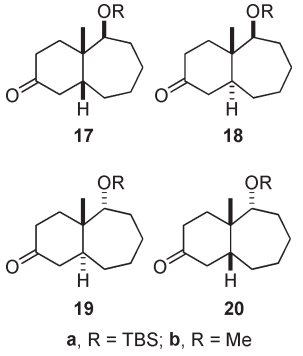
Results and Discussion

Substrate Preparation. In light of the synthetic potential offered by **3**, we have sought to explore the differences in directionality that might attend the enolization of diastereomers **17**−**20** under basic and acidic conditions. The pathway to these targeted substrates began with exhaustive reduction of the two ketone functionalities in **3** with $LiAlH_4$, followed immediately by selective oxidation of the allylic alcohol substructure with manganese dioxide in CH_2Cl_2 (Scheme 3). In this way, a separable 2.2:1 mixture of

SCHEME 3. Synthesis of the Silylated Benzo[7]annulen-2-ones 25 and 26



diastereomers **23** and **24** was generated. The relative configuration about the respective carbinol centers could be assigned following formation of the *tert*-butyldimethylsilyl (TBS) ethers **25** and **26**. In particular, the less predominant constituent was identified as **26** on the strength of NOE studies. As depicted in the structural formula, **26** exhibits an interaction between its angular methyl group and proximate carbinol proton. The same spatial characteristic is not present in **25,** which accordingly does not exhibit a comparable effect. On this basis, hydride attack on **3** is seen to occur more readily from the α-face.



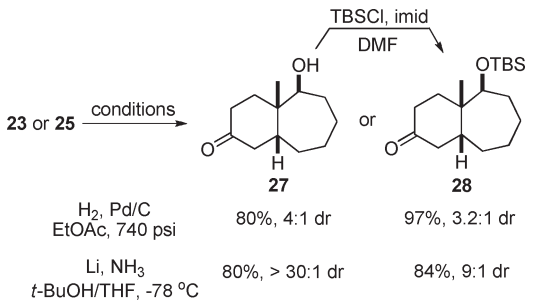
The time had now arrived to compare the directional control inherently available to **23** and **25** during catalytic hydrogenation. The most relevant issue was whether **23** is subject to hydroxyl-directed stereocontrol.[7,8] The silyl ether

(6) (a) Villotti, R.; Ringold, H. J.; Djerassi, C. *J. Am. Chem. Soc.* **1960**, *82*, 5693. (b) Dreiding, A. S. *Chem. Ind.* (*London*) **1954**, 1419. (c) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1955**, *77*, 2505. (d) Velluz, L.; Valls, J.; Nomine, G. *Angew. Chem.* **1965**, *4*, 181. (e) Liston, A. J. *J. Org. Chem.* **1966**, *31*, 2105. (f) Allinger, N. L.; Hirsch, J. A.; Miller, M. A.; Tyminski, I. J. *J. Am. Chem. Soc.* **1968**, *90*, 5773.

(7) (a) For a review, see: Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190. (b) Smith, M. E. B.; Derrien, N.; Lloyd, M. C.; Taylor, S. J. C.; Chaplin, D. A.; McCague, R. *Tetrahedron Lett.* **2001**, *42*, 1347. (c) Evans, D. A.; Morrisey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866. (d) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655. (e) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072.

(8) (a) Paquette, L. A.; Peng, X.; Bondar, D. *Org. Lett.* **2002**, *4*, 937. (b) Peng, X.; Bondar, D.; Paquette, L. A. *Tetrahedron* **2004**, *60*, 9569.

SCHEME 4. Access to Cis-Fused Bicyclic Systems



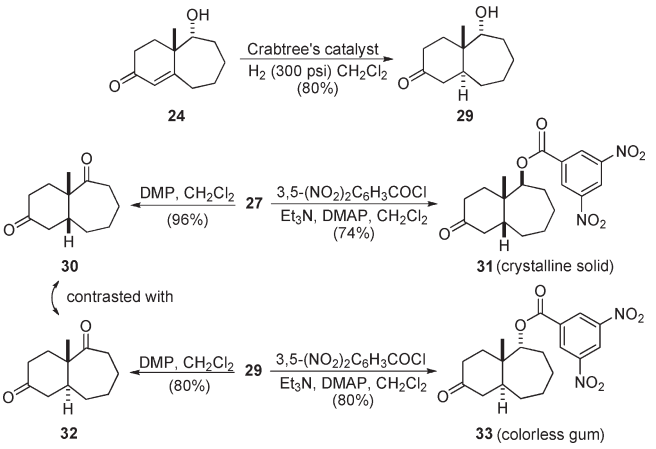
counterpart cannot avail itself of a comparable mechanistic alternative. Nonetheless, the diastereomeric ratio (3.2:1) resulting from the hydrogenation of **25** over 10% palladium on charcoal at 740 psi proved closely comparable to the dr (4:1) realized with **23** (Scheme 4). O-Silylation of **27** demonstrated that the major dihydro product in each of the two experiments had the same ring juncture configuration. However, when recourse was alternatively made to dissolving metal reduction (Li in liquid NH_3), an increase in diastereoselectivity was met with **25** (9:1), but a more dramatic bias (>30:1) was exhibited by **23**. Therefore, stereocontrol accompanies reduction of the conjugated double bond depending upon the reduction conditions.

When this phase of the investigation was expanded to include comparable metal−ammonia reduction of enone diastereomer **24**, a complex mixture resulted from which no desired product could be identified. In this instance, the hydroxyl-directed hydrogenation of **24** proceeded smoothly under a hydrogen atmosphere (300 psi) in the presence of Crabtree's catalyst (0.08 equiv) for 40 h.[7c,7e] The lone stereoisomer **29** was isolated in 80% yield (Scheme 5). The high selectivity of this process was evidenced by direct high-field ^{1}H NMR analysis of the crude reaction mixture.

Following this demonstration that the stereochemical course of bridgehead enone double-bond reduction can be completely controlled by the homoallylic hydroxyl group, **27** and **29** were both converted to their 3,5-dinitrobenzoate derivatives under standard conditions. Derivative **31** proved to be sufficiently crystalline to allow its relative configuration to be established by means of X-ray crystallography (see the Supporting Information for ORTEP diagram of **31**). The trans stereochemistry of **29** was deduced by its oxidation with the Dess−Martin periodinane (DMP) in CH_2Cl_2, and its spectra were contrasted with those recorded for **30** (obtained by DMP oxidation of **27**). As expected, both sets of ^{1}H and ^{13}C NMR spectra showed distinctive differences.

As a direct consequence of the sensitivity of **27** to alkaline fragmentation, its direct O-methylation with sodium hydride and methyl iodide was not feasible. This complication was easily skirted by initial conversion to the ethylene ketal **34** (Scheme 6), whose conversion to **36** and acidic hydrolysis leading to **17b** proceeded efficiently (84% overall yield). When efforts to bring about inversion of the hydroxyl configuration in **34** by the Mitsunobu process were met with failure, ketal **34** was subjected instead to DMP oxidation and subsequent exposure to lithium tri-*tert*-butoxyaluminum hydride. The bulkiness of this reagent led to a predominance of **38** (dr 2.3:1), and ultimately to an efficient route to **20b**.

SCHEME 5. Access to a Trans-Fused System and Stereochemistry Confirmation



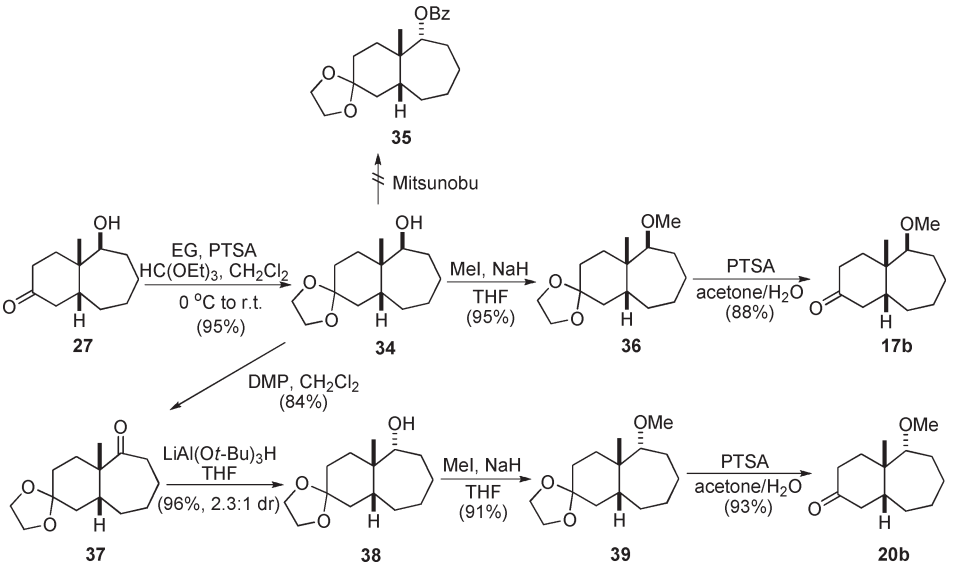
The preparation of the trans-fused isomers **18b** and **19b** followed along parallel lines (Scheme 7). As concerns **40**, the hydroxyl functionality is projected into the molecular interior such that approach of various reagents at that locale is slow. The spatial orientation of this hindered OH is also conducive to elimination as noted when treated with triflic anhydride in pyridine.

The acquisition of **40** was followed by smooth oxidation to **44** with the DMP reagent. Rather unexpectedly, exposure of **44** to various reducing agents ($NaBH_4$, $LiAlH_4$, and $BH_3 \cdot SMe_2$) served uniquely to deliver the α-hydroxy diastereomer. This striking outcome suggested that β-hydride delivery was more preferred in the trans series than the cis. This result also contrasts with the stereoselectivity exhibited by **3**. However, recourse to the reagent-controlled option involving CBS[9] proved to be sufficiently powerful to deliver **45** in useful levels (dr ~1:1.5). The carbinol was then carried on to **18b** in the predescribed manner.

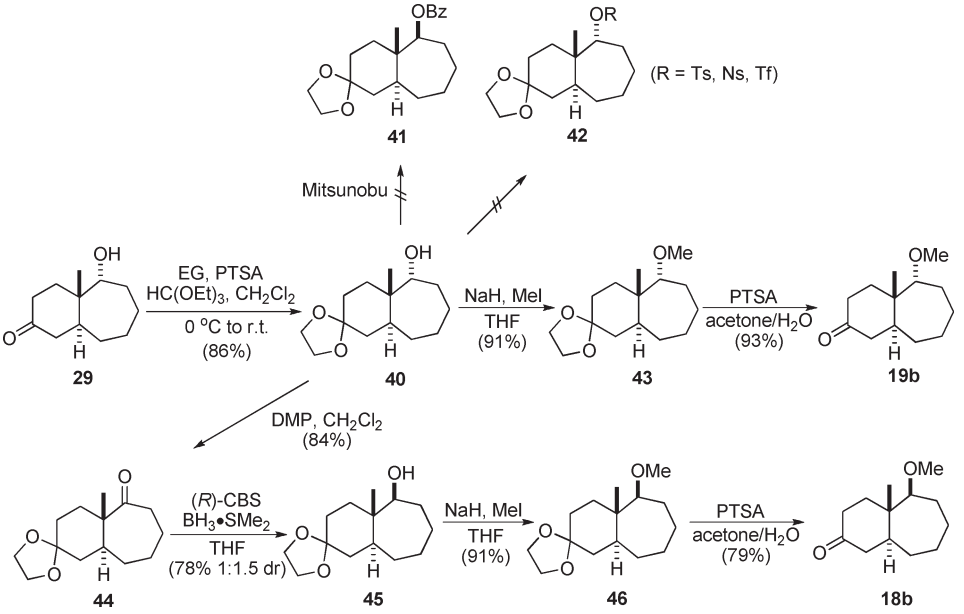
Computational Analysis of Cycloalkene Prototypes. B3LYP/6-31G* calculations were next carried out for the structurally simplified olefinic analogues **A**−**D** (Figure 1). The vinylic −OMe substituent was incorporated to offset any possible hydrogen-bonding interactions that a free OH group might participate in while also skirting those nonbonded steric effects otherwise available to the bulky OTBS units. This computational exercise provided useful evidence indicating that the energy differences between the 1,2- and 2,3-isomers, which although expectedly rather modest, point nevertheless to the more stable nature of **A** and **D** relative to **B** and **C**, respectively. These data agree well with our experimental findings. While the conformations adopted in the trans series are expected to be rather rigid, those defined by the cis-fused pair hold the potential for modest conformational mobility. The latter prospects are expectedly ameliorated by the energetic benefits associated with pseudoequatorial projection of the methoxy group at C-5. The present results indicate that while the cis-fused bicyclic ketone **17b** should enolize with an appreciable bias in the 1,2 direction, the trans-fused **18b** should prefer generation of the 2,3-double bond.

(9) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

SCHEME 6. Synthesis of the Cis-Series Substrates



SCHEME 7. Synthesis of the Trans-Series Substrates



Enolization Studies. In order to maximize our perception of the enolization regioselectivity associated with **17b**−**20b**, both basic (also kinetic) and acidic (also thermodynamic) conditions were probed. Under the first set of experiments, KHMDS in toluene was utilized to deprotonate the substrate to be followed by trapping with TBSOTf (Scheme 8). The exploratory acidic conditions involved the use of *p*-toluenesulfonic acid monohydrate in the presence of excess isopropenyl acetate[10] (Scheme 9). The enolization studies began with the cis substrate **17b**. In this instance, formation of the 1,2-dehydro isomers was invariably favored (**47**/**48** = 1:4.5 and **54**/**55** = 1:2.4). Worthy of mention is the efficiency of all the enolization experiments reported herein (>75%) and high reproducibility of the product distributions. While the predominance of **48** and **55** conforms to the theoretical calculations, evolution of the former is governed by preferred abstraction of a relatively more hindered proton by a bulky base.

The same pair of reactions was next performed with the second cis-fused isomer **20b**, which is distinguished from **17b** only by the α-orientation of the 5-methoxy group. This alteration in configuration was seen to enhance the percentage of the 2,3-dehydro isomers (**51**/**52** = 2.2:1 and **58**/**59** = 1:1.2). In line with observations made by others,[5b] we deduce that complex combinations of torsional effects, nonbonded interactions, and angle strain are responsible for the distribution of isomeric bicyclic enols and enolates (Scheme 8).

(10) (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin Inc.: Menlo Park, CA, 1972; pp 763−765. (b) Diedrich, C. L.; Frey, W.; Christoffers, J. *Eur. J. Org. Chem.* **2007**, 4731.

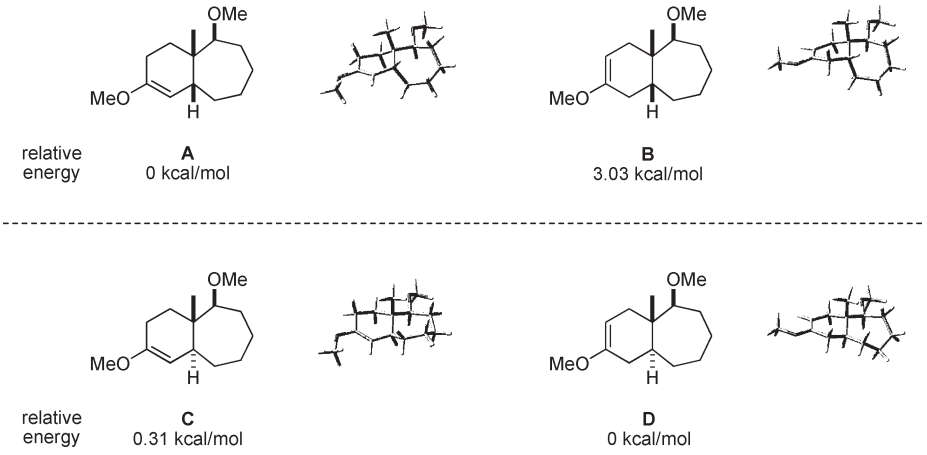
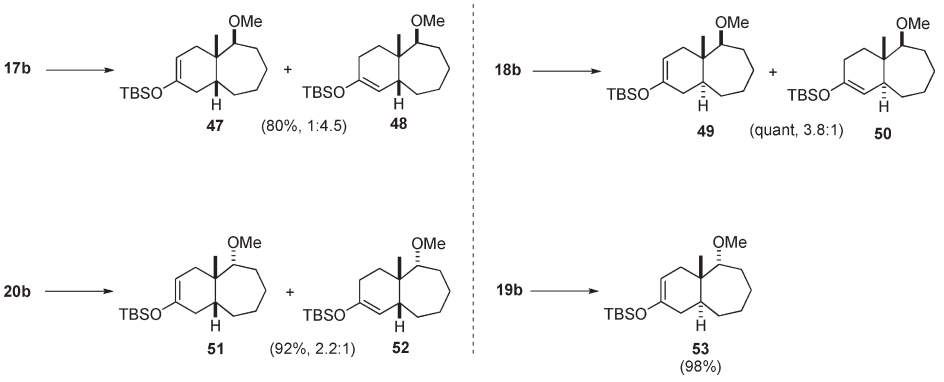
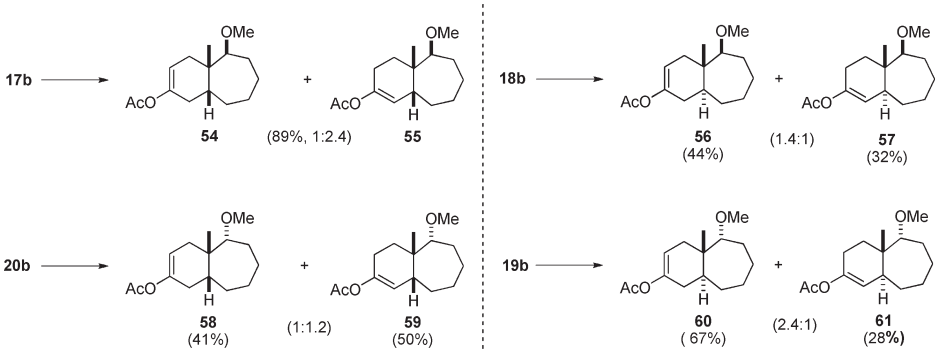


FIGURE 1. Global minimum energy conformations and relative energies for **A**−**D**.

SCHEME 8. O-Silylation of 17b−20b under Kinetic Control (KHMDS, THF/Toluene, −78 °C; then TBSOTf)



SCHEME 9. Acid-Catalyzed O-Acetylations (CH_2=C(CH_3)OAc, *p*-TsOH·H_2O, Reflux)



Our studies continued with bicyclic enones **18b** and **19b** of the trans-fused series. The dramatic effect of the angular methyl group on the same pair of reactions is reflected in Schemes 8 and 9. These latter results indicate the continued dominance of the 2,3-unsaturated derivatives in agreement with the computational studies. α-Orientation of the −OMe substituent is accompanied by a small drop-off in the percentage of the kinetically favored products. As with the enolizations of **17b**, this effect is most pronounced under basic conditions, which gave the TBS enol ether **53** as the only product in virtually quantitative yield.

Assignment of Regiochemistry. In all of the examples but one, it was necessary to make regiochemical assignments based on NMR spectroscopy. At the outset, it appeared reasonable to expect that a doublet (d) would manifest itself for H^a and a doublet of doublets (dd) for the second vinyl proton H^b (Scheme 10). However, the generation of **47** and **48** from **17b** led in both instances to the appearance of two vinyl proton signals as a dd (δ 4.71) and multiplet (m, δ 4.76−4.73), respectively. Long-range coupling to both H^a and H^b was likely operational, a conclusion supported by the close exceptional similarity of the downfield segments of the ^{1}H NMR spectra of **48** and **62** (Scheme 10). The match in

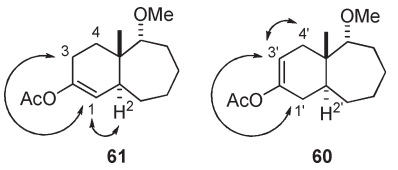
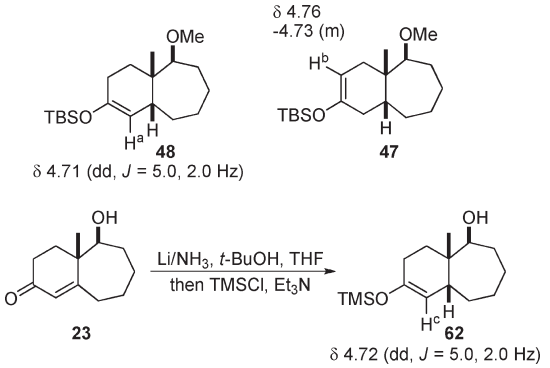


FIGURE 2. Regiochemistry assignments for the trans series as determined by COSY studies.

SCHEME 10. Regiochemistry Assignments for the Cis Series



spectral features in that region confirmed our original assumptions and supported the assignments of other members of the cis series. The trans isomers exhibited more complex olefinic splitting patterns, most particularly for H^b (Figure 2). Some clearly identified relationships included strong correlations between H-1 and H-2 alongside somewhat weaker interactions involving H-1 and H-3. As concerns **60**, additional correlations were noted between H-3′ and H-4′ as well as between H-3′ and H-1′. The remaining trans assignments followed accordingly.

Overview

The regioselectivity of the enolization of a complete set of four stereoisomeric 4a-methyl-5-methoxyperhydrobenzo-[7]annulen-2-ones has been assessed under kinetic and thermodynamic conditions. It was found that while cis-fused systems favor the introduction of a 1,2-double bond, trans-fused analogues clearly prefer the evolution of 2,3-unsaturation. The OMe substituent on the 7-membered ring proved to be another regiocontrol element, with β-OMe favoring introduction of a 1,2-double bond and α-OMe proving conducive to the development of 2,3-unsaturation. The underlying causes for this long-range regiocontrol are not yet clear, although associated conformational changes can be tacitly assumed to be contributory.

Experimental Section

General Enolization Procedure (Kinetic Conditions). To a solution of **17b** (43 mg, 0.2 mmol) in THF (4.1 mL) was added KHMDS (0.5 M in toluene, 2.5 mL, 1.25 mmol) at −78 °C. The resulting mixture was stirred at this temperature for 40 min, treated with TBSOTf (0.14 mL, 0.61 mmol), stirred at −78 °C for 1 h, and quenched by the dropwise addition of saturated $NaHCO_3$ solution (3 mL). The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. The product was purified via column chromatography (40:1 hexanes/ethyl acetate) to afford **47** and **48** (1:4.5) as a pair of diastereomers (53.4 mg, 80%). For **48**: IR (neat) 1672, 1198 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.71 (dd, J = 5.0, 2.0 Hz, 1 H), 3.30 (s, 3 H), 2.77−2.75 (m, 1 H), 2.04−1.95 (m, 1 H), 1.86−1.83 (m, 2 H), 1.78−1.73 (m, 3 H), 1.68−1.64 (m, 2 H), 1.46−1.36 (m, 2 H), 1.31−1.21 (m, 3H), 0.92 (s, 9 H), 0.88 (s, 3 H), 0.13 (s, 3 H), 0.12 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8, 110.1, 91.0, 57.4, 44.7, 38.3, 31.1, 30.4, 29.7, 28.6, 27.1, 26.8, 25.7 (3C), 18.0, 18.0, −4.3, −4.5; HRMS (ESI) calcd for $C_{19}H_{36}NaO_2Si$ $[M + Na]^+$ 347.2382, found 347.2378.

General Enolization Procedure (Thermodynamic Conditions). To a solution of **17b** (50 mg, 0.24 mmol) in isopropenyl acetate (4.8 mL) was added PTSA·H_2O (4.5 mg, 0.024 mmol) at rt. The reaction mixture was heated to reflux for 24 h, quenched with saturated $NaHCO_3$ solution (5 mL), and extracted with EtOAc (10 mL × 2). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The product was purified via column chromatography (15:1 hexanes/ethyl acetate) to afford **54** and **55** (1:2.4) as a pair of diastereomers (53.5 mg, 89%). For **55**: IR (neat) 1753, 1221 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.16 (dd, J = 5.0, 2.0 Hz, 1 H), 3.29 (s, 3 H), 2.78−2.77 (m,1 H), 2.24−2.16 (m, 1 H), 2.09 (s, 3 H), 1.97−1.90 (m, 1 H), 1.87−1.82 (m, 2 H), 1.80−1.75 (m, 2 H), 1.67−1.62 (m, 2 H), 1.49−1.41 (m, 2 H), 1.34−1.22 (m, 3 H), 0.92 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 146.9, 118.5, 90.4, 57.3, 44.5, 38.5, 30.2, 30.1, 29.4, 28.3, 26.9, 23.9, 21.0, 17.9; HRMS (ESI) calcd for $C_{15}H_{24}NaO_3$ $[M + Na]^+$ 275.1623, found 275.1627.

Acknowledgment. We thank The Ohio State University for partial financial support and Dr. Nicolas Proust for assistance with manuscript submission.

Note Added after ASAP Publication. In the version published ASAP July 30, 2009, Scheme 1 contained errors in the formulas for compounds 4 and 7; the correct version was published August 4, 2009.

Supporting Information Available: All experimental procedures, analytical data, details of the X-ray crystallographic analyses of **31**, computational data for **A**−**D**, and copies of the ^1H and ^{13}C NMR spectra of all new compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.