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New Cationic Olefin Cyclization−Pinacol Reactions. Ring-Expanding Cyclopentane Annulations That Directly Install Useful Functionality in the Cyclopentane Ring

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Two new tandem cationic olefin cyclization−pinacol reactions that provide cyclopentane-fused cycloalkanone products are described. Treatment of *cis*-1-[2-alkenyl-2-(triethylsiloxy)cycloalkyl]-but-3-en-2-ol derivatives **21**−**24** with triflic anhydride at −78 °C affords cycloalkanones **31**−**34** in 54−90% yields with diastereoselectivities of typically >20:1. In this unusual transformation, the starting cycloalkanone is ring-expanded and fused to a 2-alkenylcyclopentane fragment. Reaction of *cis*-(2-siloxy-2-alkenylcycloalkyl)pyrrolidin-1-ylethanones **15**−**17** with triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at −20 to +65 °C followed by hydrolysis of the intermediate iminium salts **64** with aqueous $KHCO_3$ affords cycloalkanediones **46**−**48** in moderate yield and high diastereoselectivity (>20:1). These are the first examples of ring-expanding cyclopentane annulations that directly introduce a carbon side chain or carbonyl functionality at the cyclopentane C2 position. The high diastereoselectivities observed in these reactions are believed to arise from reaction through highly organized cyclic transition states.

Introduction

For some years, our group has been involved in the development of tandem Prins cyclization−pinacol reactions for the synthesis of carbocyclic and heterocyclic products.[1] These reactions typically exhibit excellent levels of stereocontrol, as they are believed to occur through highly organized six-membered chairlike transition states. A wide variety of monocyclic and fused polycyclic compounds[1,2] as well as attached ring systems[3] and spirocycles[4] can be constructed in this way. One variant of this chemistry, the ring-expanding cyclopentane annulation, involves treatment of a 2-[(2,2-dialkoxy)-ethyl]-1-alkenylcycloalkanol silyl ether with a Lewis acid. The resulting oxonium ion engages the tethered alkene in a 6-endo Prins cyclization, which is followed by a pinacol rearrangement of the resulting cyclic carbenium ion to provide cycloalkanones that have been expanded by one carbon and fused to a 2-alkoxycyclopentane ring (Figure 1). Analogous ring-expanding cyclopentene[5] and cyclohexane[6] annulations have been described also. The ring-expanding cyclopentane annulation has been exploited to synthesize a number of natural products including the lycopodium alkaloid magellaninone (**1**)[7] and the diterpene shahamin K (**2**).[8]

The 2-alkoxycyclopentane unit introduced in ring-expanding cyclopentane annulations is not converted easily into congeneric 2-alkyl or 2-alkenyl derivatives. However, a number of natural products exhibiting potentially important biological activities contain a 2-alkenylcyclopentane fragment fused to various carbocyclic rings. For example, cylindramide (**3**) is cytotoxic toward B16 melanoma cells,[9a] geodin A (**4**) is a potent nematocide,[9d] and SS-8201B (**5**) exhibits antibacterial activity.[9e] Our interest in these compounds, coupled with the opportunity they provide to further expand the scope of the ring-expanding cyclopentane annulations, led us to explore the use of other functional groups as initiators for pinacol-terminated cationic cyclization reactions. In particular, we wished to examine initiating groups that would directly install alkenyl or carbonyl functionality at the C2 position of the newly formed cyclopentane ring. Herein we describe the use of allyl cations and keten-

(1) For brief reviews, see: (a) Overman, L. E. *Aldrichim. Acta* **1995**, *28*, 107−120. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352−359. (c) Overman, L. E. In *Selectivities in Lewis Acid-Promoted Reactions*; NATO ASSI Series 289; Schinzer, D., Ed.; Kluwer Academic: Dordrecht, The Netherlands, 1989; pp 1−20.

(2) (a) Hirst, G. C.; Howard, P. N.; Overman, L. E. *J. Am. Chem. Soc.* **1989**, *111*, 1514−1515. (b) Gahman, T.; Overman, L. E. *Tetrahedron* **2002**, *58*, in press.

(3) Overman, L. E.; Pennington, L. P. *Can. J. Chem.* **2000**, *78*, 732−738.

(4) Minor, K. P.; Overman, L. E. *Tetrahedron* **1997**, *53*, 8927−8940.

(5) Johnson, T. O.; Overman, L. E. *Tetrahedron Lett.* **1991**, *32*, 7361−7364.

(6) Ando, S.; Minor, K. P.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 6379−6387.

(7) Hirst, G. C.; Johnson, T. O., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992−2993.

(8) Lebsack, A. D.; Overman, L. E.; Valentekovich, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 4851−4852.

(9) (a) Kanazawa, S.; Fusetani, N.; Matsunaga, S. *Tetrahedron Lett.* **1993**, *34*, 1065−1068. (b) Gunasekera, S. P.; Gunasekera, M.; McCarthy, P. *J. Org. Chem.* **1991**, *56*, 4830−4833. (c) Shigemori, H.; Bae, M.; Yazawa, K.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 4317−4320. (d) Capon, R. J.; Skene, C.; Lacey, E.; Gill, J. H.; Wadsworth, D.; Friedel, T. *J. Nat. Prod.* **1999**, *62*, 1256−1259. (e) Kouichi, Y. Japanese patent JP59151896, Aug 30, 1984; *Chem. Abstr.* **1985**, *102*, 94328.

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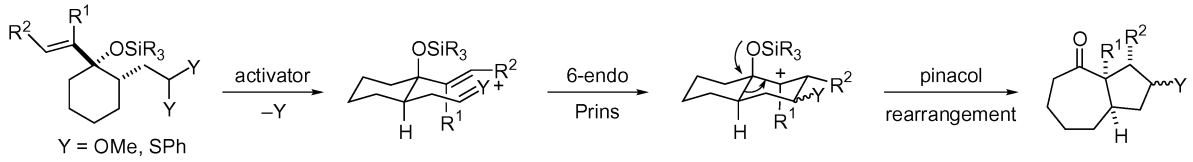
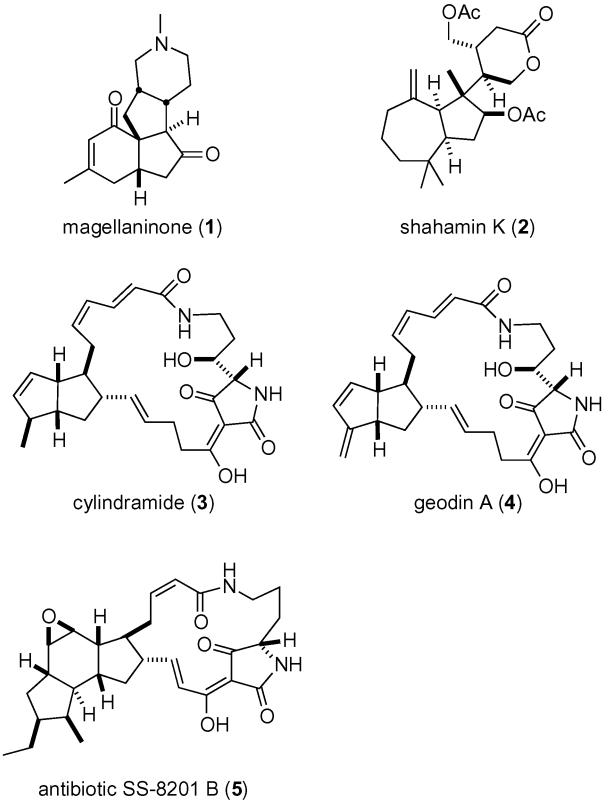


FIGURE 1.

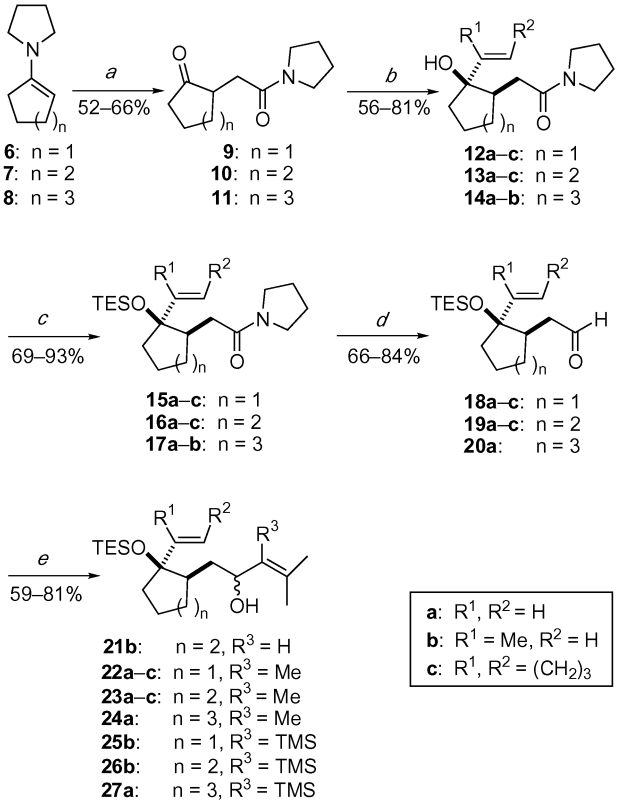
iminium ions as initiators for ring-expanding cyclopentane annulations.



Results

Allyl Cation-Initiated Tandem Cyclization−Pinacol Reactions. Since the pioneering investigations of Johnson,[10] allylic alcohols have proven to be highly efficacious initiators of cationic cyclization reactions.[11,12] We anticipated that generation of an allylic cation from a 1-[2-alkenyl-2-(trialkylsiloxy)cycloalkyl]alk-3-en-2-ol (**21**−**27**) would initiate ring-expanding cyclopentane annulation to provide a bicyclo[*n*.3.0]alkanone product containing a 2-alkenyl side chain on the cyclopentane fragment. Accordingly, substrates **21**−**27** were prepared as shown in Scheme 1. Alkylation of enamines **6**−**8**[13] with 1-(chloroacetyl)pyrrolidine[14] gave keto amides **9**−**11**, which were

SCHEME 1[a]



[a] Key: (a) 1-(chloroacetyl)pyrrolidine; (b) RLi or RMgBr/$CeCl_3$; (c) TES-Cl, DMAP, pyridine; (d) Ti(O*i*-Pr)$_4$, Ph_2SiH_2; (e) R′Li or R′MgBr.

treated with an alkenyllithium or alkenylcerium[15] reagent to afford tertiary allylic alcohols **12**−**14**. Diastereoselection in the alkenylmetal additions ranged from 3−5:1 for cyclopentanone substrates **12a**−**c** to 5−10:1 for cyclohexanone precursors **13a**−**c** and 10−20:1 for cycloheptanone amides **14a**,**b**.[16,17] Protection of the tertiary alcohols as triethylsilyl ethers,[18] followed by reduction of the amide functionality to the aldehyde oxidation state with Ti(O-*i*-Pr)$_4$/Ph_2SiH_2 provided siloxyalkenyl aldehydes **18**−**20**.[19] Reaction of these intermediates with an

(10) (a) Johnson, W. S.; Lunn, W. H.; Fitzi, K. *J. Am. Chem. Soc.* **1964**, *86*, 1972−1978. (b) Johnson, W. S.; Jensen, N. P.; Hooz, J.; Leopold, E. J. *J. Am. Chem. Soc.* **1968**, *90*, 5872−5881.

(11) Reviews: (a) Bartlett, P. A. *Asymm. Synth.* **1984**, *3*, 341−409. (b) Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 341−377. (c) Harmata, M. *Tetrahedron* **1997**, *53*, 6235−6280.

(12) For representative recent examples, see: (a) Gassman, P. G.; Riehle, R. J. *J. Am. Chem. Soc.* **1989**, *111*, 2319−2320. (b) Collins, M. P.; Mann, J.; Finch, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 239−240. (c) Doyle, T. J.; VanDerveer, D.; Haseltine, J. *Tetrahedron Lett.* **1995**, *36*, 6197−6200.

(13) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207−222.

(14) Seguin, H.; Gardette, D.; Moreau, M.-F.; Madelmont, J.-C.; Gramain, J.-C. *Synth. Commun.* **1998**, *28*, 4257−4272.

(15) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392−4398.

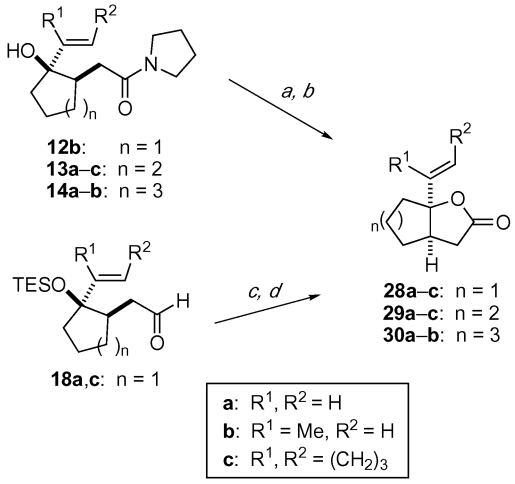
(16) The tertiary alcohol products were often accompanied by 15−30% of unreacted starting material, presumably due to competitive deprotonation of the ketone substrates. The amount of unreacted starting material was minimized by the use of alkenylcerium reagents.

(17) Diastereomer ratios were determined by ^{1}H NMR analysis.

(18) Roush, W. R.; Russo-Rodriquez, S. *J. Org. Chem.* **1987**, *52*, 598−603.

(19) Bower, S.; Kreutzer, K. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1515−1516.

SCHEME 2[a]



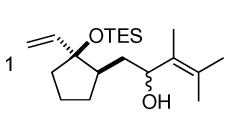
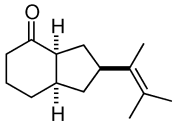
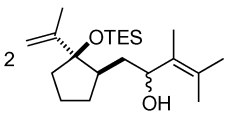
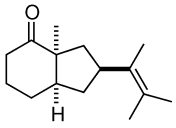
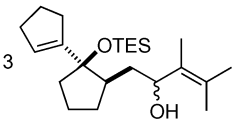
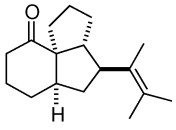
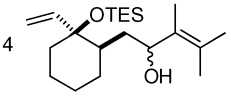
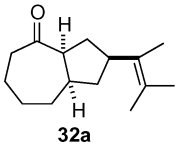
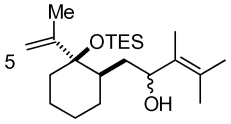
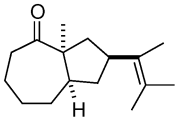
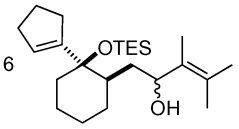
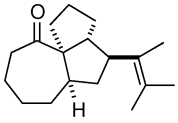
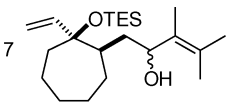
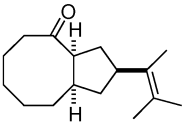
[a] Key: (a) NaOH, EtOH, H_2O, 70 °C; (b) Mukaiyama's salt, Et_3N, DMF; (c) TBAF; (d) TPAP, NMO, MeCN, H_2O.

appropriate vinyllithium or vinyl Grignard reagent gave secondary allylic alcohols **21**−**27** as ∼1:1 mixtures of alcohol epimers.

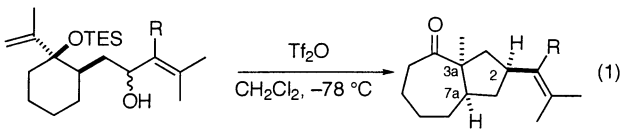
The relative configuration of the side chains of **21**−**27** was assigned by conversion of amides **12**−**14** or aldehydes **18** to the corresponding bicyclic lactones (Scheme 2), either by hydrolysis of the amides followed by lactonization with Mukaiyama's salt[20] or by desilylation of **18** followed by TPAP/NMO oxidation of the resulting lactols.[21] Analysis by ^{1}H NMR NOE confirmed the relative configuration of lactones **28**−**30**; diagnostic NOE signals were observed between the angular C3a hydrogen and the α or cis-β hydrogen(s) of the alkene substituent.

In our preliminary experiments, we found that treatment of *cis*-1-[2-isopropenyl-2-(triethylsiloxy)cyclohexyl]-4-methyl-pent-3-en-2-ol (**21b**) with 1.3 equiv of triflic anhydride at −78 °C in dichloromethane[12a] led to the formation of 3a-methyl(2-methylpropenyl)octahydroazulen-4-one (**31b**) in 64% yield as a 1.5:1 mixture of epimers at the carbon bearing the alkenyl side chain (eq 1). Both epimers had a cis ring fusion, with the major epimer having the 2-methylpropenyl side chain oriented on the more sterically congested concave β face. We reasoned that incorporation of an additional methyl group at C3 of the allyl side chain should increase the diastereoselectivity of the conversion (see below). Accordingly, *cis*-1-[2-isopropenyl-2-(triethylsiloxy)cyclohexyl]-3,4-dimethylpent-3-en-2-ol (**23b**) was allowed to react with triflic anhydride to provide a 90% yield of (1,2-dimethylpropenyl)-3a-methyloctahydroazulen-4-one (**32b**) as a 10:1 mixture of epimers (eq 1). As observed in the reaction of **21b**, the major epimer has a cis ring fusion and the alkenyl side chain is oriented on the concave face. The configuration of **32b** was assigned by ^{1}H NMR NOE studies; irradiation of the C2 hydrogen led to small NOE enhancements of both the C7a hydrogen and the C3a methyl substituent.

TABLE 1. Tandem Allyl Cation−Olefin Cyclization/ Pinacol Rearrangements

Entry	Substrate	Product	d.r.	Yield
1	 **22a**	 **33a**	>20/1	65%
2	 **22b**	 **33b**	>20/1	86%
3	 **22c**	 **33c**	>20/1[a]	73%
4	 **23a**	 **32a**	>20/1	78%
5	 **23b**	 **32b**	10/1	90%
6	 **23c**	 **32c**	>20/1[a]	54%
7	 **24a**	 **34a**	>20/1	85%

[a] This material contained ∼5% of an unidentified isomeric product.



21b: R = H
23b: R = Me

31b: R = H 64%, 1.5:1 β:α
32b: R = Me 90%, 10:1 β:α

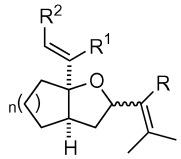
To probe the scope and limitations of the allyl cation-initiated ring expanding cyclopentane annulations, allylic alcohol substrates **22**−**24** were prepared and allowed to react with triflic anhydride at −78 °C. As summarized in Table 1, products **32**−**34** were obtained in good to

(20) Funk, R. L.; Abelman, M. M.; Jellison, K. M. *Synlett* **1989**, 36−37.

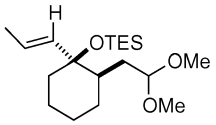
(21) Paquette, L. A.; Kang, H.-J.; Ra, C. S. *J. Am. Chem. Soc.* **1992**, *114*, 7387−7395.

excellent yields (54−90%).[22] In all cases, the bi- or tricyclic ketone product had a cis ring fusion; in all reactions but one, the alkenyl side chain was incorporated with >20:1 stereocontrol as judged by ^{1}H NMR and/or GC analysis of crude reaction mixtures.[23] Substrates bearing a weakly nucleophilic vinyl group (**22a**−**24a**), as well as those containing a more reactive 2-propenyl (**22b**−**23b**) or 1-cyclopentenyl (**22c**−**23c**) unit were transformed in good yields.[24] Disubstitution at the terminus of the allylic initiator was required for successful transformation, as substrates containing an allylic initiator having a single carbon substituent at the allyl terminus failed to undergo the desired rearrangement.

The major side products formed in these allyl cation-initiated annulations are bicyclic ethers **35**, which presumably arise from capture of the allyl cation by the silyl ether (or possibly the free tertiary alcohol formed by prior cleavage of the silyl ether). Attempts to minimize the formation of **35** by protecting the tertiary alcohol as a diisopropylethylsilyl ether failed to improve the yields.[25] Use of other anhydrides or Lewis acids to initiate the reactions did not lead to increased yields; moreover, addition of the hindered base, 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), led to slower reaction rates with no improvement in yields.



35

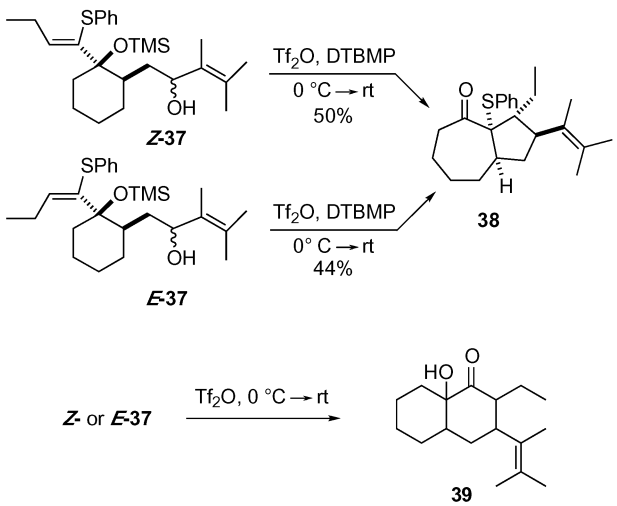


36

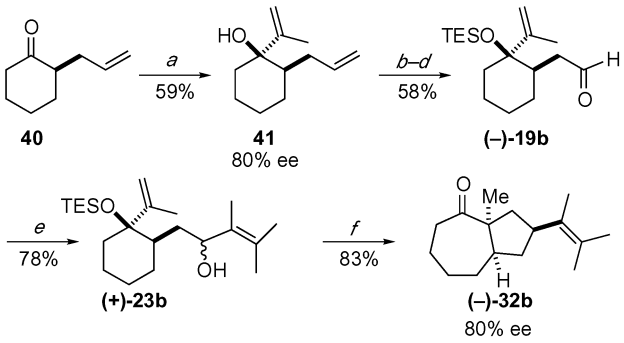
Previous studies of the scope and limitations of the oxonium ion-initiated ring expanding cyclopentane annulations showed that substrates such as **36** that contain an unbranched vinyl substituent such as 1-propenyl fail to undergo ring-enlarging cyclopentane annulation to deliver octahydroazulen-4-ones having a hydrogen substituent at the angular position and a carbon side chain at C3.[2,26]

To potentially arrive at products of this type by a two-step sequence, reactions of substrates **37** containing a 1-(thiophenyl)alkenyl substituent were examined.[27] As shown in Scheme 3, both ***Z*-37** and ***E*-37** were transformed in the presence of triflic anhydride and DTBMP to octahydroazulen-4-one **38** (44−50%) with >20:1 diastereoselectivity. It was essential in these cases to add the substrate to a solution of triflic anhydride and DTBMP at 0 °C; reactions carried out in the absence of the hindered base DTBMP provided complex mixtures of products. This procedure also minimized formation of a side product provisionally assigned, on the basis of ^{1}H NMR, IR, and MS data, as α-hydroxy decalone **39**.[28]

SCHEME 3



SCHEME 4[a]



[a] Key: (a) 2-propenylMgBr, $CeCl_3$; (b) *n*-BuLi, TES-OTf; (c) OsO_4, NMO; (d) $Pb(OAc)_4$, $NaHCO_3$; (e) 2-bromo-3-methyl-2-butene, *s*-BuLi; (f) Tf_2O, −78 °C.

To illustrate the feasibility of synthesizing enantioenriched cycloalkanones in this way, cyclohexyl precursor (+)-**23b** was prepared as shown in Scheme 4. Addition of 2-propenylmagnesium bromide to (−)-2-allylcyclohexanone[29] provided alcohol **41** with >20:1 diastereoselectivity; this product was judged to be 80% ee by chiral HPLC analysis. In a three-step sequence, alcohol **41** was converted to aldehyde (−)-**19b** in 58% overall yield by silylation of the free alcohol using *n*-BuLi/TES-OTf,[30] followed by OsO_4-catalyzed dihydroxylation of the terminal olefin and cleavage of the resulting diol with lead tetraacetate. Addition of 2-lithio-3-methyl-2-butene[31] to (−)-**19b** provided (+)-**23b** in 78% yield. Reaction of this

(22) It is extremely important that the triflic acid formed under the reaction conditions be neutralized at −78 °C by the addition of aqueous $NaHCO_3$ prior to warming. Failure to quench the reactions at low temperature led to double-bond isomerization.

(23) The stereochemistry of all products was assigned by NOE studies. See the Supporting Information for details.

(24) Analogous precursors containing an alkyne rather than an alkene reacted to give complex mixtures of products; only low yields (<30%) of products of ring-enlarging cyclopentene annulation were obtained.

(25) It was not possible to prepare substrates containing silyl ethers larger than diisopropylethylsilyl.

(26) For a notable exception using a thionium ion initiator, see ref 8.

(27) The stereochemistry of ***E*-** and ***Z*-37** was assigned by analogy to the other substrates.

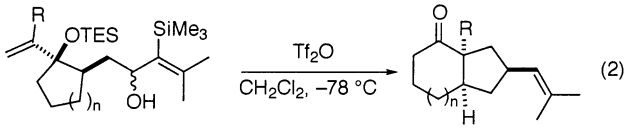
(28) The side product had a molecular weight of 264 and showed IR stretches at 3549 and 1702 cm^{-1}. The alkenyl methyl groups and the ethyl substituent were clearly visible in the ^{1}H NMR, as were signals at 3.05, 2.59, and 1.83 that are consistent with the presence of an allylic hydrogen, a hydrogen adjacent to a ketone, and a hydrogen at a ring fusion.

(29) This material was prepared according to the literature procedure and was estimated to be 80% ee by optical rotation; see: Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am Chem. Soc.* **1981**, *103*, 3081−3087.

(30) Other methods to install a TES ether failed; epimerization of the C1 stereocenter occurred if the TES-OTf-mediated silylation reactions were warmed above −40 °C.

intermediate with triflic anhydride gave rise to (−)-**32b** in 83% yield and 80% ee, confirming that ring-enlarging cyclopentane annulation occurred without detectable loss of enantiomeric purity.

The low stereoselection observed in the conversion of **21b** to **31b** (see eq 1) makes this variant of the allyl cation-initiated cyclization−pinacol rearrangement sequence impractical for the preparation of products containing an unbranched alkenyl side. To address this problem, we reasoned that such products might be produced from cyclization substrates bearing a trialkylsilyl group at C3 of the allylic alcohol side chain. We expected such precursors to react with high diastereoselectivity to deliver products that upon protodesilylation would have an unbranched alkenyl side chain. Accordingly, *cis*-1-[2-isopropenyl-2-(triethylsiloxy)cyclohexyl]-4-methyl-3-(trimethylsilyl)pent-3-en-2-ol (**26b**) was prepared and cyclized by reaction with triflic anhydride at −78 °C in dichloromethane (eq 2). To our delight, hydroazulenone **31b** was formed with >20:1 stereoselectivity and 80% yield (eq 2), protodesilylation having occurred under the reaction conditions. Monitoring the reaction by GC−MS confirmed that the hydroazulenone having a 2-methyl-1-trimethylsilyl-1-propenyl side chain was generated initially and then more slowly underwent protodesilylation.[32] In a similar fashion, substrates **25b** and **27a** were, respectively, transformed to **42b** and **43a** (eq 2). Again in these cases, diastereoselection was excellent (>20:1); however, yields were modest (54% in each case). Unfortunately, substrates that contained a trimethylsilyl group at C3 and a single alkyl substituent at C4 of the allylic alcohol side chain provided low yields of the desired products.

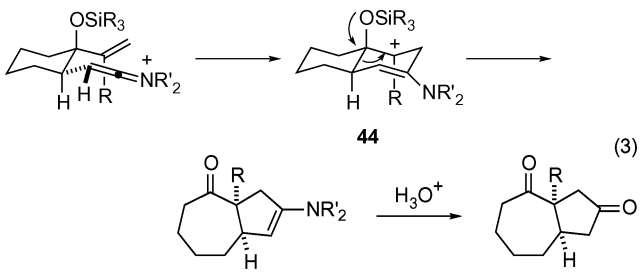


(2)

26b: n = 2, R = Me
25b: n = 1, R = Me
27a: n = 3, R = H

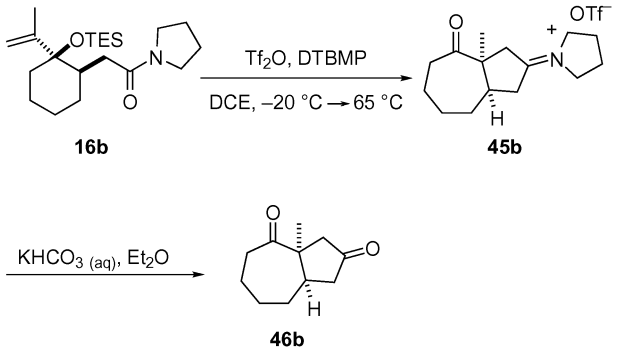
31b: 80%, >20:1 β:α
42b: 54%, >20:1 β:α
43a: 54%, >20:1 β:α

Keteniminium Ion-Initiated Cyclization−Pinacol Rearrangements. To further expand the scope of ring-enlarging cyclopentane annulations, we briefly examined the use of keteniminium ions to initiate ring-enlarging cyclopentane annulations. Our expectation was that upon aqueous workup these reactions would deliver directly dione products having a carbonyl group in the newly formed cyclopentane ring (eq 3). The cyclopentanone carbonyl could then serve as a locus for further functionalization of the five-membered ring.



(3)

SCHEME 5



Ghosez and co-workers have extensively developed the synthesis of cyclobutanones by the reaction of keteniminium ions with alkenes.[33] Keteniminium ions are typically generated from tertiary amides by reaction with triflic anhydride and a hindered pyridine base and react with alkenes to provide iminium salts, which when hydrolyzed under biphasic conditions yield cyclobutanone products. In incisive mechanistic investigations, Ghosez showed that these formal cycloadditions are not concerted, but instead proceed in a stepwise manner by way of cationic intermediates.[34] In our projected application (eq 3), geometric constraints should result in the initially generated bicyclic cation **44** undergoing pinacolic ring expansion rather than intramolecular reaction with the enamine functionality to generate a product containing a high energy bicyclo[2.2.0]hexane unit.

This new annulation sequence was initially examined with *cis*-1-pyrrolidin-1-yl-2-[2-triethylsiloxy-2-isopropenylcyclohexyl]ethanone (**16b**) (Scheme 5). Reaction of this unsaturated siloxy amide with triflic anhydride and DTBMP at −20 °C, followed by heating overnight at 65 °C in 1,2-dichloroethane generated iminium salt **45b**. This intermediate was characterized by diagnostic ^{13}C NMR signals at δ 213.3 and 192.7 ppm and IR stretches at 1702 and 1620 cm^{-1}. Hydrolysis of the crude iminium salt with aqueous $KHCO_3/Et_2O$ provided *cis*-3a-methyloctahydroazulene-2,4-dione (**46b**) in 72% yield. Stereoselection in generating the cis isomer was >20:1 as judged by comparison of the ^1H and ^{13}C NMR spectra of the product to those previously reported for **46b**.[2]

As summarized in Table 2, a number of related unsaturated siloxy amides were converted to the bicyclo[*n*.3.0]alkanediones. Although diastereoselection was generally >20:1 favoring formation of the cis isomer, yields varied widely (27−80%).[35] This reaction is not as general as the allyl cation-initiated cyclizations discussed

(31) Pasynkiewicz, S.; Pietrzykowski, A.; Buchowicz, W.; Poptawska, M. *J. Organomet. Chem.* **1993**, *463*, 235−238.

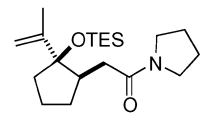
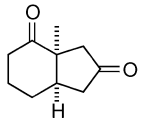
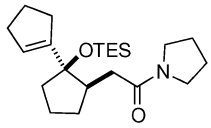
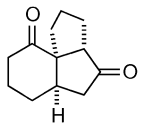
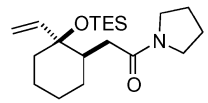
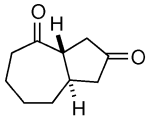
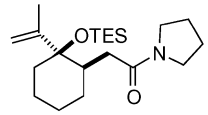
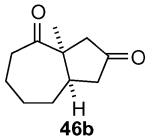
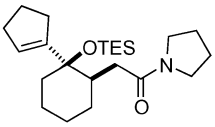
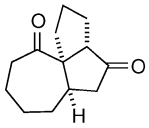
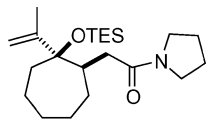
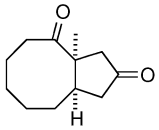
(32) Mixtures of silylated and desilylated products were isolated from incomplete reactions.

(33) (a) Falmagne, J.-B.; Escudero, J.; Taleb-Sahraoui, S.; Ghosez, L. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 879−880. (b) Ghosez, L.; Marko, I.; Hesbain-Frisque, A.-M. *Tetrahedron Lett.* **1986**, *27*, 5211−5214. (c) Schmidt, C.; Falmagne, J. B.; Escudero, J.; Vanlierde, H.; Ghosez, L. *Org. Synth.* **1990**, *69*, 199−204. (d) For a review, see: Snider, B. B. *Chem. Rev.* **1988**, *88*, 793−811.

(34) Saimoto, H.; Houge, C.; Hesbain-Frisque, A.-M.; Mockel, A.; Ghosez, L. *Tetrahedron Lett.* **1983**, *24*, 2251−2254.

(35) The stereochemistry of **46a**,**b** and **47b**,**c** was assigned by comparing the ^1H and ^{13}C NMR spectra of these products to the previously published data. The stereochemistry of **46c** and **48b** was assigned by analogy to the related compounds **47c** and **46b**.

TABLE 2. Tandem Keteniminium Ion−Olefin Cyclization/Pinacol Rearrangements

Entry	Substrate	Product	d.r.	Yield
1	 **15b**	 **47b**	>20/1	80%
2	 **15c**	 **47c**	>20/1	27%
3	 **16a**	 **46a**	10/1	60%
4	 **16b**	 **46b**	>20/1	72%
5	 **16c**	 **46c**	>20/1	34%
6	 **17b**	 **48b**	>20/1	56%

previously. For example, cyclopentyl amide **15a** and cycloheptyl amide **17a** bearing vinyl substituents (see Scheme 1) provided <10% yield of the desired product, whereas cyclohexyl amide **16a** was transformed in 60% yield to *trans*-octahydroazulene-2,4-dione (**46a**). Analysis of crude reaction mixtures by ^{1}H NMR indicated that the intermediate iminium salts were generated in >80% yields in the reactions of the propenyl substrates **15b**, **16b**, and **17b** and 50−60% yield from cyclopentenyl substrates **15c** and **16c**.[36] Attempts to modify the hydrolysis conditions to improve the yields of the dicarbonyl products were unsuccessful. For example, hydrolysis of the intermediate iminium salts using mixtures of ether, acetone or methanol and aqueous NaOH, Na_2CO_3, $NaHCO_3$, or pH 7 phosphate buffer failed to improve the yields. In the absence of the pyridine base, no reaction was observed. [37]

Discussion

Synthetic Scope. The scope of the two new ring-expanding cyclopentane annulations reported herein is more limited than that of related annulations initiated by α-heterocarbenium ions.[2−8] Ring-enlarging cyclopentane annulations that directly introduce an alkenyl side chain in the newly formed cyclopentane ring can be accomplished by the reaction of *cis*-1-[2-alkenyl-2-(triethylsiloxy)cycloalkyl]but-3-en-2-ol derivatives with triflic anhydride at −78 °C. As summarized in Table 1, *cis*-bicyclo[*n*.3.0]alkanones and related tricyclic products incorporating a tetrasubstituted alkene side chain on the more-hindered concave face are formed in yields ranging from 54 to 90% and with diastereoselectivities typically in excess of 20:1. Introduction of a trimethylsilyl group at C3 of the allylic alcohol side chain of the cyclization precursor allows *cis*-bicyclo[*n*.3.0]alkanones having a 2-methyl-2-propenyl side chain to be prepared with high stereocontrol, but in slightly lower yields (54−80%). In contrast, reaction of **21b**, which bears a hydrogen rather than a methyl or trimethylsilyl group at C3 of the allyl alcohol side chain, produced hydroazulenone **31b** with low diastereoselectivity (1.5:1).

Bicyclo[*n*.3.0]alkanones having carbon side chains at both C2 and C3 can be synthesized by rearrangement of substrates having a phenylthio substituent at the internal alkene carbon; excellent diastereoselectivities (>20:1) are observed, although yields are modest (44−50%). Only products in which the C1 substituent is oriented on the convex face of the cis-fused bicyclic product are accessible, because both vinyl sulfide stereoisomers provide the same product.

Whereas the present study focused solely on ring-enlarging cyclopentane annulations of five- to seven-membered ring precursors, this new ring-enlarging cyclopentane annulation is expected to be applicable to cyclic precursors of various ring sizes.[2] Moreover, as no loss of enantiopurity was observed during allyl cation-initiated cyclization−pinacol rearrangement reaction of enantioenriched precursor (+)-**23b**, this chemistry should be useful for enantioselective synthesis of polycarbocyclic products whenever the starting 2-substituted alkanone is readily available in high enantiopurity.

Ring-enlarging cyclopentane annulations that directly introduce carbonyl functionality in the newly formed cyclopentane ring were developed also. In this case, keteniminium ions generated from the reaction of *cis*-(2-siloxy-2-alkenylcycloalkyl)pyrrolidin-1-ylethanones with triflic anhydride and DTBMP at −20 to +65 °C initiate the cyclization rearrangement cascade. After hydrolysis of the crude keto iminium ion product with aqueous $KHCO_3$, *cis*-bicyclo[*n*.3.0]cycloalkane-2,4-diones are formed in low to moderate yields (see Table 2). The cis stereoisomer was produced in these reactions with high selectivity (>20:1), except for reactions of substrates bearing a 2-vinyl substituent, where epimerization of the bicyclo[*n*.3.0]cycloalkane-2,4-dione product is possible. The scope of the keteniminium ion-initiated ring-enlarging cyclopentanone annulation is more limited than related annulations initiated by α-heterocarbenium ions[2−8] or allyl cations.

Mechanism and Stereochemistry. Our analysis of the mechanism of allyl cation-initiated cyclization−pinacol reactions, which parallels that postulated for related transformations initiated by oxonium ions, is shown in Figure 2.[1,2] Initial reaction of the allylic alcohol substrate with triflic anhydride affords an allyl cation,[12]

(36) NMR yields were judged using 4-iodotoluene as an internal standard.

(37) Analogous substrates containing a C1 alkyne substituent provided only trace amounts of related enedione products.

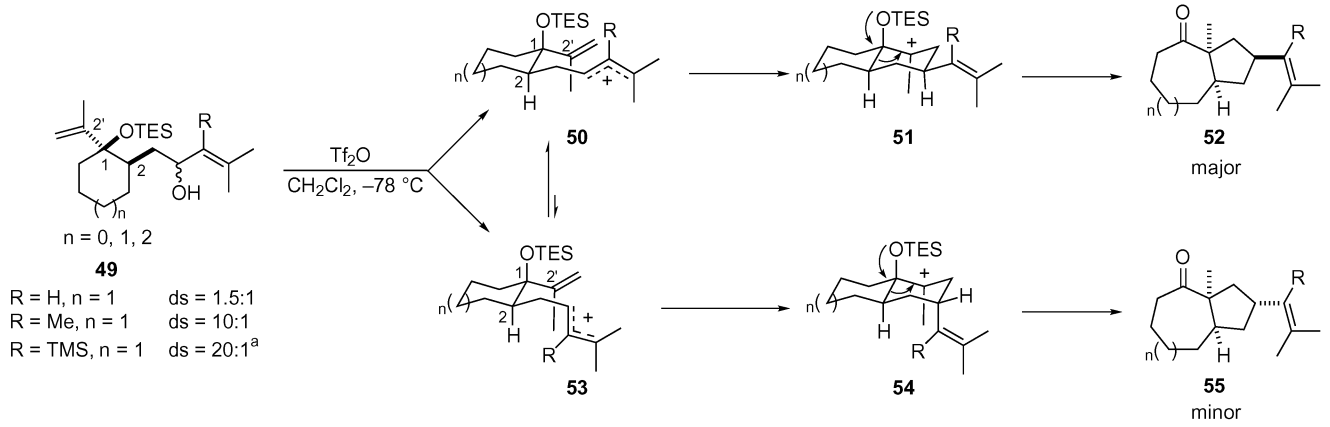


FIGURE 2. Key: the TMS group is cleaved from the initially formed product under the reaction conditions to provide a product having R = H.

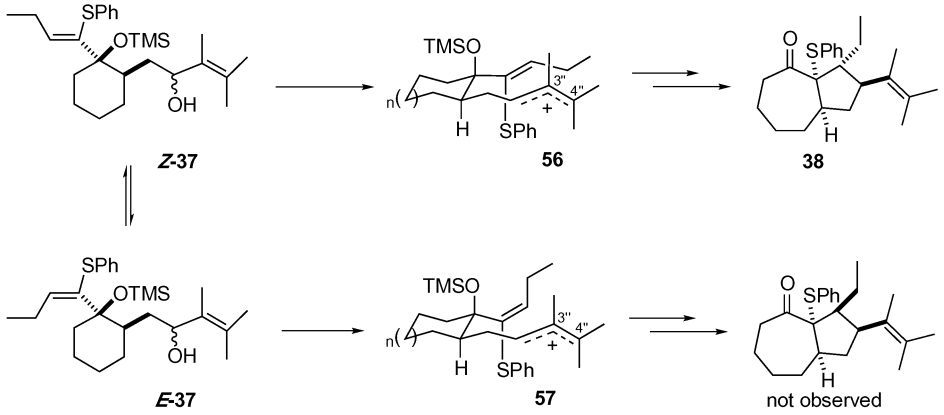


FIGURE 3.

which can react with the tethered alkene by either of two favored chair-topography pathways: **50** → **51** or **53** → **54**. The transition structure of the latter pathway suffers from unfavorable 1,3-diaxial interactions between the terminal carbons of the original allyl unit and the C2 and C2' substituents; these destabilizing steric interactions are avoided in the **50** → **51** pathway. This analysis nicely rationalizes the observation that stereoselection is typically >20:1 when the internal carbon of the allyl cation is substituted, but much less when this substituent is hydrogen.

Stereoisomeric vinyl sulfides ***Z*-37** and ***E*-37** both provided diastereomer **38**, which suggests that the vinyl sulfide stereoisomers interconvert more rapidly than they react (Figure 3). The preference for forming **38** likely arises from preferential reaction of the *Z* vinylsulfide stereoisomer by chair cyclization topography **56** in which the ethyl group adopts a favorable quasiequatorial orientation. The related chair transition structure for cyclization of the *E* stereoisomer that evolves from **57** would be destabilized by developing *syn*-pentane interactions between the ethyl substituent and both the siloxy group and the methyl substituent at C3″ of the original allyl cation side chain.

The α-hydroxydecalone side product **39** observed in reactions of the vinyl sulfide substrates ***E*-37** and ***Z*-37** presumably arises from the high stability[38] of the proposed thionium ion intermediate **58** (Figure 4). Apparently pinacol rearrangement of **58** is sufficiently slow that competitive trapping of the thionium ion with adventitious water (or the triflate anion) occurs to provide a thiohemiacetal (or α-trifluoroacetoxy sulfide) intermediate that evolves to the decalone product.

The keteniminium ion-initiated ring-expanding cyclopentanone annulation is believed to proceed by the sequence outlined in Figure 5. Thus, reaction of the pyrrolidine amide with triflic anhydride in the presence of DTBMP leads initially to the formation of a *O*-trifluoromethansulfonylated amide **60**,[39] which is deprotonated to provide keteniminium ion **61** (Figure 4).[33] The intermediacy of a keteniminium ion is supported by the requirement for an added pyridine base; direct cyclization of the *O*-acylated amide would not be consistent with the observation that no reaction was observed in the absence of DTBMP. Cyclization of the keteniminium ion through a chairlike conformer then provides carbenium ion **62**, which undergoes pinacol rearrangement to afford enamine **63**. This intermediate is protonated under the reaction conditions by the pyridinium triflate salt to give iminium salt **64**,[40] which is hydrolyzed upon treatment with aqueous base to yield the observed diketone prod-

(38) Hevesi, L. *Bull Chem. Soc. Fr.* **1990**, *127*, 697−703.
(39) Charette, A. B.; Chua, P. *Tetrahedron Lett.* **1998**, *39*, 245−248.
(40) Paukstelis, J. V. In *Enamines: Synthesis, Structure, and Reactivity*; Cook, A. G., Ed; Marcel Dekker: New York, 1969; pp 169−209.

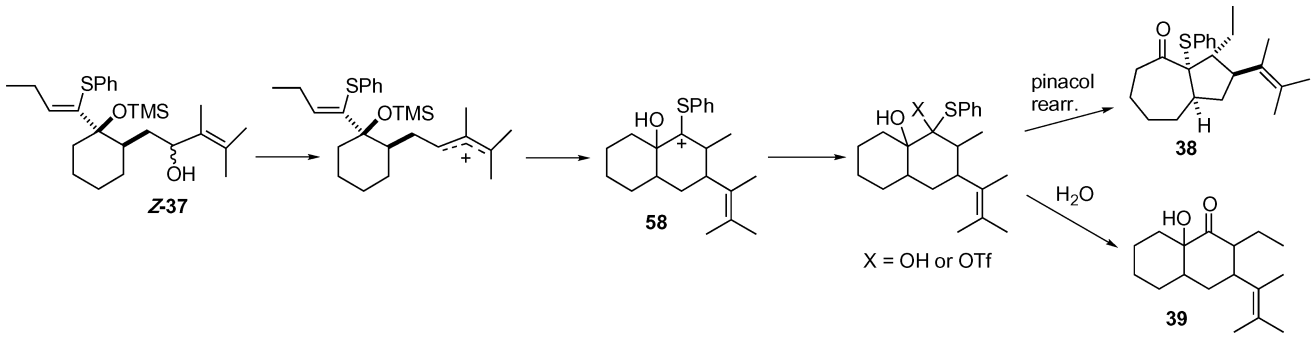


FIGURE 4.

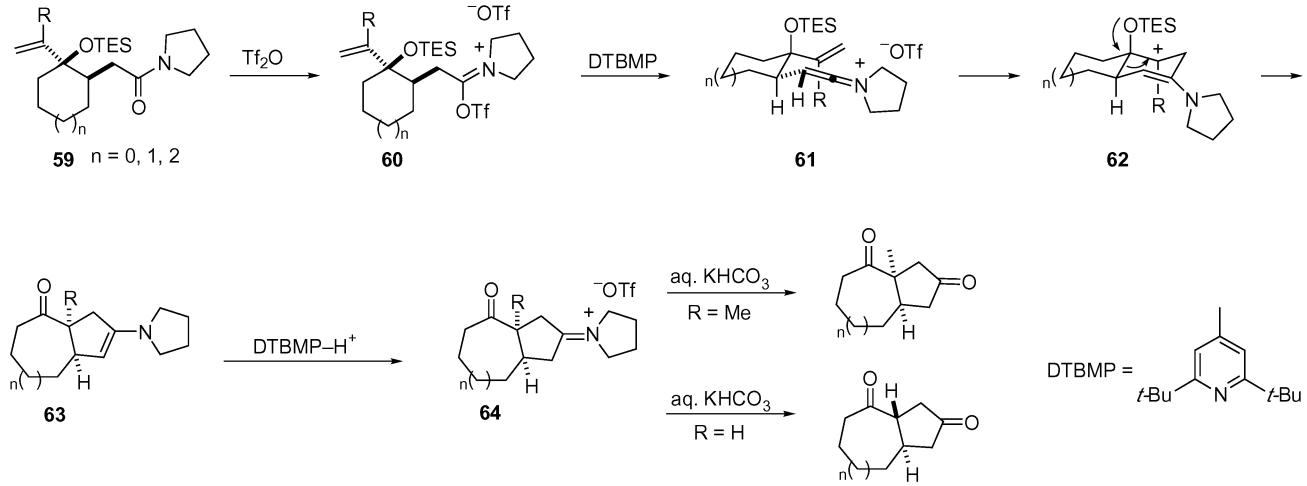


FIGURE 5.

ucts. In the case of intermediates **64** having R = H, epimerization of the C3a stereocenter likely occurs under the reaction conditions to afford a mixture of products favoring the more stable trans diastereomer.[41]

Conclusions

Two new variants of ring-enlarging cyclopentane annulations were developed. In one, an allyl cation, generated by reaction of an allylic alcohol with triflic anhydride, initiates a cyclization-pinacol cascade that expands the starting ring and fuses in cis fashion a cyclopentane ring bearing a 2-alkenyl side chain. Yields of this sequence are generally good and diastereoselection is high (typically >20:1). In the second more limited variant, a keteniminium ion, formed by the reaction of a pyrrolidine amide with triflic anhydride and a hindered base, initiates the cyclization−pinacol rearrangement sequence.

Experimental Section[42]

General Procedure for Allyl Cation-Initiated Cyclization−Pinacol Rearrangement Reactions. A solution of the appropriate allylic alcohol (1.0 equiv) in dichloromethane (0.1 M) was cooled to −78 °C, and trifluoromethanesulfonic anhydride (1.3 equiv) was added dropwise. The mixture was stirred at −78 °C until the starting material had been completely consumed as judged by TLC analysis (∼3 h). The reaction then was quenched at −78 °C with aqueous $NaHCO_3$ (equal volume to solvent) and allowed to warm to rt. The resulting mixture was extracted with ether (3 × 30 mL), and the combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel using ethyl acetate/hexanes (1% → 2%) as the eluant.

(2*S*,3a*R*,7a*R*)-2-(1,2-Dimethylpropenyl)-3a-methyloctahydroazulen-4-one (32b). Reaction of 0.22 mmol of **23b** following the general procedure afforded 46 mg (90%) of the title compound as a colorless oil. This material was judged to be a 16:1 mixture of diastereomers by ^{1}H NMR analysis (the crude reaction mixture was found to be a 10:1 mixture of diastereomers): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20−3.13 (m, 1 H), 2.70 (td, J = 2.8, 8.5 Hz, 1 H), 2.41−2.36 (m, 1 H), 2.04−1.98 (m, 2 H), 1.89−1.78 (m, 3 H), 1.68 (d, J = 1.2 Hz, 3 H), 1.64−1.59 (m, 4 H), 1.55 (s, 3 H), 1.54−1.40 (m, 2 H), 1.30−1.20 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.2, 128.1, 124.7, 58.4, 47.4, 40.2, 39.1, 38.10, 38.06, 35.2, 21.1, 19.9, 13.3; IR (film) 1698 cm^{-1}. Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 82.05; H, 11.29.

General Procedure for Tandem Keteniminium Ion Olefin Cyclization−Pinacol Rearrangements. A solution of the appropriate amide substrate (1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (1.25 equiv), and 1,2-dichloroethane (0.1 M) was cooled to −20 °C, and trifluoromethanesulfonic anhydride (1.25 equiv) was added dropwise. The mixture was allowed to slowly warm to rt and then was heated to 65 °C for 18 h. The

(41) The NMR yield of iminium salt **44a** (judged against 4-iodotoluene as an internal standard) was 74%. Approximately 15% of the material contained side products retaining a terminal vinyl group. The remainder of the material was not identified. As a result of the complexity of the crude ^{1}H NMR spectra, we were unable to ascertain the epimeric purity of iminium salt **44a**.

(42) General experimental details have been described.[6]

reaction mixture was cooled to rt and concentrated; the resulting residue was dissolved in aqueous $KHCO_3$ (3 mL) and ether (3 mL) and stirred vigorously at rt for 5 h. This mixture was extracted with ether (3 × 20 mL), and the combined organic extracts were dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography on silica gel using ethyl acetate/hexanes (10% → 20%) as the eluant.

(3a*R*,5a*R*)-3a-(Methyl)octahydroazulene-2,4-dione (46b). Reaction of 0.26 mmol of **16b** following the general procedure afforded 29 mg (61%) of the title compound as a colorless oil. This material was judged to be a >20:1 mixture of diastereomers by NMR analysis. Data for this compound have been reported previously.[2]

Acknowledgment. We thank the NIH (NS-12389) for financial support of this research. Additional unrestricted support from Merck, Pfizer, and Roche Biosciences is gratefully acknowledged as is NIH postdoctoral fellowship (GM 20140) support of J.P.W. NMR and mass spectra were determined at UC Irvine using instruments acquired with the assistance of NSF and NIH shared instrumentation grants.

Supporting Information Available: Complete experimental details and characterization data for compounds **9**−**48**, tables of NOE data, and copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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