On the Diastereoselectivity of Intramolecular Pd-Catalyzed TMM Cycloadditions. An Asymmetric Synthesis of the Perhydroazulene (−)-Isoclavukerin A

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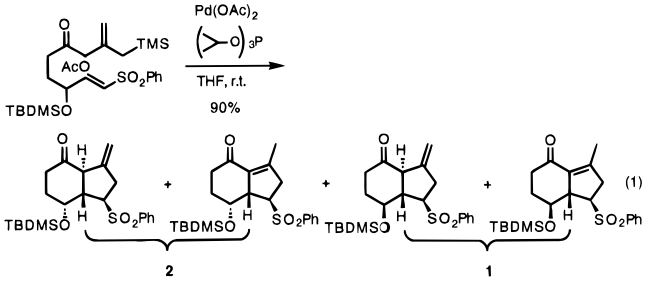
Abstract: The factors that influence the stereocontrol of trimethylenemethane (TMM) cycloadditions are examined in the context of a synthesis of a perhydroazulene. The diastereofacial selectivity with respect to the acceptor is established in an intramolecular [3 + 2] reaction with a five-carbon tether. When a doubly activated acceptor is utilized, complete selectivity is observed wherein the *Z*-situated activating group is proposed as a diastereoselectivity control element. Further, the use of trimethylstannyl acetate as a cocatalyst for cycloadditions to electron deficient alkenes is illustrated for the first time. A one-pot, three-component coupling protocol provides a facile new entry into acyl-substituted TMM precursors specifically and α-hydroxy ketones more generally. The methodology led to a total synthesis of (−)-isoclavukerin A. The shortest version of the synthesis involves eleven steps from methallyl alcohol.

Net cycloadditions (i.e., involving either concerted or a series of stepwise events) generally represent efficient methods for ring construction since they create molecular complexity rapidly.[1] The palladium-catalyzed cycloadditions involving trimethylenemethane (TMM) palladium complexes (TMM−PdL_2) constitute a promising class of such cycloadditions.[2−4] For their evolution as synthetically useful reactions, understanding the factors that influence stereocontrol represents an important goal.

Previously, we have shown that palladium-catalyzed cycloadditions involving the palladium complex of trimethylenemethane (TMM−PdL_n) can be practiced intramolecularly.[5] During the formation of the perhydroindane ring system as shown in eq 1, only a 2:1 diastereofacial selectivity was observed. This result did not bode well for other ring systems, since we anticipated that formation of a six-membered ring would be more conformationally demanding than other ring sizes such as five or seven. At the same time, this result stimulated us to probe the question as to whether any system can exercise diastereofacial selectivity in the intramolecular TMM−PdL_n reaction.

The broad range of biological activities of perhydroazulene natural products, ranging from diuretic and anti-inflammatory to antitumor, combined with their structural diversity and ubiquitousness makes them interesting synthetic targets.[6] Outside of strategies that begin with a preformed seven-membered ring, synthetic strategies have largely focused on two concepts.



In the first, rings are formed by cyclization involving formation of a single bond illustrated by simple alkylations, aldol condensations, Alder ene reactions, etc.[7] In the second, the more readily understood and available six-membered ring is adjusted in size, expanded for the seven- and contracted for the five-membered ring. One common scenario invokes the ring expansion of perhydroindanes to perhydroazulenes. A particularly effective version creates the perhydroazulene by simultaneous ring expansion−contraction of a perhydrodecalin.[8]

The perhydroazulenes become an attractive target not only because of their importance but also because the conformationally more flexible seven-membered ring represents an even more demanding challenge than the conformationally more well-behaved six-membered ring. Only recently have net cycloadditions addressed the perhydroazulene problem. Metal carbenes, generated either stoichiometrically or catalytically, have led to the perhydroazulene system.[9] In many of these cases, the

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(1) Bertz, S. H. *J. Am. Chem. Soc.* **1982**, *104*, 5801. Bertz, S. H.; Sommer, T. J. *Org. Synth. Theory Appl.* **1993**, *2*, 67. Wender, P. A.; Miller, B. L. *Org. Synth. Theory Appl.* **1993**, *2*, 27.

(2) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. Chan, D. M. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 271−273.

(3) For some recent work, see: Trost, B. M.; Parquette, J. R.; Nübling, C. *Tetrahedron Lett.* **1995**, *36*, 2917. Trost, B. M.; Parquette, J. R.; Marquart, A. L. *J. Am. Chem. Soc.* **1995**, *117*, 3284. Trost, B. M.; Parquette, J. R. *J. Org. Chem.* **1994**, *59*, 7568.

(4) For related cycloadditions, see: Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. Ohta, T.; Takaya, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds. Pergamon: Oxford, 1991; Vol. 5, pp 1185−1205 and also ref 2.

(5) Trost, B. M.; Grese, T. A.; Chan, D. M. T. *J. Am. Chem. Soc.* **1991**, *113*, 7350. Trost, B. M.; Grese, T. A. *J. Am. Chem. Soc.* **1991**, *113*, 7363. Trost, B. M.; Grese, T. A. *J. Org. Chem.* **1992**, *57*, 686.

(6) Jenniskens, L. H. D.; Wijnberg, J. P. B. A.; De Groot, A. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1994; Vol. 14, p 355. Fraga, B. M. *Nat. Prod. Rep.* **1992**, *9*, 217. Ho, T. L. *Carbocyclic Construction in Terpene Synthesis*; VCH Publishers: New York, 1988. Rigby, J. H. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1, pp 545−576. Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *Total Synthesis of Natural Products*; Ap Simon, J., Ed.; Wiley: New York, 1982; Vol. 5, pp. 333−384.

(7) For a recent example, see: Majetich, G.; Song, J. S.; Leigh, A. J.; Condon, S. M. *J. Org. Chem.* **1993**, *58*, 1030.

(8) For a recent example, see: Takeuchi, N.; Fujita, T.; Goto, K.; Morisaki, N.; Osone, N.; Tobinaga, S. *Chem. Pharm. Bull.* **1993**, *41*, 923.

(9) Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 5066. Harvey, D. F.; Brown, M. F. *J. Org. Chem.* **1992**, *57*, 5559. Padwa, A.; Krumpe, K. E.; Gareau, Y.; Chiacchio, U. *J. Org. Chem.* **1991**, *56*, 2523.

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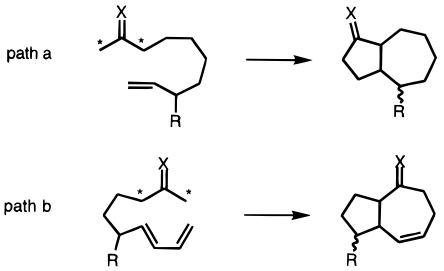
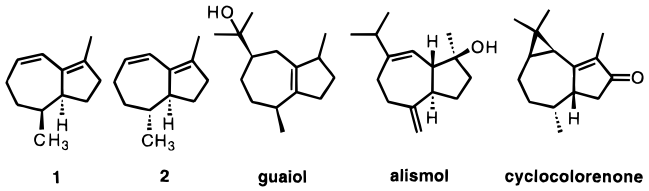
Scheme 1. TMM Strategies to Perhydroazulenes



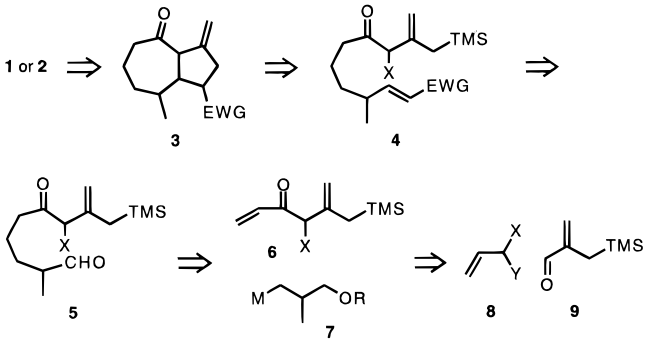
formation and subsequent rearrangement of a divinylcyclopropane accounts for the product.[10] A recent report describes a Rh-catalyzed intramolecular [5 + 2] cycloaddition of vinylcyclopropanes.[11] The trimethylenemethane (TMM) unit and its analogues create useful flexibility for the synthesis of perhydroazulenes via cycloaddition reactions, as represented in Scheme 1. Thus, an acyclic substrate can be sculpted into the desired ring system by choosing either a [3 + 2] (path a) or [3 + 4] (path b) process.

The key question that then arises is diastereoselectivity. To test path a, we chose the simple target of the clavukerins, since clavukerin A (**1**)[12] and isoclavukerin A (**2**),[13] both of which are known natural products, allow us (1) to focus on the diastereoselectivity issue at hand, (2) to assign stereochemistry unambiguously, and 3) to evolve what could become a more general strategy. The clavukerins were isolated from the Okinawan soft coral *Clavularia koellikeri* during a search for biologically active substances from marine sources. A number of other perhydroazulenes such as the guaiazulenes represented by guaiol,[14] alismol,[15] and cyclocolorenone[16] incorporate the clavukerin skeleton.



A number of previous syntheses has been reported. Shimizu and Ishikawa utilize the one bond formation strategy whereby the seven-membered ring is formed by a reductive coupling of a dicarbonyl intermediate.[17] Asaoka et al.,[18] Honda et al.,[19] and Kim and Pak[20] all employ a ring expansion strategy. In this paper, we describe our studies to elucidate the diastereoselectivity of the intramolecular [3 + 2] palladium-catalyzed TMM reaction which has led to an efficient synthetic strategy for construction of the perhydroazulene ring system and culminated in an asymmetric synthesis of (−)-isoclavukerin A (**2**).

Scheme 2. A Retrosynthetic Analysis of Isoclavukerin A

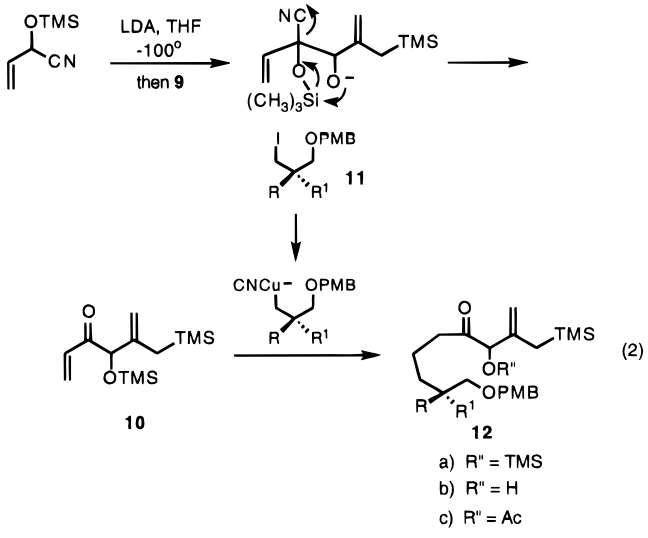


Determination of Cycloaddition Substrates

Scheme 2 outlines the retrosynthetic analysis for the clavukerins. The diene portion should nicely derive from the β,γ-unsaturated ketone **3** that results from the intramolecular TMM−PdL_n reaction of substrate **4**. Previous studies[5] indicate that introduction of the donor TMM portion should precede the acceptor thereby suggesting **5**. Utilizing a conjugate addition concept brings us to **6** and **7**, the latter simply a 2-methylpropane-1,3-diol derivative. The former deconvolutes into a derivative of acrolein that converts to an acyl anion and the known aldehyde **9**.[21]

Synthesis of Cyclization Substrates

The silylated cyanohydrin of acrolein as the acyl anion equivalent[22] possesses the advantage that it unmasks *in situ*. As shown in eq 2, this protocol works well, giving the desired Michael acceptor **10** in 58% yield in a single step. Addition of



the organocuprate formed by metal−halogen exchange of the racemic iodide **11** (R = CH_3, R^1 = H and R = H, R^1 = CH_3) with 2 equiv of *tert*-butyllithium followed by addition of copper

(10) Cantrell, W. R., Jr.; Davies, H. M. L. *J. Org. Chem.* **1991**, *56*, 723. Davies, H. M. L.; Huby, N. J. S.; Cantrell, W. R., Jr.; Olive, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 9468. For a review, see: Davies, H. M. L. *Tetrahedron* **1993**, *49*, 5203. Also, see: Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 9919.

(11) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720.

(12) Kobayashi, M.; Son, B. W.; Kyogoku, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1984**, *32*, 1667. Kobayashi, M.; Son, B. W.; Kido, M.; Kyogohu, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1983**, *31*, 6.

(13) Kusumi, T.; Hamada, T.; Hara, M.; Ishitsuka, M. O.; Ginda, H.; Kakisawa, H. *Tetrahedron Lett.* **1992**, *33*, 2019.

(14) Andersen, N. H.; Uh, H.-S. *Tetrahedron Lett.* **1973**, *23*, 2079. Marshall, J. A.; Greene, A. E. *J. Org. Chem.* **1972**, *37*, 982.

(15) Yoshikawa, M.; Yamaguchi, S.; Matsuda, H.; Kohda, Y.; Ishikawa, H.; Tanaka, N.; Yamahara, J.; Murakami, N. *Chem. Pharm. Bull.* **1994**, *42*, 1813.

(16) Rao, K. V.; Davis, T. L. *Planta Med.* **1982**, *44*, 249. For a synthesis, see: Saha, M.; Bagby, B.; Nicholas, K. M. *Tetrahedron Lett.* **1986**, *27*, 915.

(17) Shimizu, I.; Ishikawa, T. *Tetrahedron Lett.* **1994**, *35*, 1905.

(18) Asaoka, M.; Kosaka, T.; Itahana, H.; Takei, H. *Chem. Lett.* **1991**, 1295.

(19) Honda, T.; Ishige, H.; Nagase, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3305.

(20) Kim, K. S.; Pak, C. S. *J. Org. Chem.* **1991**, *56*, 6829.

(21) Trost, B. M.; Nanninga, T. N.; Satoh, T. *J. Am. Chem. Soc.* **1985**, *107*, 721.

(22) Jacobsen, R. M.; Lahm, G. P.; Clader, J. W. *J. Org. Chem.* **1980**, *45*, 395.

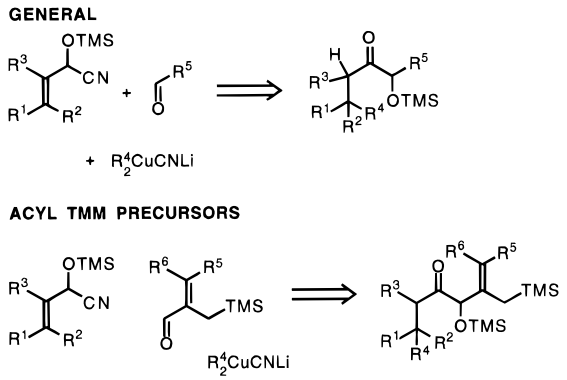
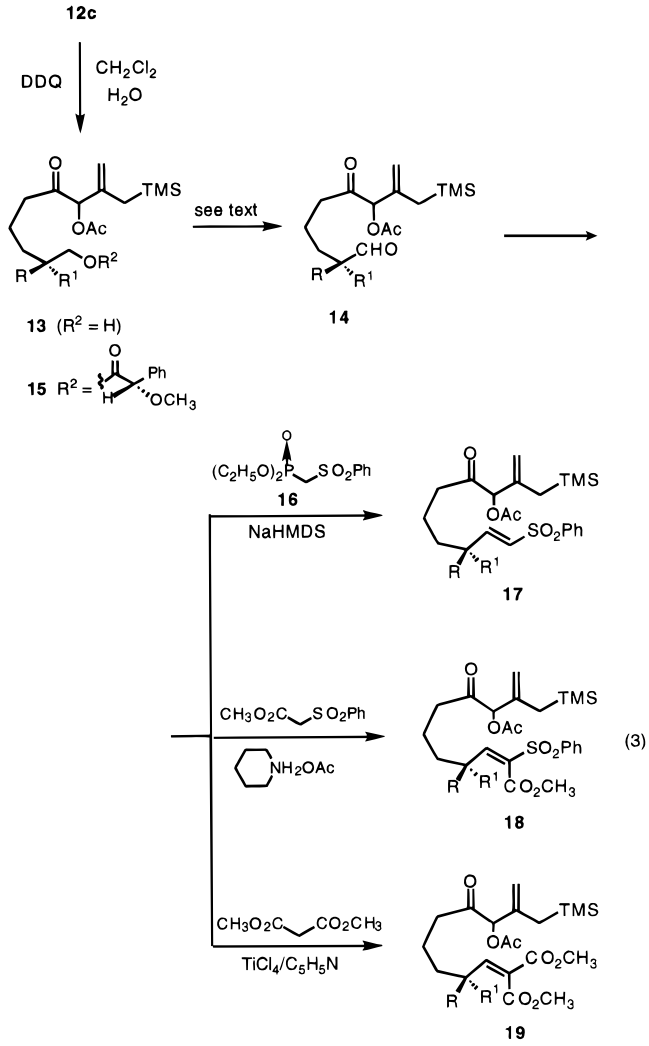


Figure 1. A three-component coupling.

cyanide[23] gives an 88% yield of the conjugate adduct **12a**. While **12a** may be obtained pure, operationally, the crude material was subjected to acid hydrolysis (H_2SO_4, H_2O, THF, room temperature (rt)) to alcohol **12b** and direct acetylation (Ac_2O, C_5H_5N, 4-(dimethylamino)pyridine (DMAP), 0 °C) to give **12c** which sets the functionality to generate the TMM−PdL_n intermediate.

Since the enone **10** is liberated in the reaction mixture of the carbonyl addition simultaneously with *in situ* protection of the secondary alcohol, direct addition of the cuprate to that reaction mixture in the same pot is conceivable. In this scenario, the cuprates from the enantiomerically pure iodides[24] **11** (R = CH_3, R^1 = H) and **11** (R = H, R^1 = CH_3) were added to the cold (−90 °C) initial reaction mixture. Workup of the reaction with dilute aqueous sulfuric acid gave **12b** in 56% yield (from **9**) in this one step. Precipitates form during the course of this reaction which may cause some problems. To minimize their formation, the reaction concentration should be kept <0.3 M and any precipitates formed during the carbonyl addition should be broken up before addition of the cuprate. Although the product **12** is a mixture of diastereomers (epimeric at the secondary alcohol), the properties (except for doubling of a few signals in the ^{13}C NMR spectrum) do not reveal this fact. Telescoping the carbonyl addition of the acyl anion equivalent with the cuprate addition creates a three-component coupling sequence which, as summarized in Figure 1, provides a very simple strategy for α-hydroxy ketone synthesis in general and for access to acyl bifunctional conjunctive reagents that are TMM precursors in particular.

The stage is set for creation of the acceptor unit for which the aldehyde **14** is pivotal (eq 3). Oxidative cleavage of the PMB (*p*-methoxybenzyloxy) group proceeded uneventfully to afford alcohol **13**. A Moffatt−Swern oxidation[25] (96% yield) gave significantly higher yields than the pyridinium dichromate (PDC) oxidation[26] (75% yield). However, with enantiomerically pure **12c** (R = H, R^1 = CH_3), chemoselective reduction of aldehyde **14** back to alcohol **13** [$LiAlH(O\text{-}t\text{-}C_4H_9)_3$, THF, −78 °C, 83%] and examination of the NMR spectrum of the *O*-methylmandelate ester[27] **15** in the region for the methyl doublet (δ 0.75−0.85) revealed its ee to be only 76%. Replacing the Moffatt−Swern protocol with the Dess−Martin periodinane[28] resolved this problem. While the yield diminished to 83%, reduction (86% yield) and esterification to **15** showed the latter to be diastereomerically pure and, by default, **14** to be enantiomerically pure.



(3)

Olefination using the phosphonate **16**[29] gave only the *E*-sulfone **17**, readily established by the 15.2 Hz coupling constant, in 99% yield. Diactivated acceptors were also synthesized. Bearing in mind that, for a completion of the synthesis of the clavukerins, the activating groups ultimately need to be removed, we chose the sulfone ester **18**. Standard Knoevenagel conditions[30] effect smooth addition to generate a single alkene isomer in 85% yield. It is tentatively assigned as *E*, as depicted, on the basis of the expectation that the bulky sulfone would prefer to be *trans* to the bulkier substituent on the β-carbon in what should be a thermodynamically controlled elimination.

A potential problem with respect to the choice of this substrate is racemization during the Knoevenagel condensation. Indeed, subsequent studies revealed that problem to be valid (*vide infra*). Racemization derives from an equilibrium between the iminium species that undergoes the addition of the anion of methyl-(phenylsulfonyl)acetate and the corresponding enamine. We therefore sought other methods for the synthesis of **18**, unfortunately to no avail. We therefore turned to dimethyl malonate since the Lehnert modification[31] of the Knoevenagel, which fails with the sulfone ester, proceeds well. The fact that it avoids iminium salt formation, since it employs pyridine and titanium tetrachloride to promote condensation, suggested that

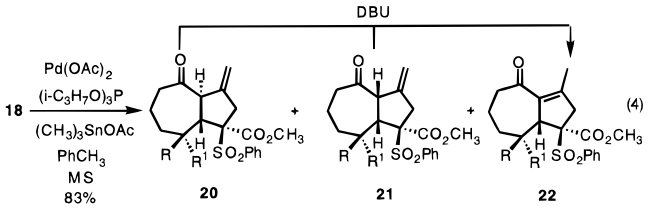
(23) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 3938.
(24) Walkup, R. D.; Boatman, P. D., Jr.; Kane, R. R.; Cunningham, R. T. *Tetrahedron Lett.* **1991**, *32*, 3937.
(25) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(26) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.
(27) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.
(28) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(29) Shahak, I.; Almog, J. *Synthesis* **1970**, 145.
(30) Tietze, L. F.; Beifuss, U. *Annalen* **1988**, 321.
(31) Lehnert, W. *Tetrahedron* **1973**, *29*, 635.

racemization could be avoided. The adduct **19** formed satisfactorily in 71% yield. Subsequent studies (*vide infra*) revealed very little racemization.

Cyclization Studies

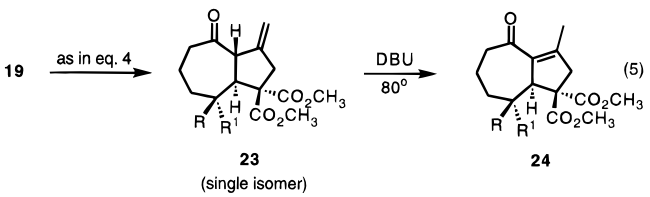
Initial attempts to effect the cyclization of sulfone **17** proved surprisingly disappointing. Our standard conditions involve palladium acetate with sufficient triisopropyl phosphite to serve as both ligand and reductant.[32] Addition of trimethyltin acetate as a cocatalyst failed to have any beneficial effect. To the extent that identifiable products formed, they appeared to result from protodesilylation. In one experiment where the reaction was performed at 10 kbar,[3] possible traces of product were observed, unfortunately in far too low of a yield to pursue this method.

The use of doubly activated acceptor **18** (R = CH_3, R^1 = H) proved to be a completely different story. Using trimethyltin acetate as a cocatalyst, within 3 h at 110 °C, the reaction was complete (eq 4). While we had employed this cocatalyst for



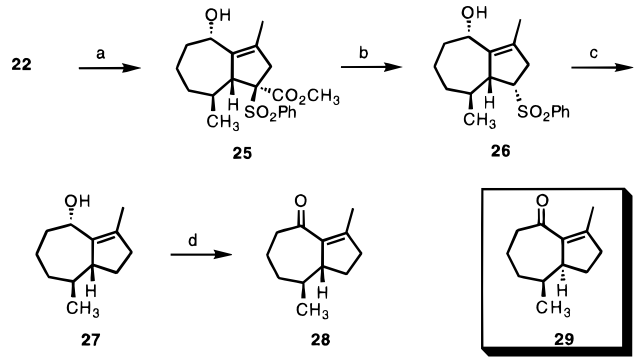
cycloadditions to carbonyl partners,[33] this example represents its first use in additions to double bond acceptors. NMR analysis of the initial product mixture showed a 1.9:1.0:0.2 ratio of **20**/**21**/**22**. Column chromatography allowed separation of a pure sample of crystalline **20** (43% yield) from a mixture of **20**, **21**, and **22** (40% yield). Upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), cycloadducts **20** and **21** converged to cycloadduct **22**—a fact that indicates they differ only in the ring junction stereochemistry α to the carbonyl group. The major adduct is assigned as the *trans*-fused bicycle on the basis of the 10.7 Hz coupling of the bridgehead protons compared to a 9.8 Hz coupling for the *cis*-fused isomer. These large coupling constants for both ring fusions reflect approximately 180° and 0° dihedral angles, respectively, in accord with molecular mechanics calculations. Preparatively, the cycloaddition/isomerization may be performed in the same pot by adding DBU directly to the cooled reaction mixture after the intramolecular cycloaddition and by heating at 50−55 °C for 1 h. In this way, cycloadduct **22** was isolated in 57% yield as a crystalline solid and as a single diastereomer.

To determine the role, if any, of the sulfone group in controlling the diastereoselectivity, we also cyclized the malonate **19** (eq 5). Interestingly, only a single cycloadduct **23** was observed in the ^{1}H NMR spectrum of the crude reaction mixture and was isolated in 50% yield. In contrast to the sulfone



substrate, double-bond isomerization under the cycloaddition conditions was less pronounced and all three stereogenic centers

Scheme 3. Determination of Diastereoselectivity[a]



[a] (a) $CeCl_3$, $NaBH_4$, CH_3OH, 0 °C, 85%; (b) NaI, DMF, 150 °C, 83%; (c) Na(Hg), NaH_2PO_4, CH_3OH, rt, 82%; (d) MnO_2, CH_2Cl_2, rt, 71%.

of the initial cycloadduct were controlled. A one-pot TMM cycloaddition/isomerization gave **24** directly in 71% yield as a single diastereomer. The 11 Hz coupling constant for the bridgehead hydrogens in **23** suggests a *trans* ring juncture, in accord with the adduct in the sulfone ester series. Base-catalyzed double-bond isomerization generated a single cyclopentene **24**.

Determination of Diastereoselectivity of Cycloaddition

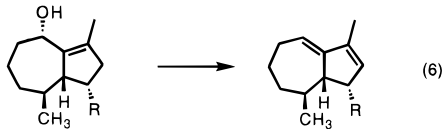
The stereochemistry of cycloadduct **22** was established by correlation as shown in Scheme 3. Sodium borohydride reduction in the presence of cerium chloride[34] generated a single diastereomeric alcohol. Anticipated delivery of hydride on the convex face of the molecule led to the assigned configuration. This assignment was supported by an analysis of the mandelate esters in the enantioenriched series and described in detail for the malonate series (*vide infra*) because of the high ee in that case. Interestingly, dealkylative decarboxylation to produce sulfone **26** also proceeded with complete diastereoselectivity. The stereochemistry was assigned on the basis of protonation of the intermediate anion from the least hindered convex face of the molecule. Attempts to more rigorously define these stereocenters were not undertaken since they were inconsequential to the task at hand. Nevertheless, the results show this perhydroazulene system has a strong conformational bias in directing the stereochemistry of reactions. Desulfonylation according to our general procedure[35] and oxidation of the allylic alcohol produced the known ketone **28**.[20,36] Diagnostic of the differences between the two diastereomers **28** and **29** is the chemical shift of the secondary methyl group appearing at δ 0.95 for **28** and 0.75 δ for **29**. The diastereoselectivity of cycloaddition to form **23** and **24** was assigned by analogy and proven by the completion of the synthesis of (−)-isoclavukerin.

Introduction of Diene

Creation of the diene moiety of the clavukerins proved elusive. Normal dehydration protocols either proved messy (e.g., $SOCl_2$, C_5H_5N) or selectively formed the 1,3-diene **30b** [eq 6, $CH_3OC(O)N^-$ $SO_2N^+(C_2H_5)_3$, PhH, 50 °C, 52%].[37] In an attempt to form a selenide from **26**, only an elimination

(32) Trost, B. M.; Nanninga, T. N. *J. Am. Chem. Soc.* **1985**, *107*, 1293. Trost, B. M.; Renaut, P. *J. Am. Chem. Soc.* **1982**, *104*, 6668.
(33) Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902. Trost, B. M.; King, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 408.
(34) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(35) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.
(36) Posner, G. H.; Babiak, K. A.; Loomis, G. L.; Frazee, W. J.; Mittal, R. D.; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 7498.
(37) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

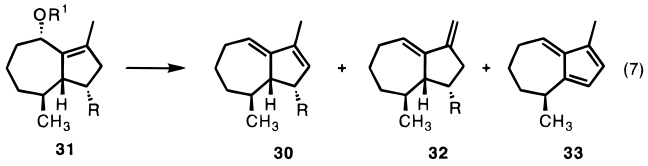
product identified as **30a** was observed.



26 R = SO_2Ph
27 R = H

30
a) R = SO_2Ph
b) R = H

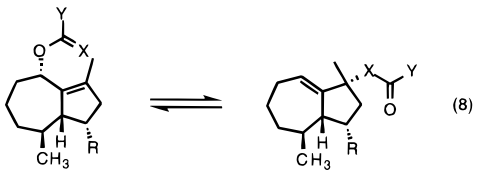
Use of ester thermolysis methods proved equally unsuccessful. Initial efforts focused on the thionocarbonate because of the lower temperatures normally required. Heating the thionocarbonate **31a** in toluene at reflux produced only diene **30** at partial conversion. Subjecting **31a** to flash vacuum thermolysis (FVT) at 350 °C produced **32** (eq 7). In addition, the doubly



31 **30** **32** **33**

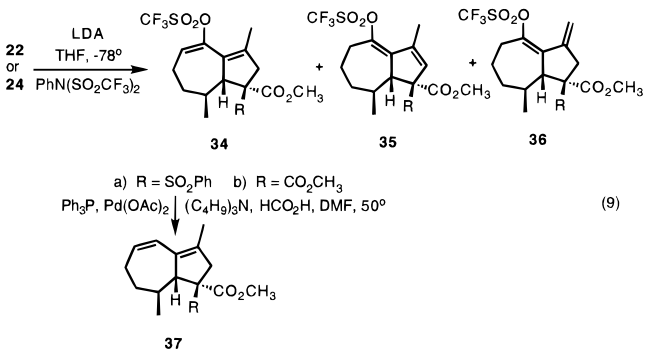
a) R = SO_2Ph, R^1 = C(=S)OC_6H_4F
b) R = H, R^1 = Ac

eliminated product, triene **33**, was isolated. The formation of the rearranged dienes may derive from a [3,3] sigmatropic rearrangement to generate a thiocarbonate (eq 8). Thus, thermolysis of a simple ester, although requiring higher temperatures, would be devoid of this driving force. To avoid any



conformational issues that the presence of the sulfone would introduce, we explored FVT of acetate **31b**. Again, only rearranged dienes **30** and **32** were formed. Their ratio was a function of temperature—1:1 at 480 °C and 1:1.7 at 325 °C. The above results are quite surprising in light of molecular mechanics calculations (CAChe molecular modeling system) which indicate that isoclavukerin A is 1.6 kcal/mol more stable than **30b**.

To avoid this issue of positional isomerization, conversion of one of the ketone intermediates to a diene was pursued. Initially, deoxygenation via a vinyl triflate was examined as illustrated in eq 9. Kinetic enolate formation from sulfone ester



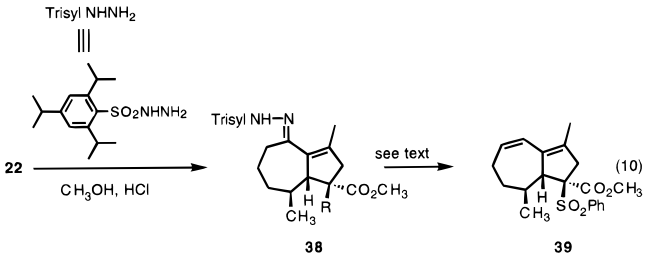
34 **35** **36**

a) R = SO_2Ph b) R = CO_2CH_3

37

22 (lithium diisopropylamine (LDA) or potassium hexamethyldisilazane (KHMDS)) followed by quenching with *N*-phenyltriflimide[38] or (4-chloropyridyl)triflimide[39] proved to be complicated by the formation of a mixture of regioisomers **35** and/or **36** as well as products derived from elimination of benzenesulfinic acid. The only conditions that gave an acceptable yield involved treating **22** with triflic anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine. Expectedly, this procedure generated the thermodynamic dienolate derivative **35** selectively in 60% yield. To avoid the elimination complications of the sulfone ester, the diester **24** was also investigated briefly. Using LDA and *N*-phenyltriflimide, a 2.3:1 ratio of **34** and **36** was obtained with a large amount of starting material recovered. Subsequent Pd(0)-catalyzed reductive cleavage gave a 12% yield (overall from **24**) of diene **37** (eq 9).

Resolution of this problem lay in the use of the Bamford-Stevens reaction.[40] The trisylhydrazone[41] of sulfone ester **22** formed readily in 63% yield (eq 10). Use of strong base (Shapiro conditions, RLi or LDA)[40−42] led only to uncharacterizable decomposition products. Concerns of chemoselectivity



38 **39**

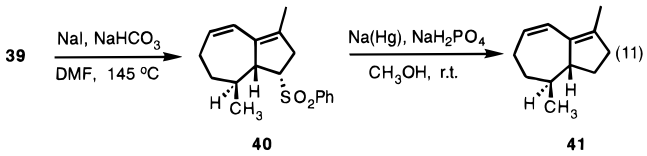
directed us away from protic conditions. An earlier report of lithium hydride in toluene[43] seemed intriguing because an insoluble kinetically sluggish base may minimize the basicity of the medium and thereby minimize indiscriminate base-catalyzed decomposition. Heating trisylhydrazone **38** with lithium hydride in toluene at reflux proved too sluggish. However, addition of a small amount of diglyme allowed the reaction to go to completion within 4 h and gave an 87% yield of desired diene **39**. The tosylhydrazone also eliminated smoothly under these conditions. Unfortunately, the product was contaminated by a difficult to separate impurity. The trisylhydrazone protocol was adopted for synthetic purposes. With a protocol to create the proper perhydroazulene ring system in place, the stage was set for a completion of the synthesis of isoclavukerin A.

The Racemization Problem

The completion of a synthesis of the clavukerin family now required removal of the two activating groups. Fortunately, this task proved straightforward. Dealkylative decarboxylation (eq 11) afforded a diastereomerically pure sulfone **40** in 82% yield. The stereochemical assignment is based upon protonation from the least hindered face. Reductive desulfonylation proceeded facilely to give the tris-nor-sesquiterpene **41** in 58% yield.

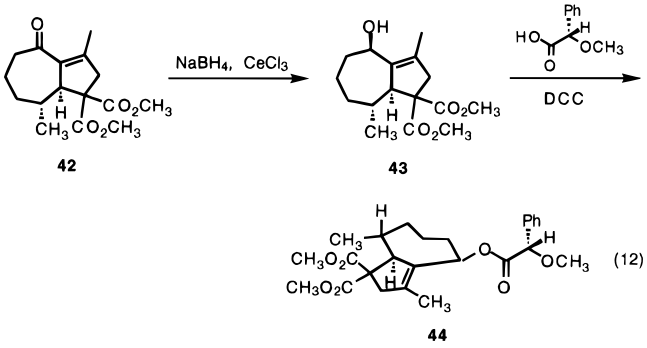
Since at the outset of this program we did not know what the diastereoselectivity of the cycloaddition would be, we chose **11** (R = CH_3, R^1 = H) for the cuprate addition. If addition would occur to produce an α bridgehead proton, this route would create the natural configuration for clavukerin A. Since the

(38) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.
(39) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.
(40) Shapiro, R. H. *Org. React.* **1976**, *23*, 406.
(41) Chamberlin, A. R.; Bloom, S. H. *Tetrahedron Lett.* **1986**, *27*, 551 and earlier references cited therein. Baba, T.; Avasthi, K.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1571.
(42) Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5736.
(43) Caglioti, L.; Grasselli, P.; Selva, A. *Gazz. Chim. Ital.* **1964**, *94*, 537.

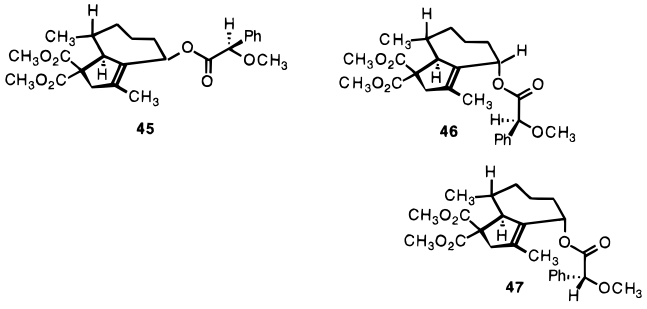


diastereoselectivity of the cycloaddition generates a β bridgehead hydrogen, the resultant **41** has a stereochemistry that corresponds to the enantiomer of isoclavukerin A. Thus, all the properties of synthetic **41** are in agreement with those recorded for **2** except for optical rotation. While the opposite sign of the rotation is expected, its magnitude, $[\alpha]^{25}_D$ +33 (*c* 0.61, $CHCl_3$), compared to the natural product, $[\alpha]^{25}_D$ −100 (*c* 1.00, $CHCl_3$),[13] indicated that significant racemization had occurred.

As pointed out earlier, the most likely point for racemization was the Knoevenagel condensation. We developed the synthesis of the malonate derivative **19** under conditions that should avoid the pitfalls of the classical Knoevenagel reaction.[44] The absolute stereochemistry of **19** was chosen with R = H and $R^1 = CH_3$, and cycloaddition produced **42** in 71% yield in the one-pot cycloaddition−isomerization procedure (eq 12).



Reduction to the alcohol as before generated a single diastereomer **43** in 86% yield. The enantiomeric purity was established by conversion to the *O*-methylmandelate **44** in 79% yield. For analytical purposes, the diastereomeric complex **45** was prepared as a 1:1 mixture with **44** using racemic *O*-methylmandelic acid. The ^{1}H NMR spectrum of **45** will be



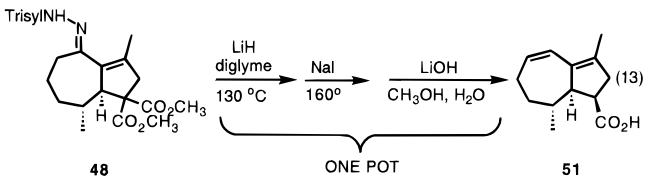
identical to the NMR spectrum of its mirror image which corresponds to the diastereomer that would be obtained by esterification of the enantiomer of **43** with (*S*)-*O*-methylmandelic acid. Several signals in the ^{1}H NMR spectrum are very well-resolved to allow easy determination of de (e.g., methyl doublets at δ 0.89 and 1.00, allylic methylenes AB at δ 2.67, 2.53 and δ 3.18, 3.09, benzylic resonances at δ 4.74 and δ 4.71). In this way, we could establish the ee of **43** to be 93%. Thus, 3.5% epimerization occurred in the malonate condensation step.

This mandelate analysis[27] also suggests that the stereochemical assignment of the secondary alcohol is correct. When **44** and **45** are compared, the vinyl methyl group should experience shielding by the phenyl group in **45** and therefore its signal in the ^{1}H NMR spectrum should be at higher field than that for the methyl group in **44**. Indeed, this signal shifts dramatically from δ 1.64 in **44** to δ 1.16 in **45**. If the alcohol were epimeric, then switching from (*S*)-*O*-methylmandelate (**46**) to its *R*-isomer **47** should produce the reverse effect.

Completion of Total Synthesis of (−)-Isoclavukerin A

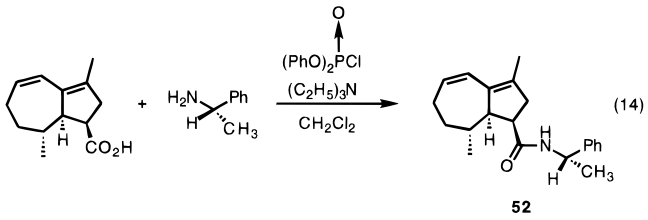
Scheme 4 outlines the final stages of the synthesis. The lithium hydride version of the Bamford−Stevens reaction employing the trisylhydrazone,[43] which formed quantitatively, was performed in diglyme as solvent to give diene **49** in 85% overall yield from ketone **24**. Dealkylative decarboxylation formed a diastereomerically pure monoester **50** assigned as depicted on the basis of protonation of an intermediate enolate from the least hindered face. Ester hydrolysis gave the acid **51**.

Since the conditions for the three steps of elimination of the trisylhydrazone, dealkylative decarboxylation, and hydrolysis appeared compatible with each other, we pursued a one-pot conversion of **48** to **51** as shown in eq 13. Initially, the



trisylhydrazone **48** was heated at 130 °C in diglyme with lithium hydride. After 1.5 h, sodium iodide was added and the temperature raised to 160 °C. The mixture was cooled to room temperature at which point methanolic lithium hydroxide containing water was added. After reacting the mixture overnight at room temperature, the hydrolysis was completed by heating to 50 °C for 4 h. In this way, an unoptimized yield of 46% of pure acid **51** in addition to 16% of an impure sample was obtained in one pot.

The ee of the carboxylic acid was investigated as a check on the *O*-methylmandelate protocol. Amide formation[45] with (*S*)-α-methylbenzylamine produced the amide **52** whose ^{1}H NMR spectrum indicated a de of 92%, in excellent agreement with the earlier analysis (eq 14).



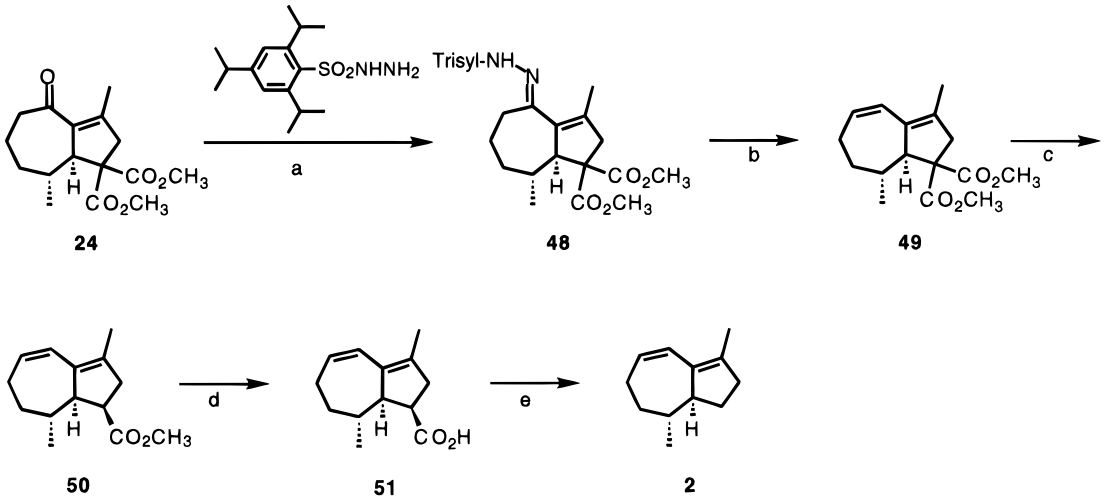
The Barton protocol[46] was exploited for removal of the carboxylic acid. The hydroxamic ester (formed *in situ*) did not undergo thermal decarboxylation in the presence of *tert*-butyl thiol thermally. On the other hand, irradiation with sunlight produced isoclavukerin **2** whose properties are identical in every respect with those recorded for the natural product. The observed rotation $[\alpha]^{25}_D$ −99.9 (*c* 2.02, $CHCl_3$) is identical, within experimental error, to that reported for the natural product, $[\alpha]^{25}_D$ −100 (*c* 1.0, $CHCl_3$). Since our material should

(44) For an example, see: Trost, B. M.; Ohmori, M.; Boyd, S. A.; Okawara, H.; Brickner, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 8281.

(45) Bernasconi, S.; Comini, A.; Corbella, A.; Gariboldi, P.; Sisti, M. *Synthesis* **1980**, 385.

(46) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.

Scheme 4. Final Stages of Total Synthesis of (−)-Isoclavukerin A[a]



[a] (a) 1.2 M HCl, CH_3OH, reflux, 100%; (b) LiH, diglyme, 125 °C, 85%; (c) NaI, $NaHCO_3$, DMF, 160 °C, 95%; (d) LiOH, CH_3OH, H_2O, 97%; (e) $(COCl)_2$, C_5H_5N, cat. DMF, PhH, sodium salt of *N*-hydroxypyridin-2-thione, *t*-C_4H_9SH, hν, 57%.

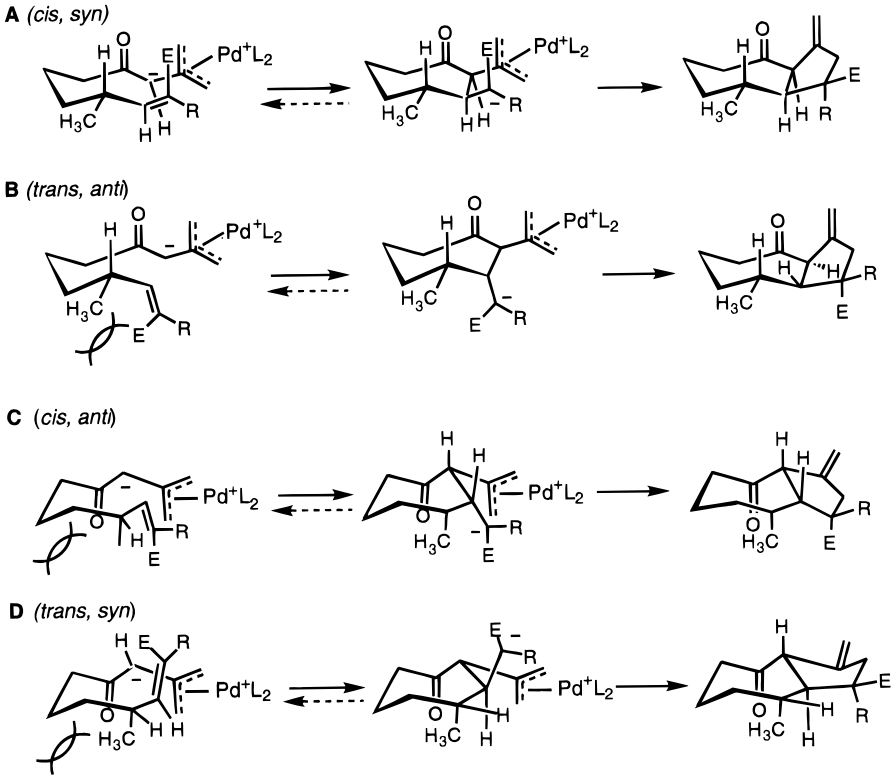


Figure 2. A rationalization of the diastereoselectivity (E = CO_2CH_3, R = CO_2CH_3 or $PhSO_2$).

have an ee of 92−93%, the rotation of enantiomerically pure (−)-isoclavukerin should be 108−109 °C, which agrees with the rotation reported by Asoaka for his synthetic sample.[18]

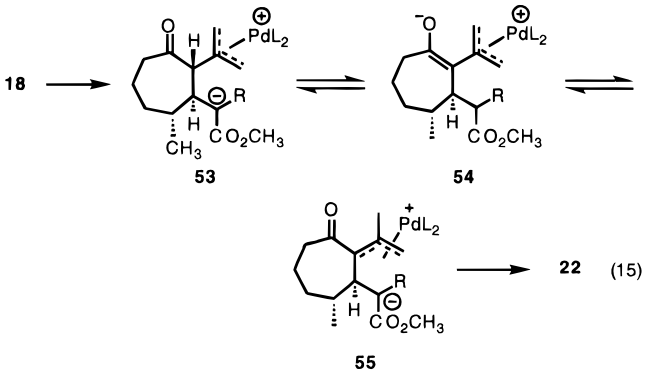
Discussion

The diastereoselectivity of the palladium-catalyzed TMM cycloaddition with respect to a stereogenic center adjacent to the acceptor has been shown to be very high with doubly activated acceptors. An analysis of the possible cyclization intermediates as shown in Figure 2 offer a rationalization of this effect. The four possible reactive conformers for the TMM are indicated by the orientation of the two probridgehead hydrogens with respect to each other (*cis* or *trans*) and the orientation of the methyl substituent with respect to the adjacent probridgehead hydrogen (*syn* or *anti*). When the *trans, anti* conformer B is considered, a severe destabilization arises from the *cis*-alkene substituent with both the methyl group and chain which disfavors this orientation. The *cis, anti* conformer C experiences a debilitating A 1,3-strain between this same *cis*-alkene substituent and the methyl group. These unfavorable interactions are generally absent from the *cis, syn* (A) and *trans, syn* (D) conformers. The former will experience a destabilizing nonbonded interaction by placing the bulky π-allylpalladium and stabilized anion units *cis*. The latter mainly experiences gauche interactions between the methyl group and the chain and the acceptor and the chain.

This analysis suggests that reaction with these doubly activated acceptors should proceed via conformer A or D. Steric considerations with respect to the two chains on the nascent seven-membered ring then suggest that reaction via the *trans,syn*

conformer D should be preferred over the *cis,syn* conformer A,[47] as observed. The difference between the malonate and sulfone ester substrates in the degree of stereoselectivity with respect to the ring juncture is striking and obviously useful. Its source is unclear. These results suggest that the presence of *cis*-substituents on the alkene, as in these two examples, is necessary for good diastereoselectivity since it is the interactions associated with this substituent as shown in B and C that disfavors these conformations. Thus, these easily removed *cis*-alkene substituents then serve two functions: (1) to enhance the acceptor property of the alkene and (2) to serve as a diastereoselectivity control element.

The formation of the alkene isomerization product **22** for the sulfone ester substrate **18** but not for the malonate **19** is somewhat perplexing. If this product simply arose by a base-catalyzed isomerization under the reaction conditions for the cyclization, it is difficult to see why such a difference should exist. An alternative explanation[5] invokes an isomerization prior to the second C−C bond formation, as shown in eq 15.



(15)

In addition to establishing the protocol necessary to achieve diastereofacial selectivity with respect to the acceptor alkene for a TMM−PdL_2 cycloaddition, this study has provided insight into a number of other useful synthetic protocols. The use of trimethyltin acetate as a coordinative cocatalyst presumably facilitates the nucleophilic addition of the TMM−PdL_2 species to the acceptor which appears to be the slow step in many cases. More typical Lewis acids simply destroy the catalyst system and stop reaction. The ability to effect this type of coordinative catalysis may prove more generally useful. The three-component one-pot formation of α-hydroxy ketones, in general, and the keto-substituted TMM precursors, specifically, should facilitate their use in synthesis. The success of the use of lithium hydride in diglyme with the trisylhydrazone (or tosylhydrazone) for conversion of ketones to alkenes in a situation wherein the regioselectivity of simple eliminations resisted forming the requisite diene attests to its utility. This strategy for the synthesis of perhydroazulenes offers flexibility and efficiency by constructing the target from small basic building blocks in a modular convergent fashion.

Experimental Section

Reactions were conducted under a positive pressure of dry nitrogen within glassware which had been flame dried under a stream of nitrogen unless indicated otherwise. Flash chromatography employed ICN silica gel (Kiesselgel 60, 230−400 mesh). Analytical TLC was performed with 0.2 mm coated commercial silica gel plates (E. Merck, DC-Plastikfolien, Kieselgel 60 F_{254}). Chemical shifts are reported in δ units, parts per million from the central peak of $CDCl_3$ (δ = 77.0), C_6D_6 (128.0) as an internal reference, or from an internal *t*-BuOH standard (32.10, 72.25) in D_2O. Analytical gas chromatography was performed on a Varian 3700 gas chromatograph using a 25 m × 0.25 mm poly(dimethylsiloxane) column from Alltech. Microanalyses were performed by M-H-W Laboratories, Phoenix, AZ.

5-((Trimethylsilyl)methyl)-4-(trimethylsiloxy)hexa-1,5-dien-3-one (10). To a solution of diisopropylamine (0.308 mL, 223 mg, 2.30 mmol) was added 1.58 M *n*-butyllithium in hexanes (1.33 mL, 2.10 mmol) at 0 °C. The solution was cooled to −100 °C and acrolein cyanohydrin silyl ether was added slowly dropwise over 5 min. The solution turned yellow immediately. The cooling bath temperature ranged from −85 to −100 °C. After 20 min, aldehyde **9** (284 mg, 2.00 mmol) in 4.0 mL of THF was added via cannula. After 30 min, the solution was poured into a vigorously stirred mixture of phosphate buffer (pH 6.88, 100 mL) and ether (100 mL). The aqueous layer was extracted with ether (50 mL). The organic layers were washed with phosphate buffer (pH 6.88, 50 mL) and brine (50 mL), dried over sodium sulfate, filtered, and concentrated to an oil. Flash chromatography (39:1 pentane/ether) afforded 316 mg (58.4%) of **10** as a colorless oil, R_f 0.50 (19:1 hexanes/ether). IR (neat): 1702 (s), 1634 (m), 1617 (m), 1401 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.79 (dd, J = 18.2, 10.5 Hz, 1 H), 6.36 (dd, J = 17.4, 2.0 Hz, 1 H), 5.67 (dd, J = 10.5 Hz, 2.0 Hz, 1 H), 5.24 (s, 1 H), 4.82 (s, 1 H), 4.38 (s, 1 H), 1.49 (d, AB, J = 14.2 Hz, 1 H), 1.37 (d, AB, J = 14.2 Hz, 1 H), 0.11 (s, 9 H), 0.023 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 143.2, 130.3, 128.8, 110.2, 81.8, 21.4, −0.11, −1.33. Anal. Calcd for $C_{13}H_{26}O_2Si_2$: C, 57.72; H, 9.69. Found: C, 57.72; H, 9.80.

(±)-9-(4-Methoxybenzyloxy)-8-methyl-2-((trimethylsilyl)methyl)-3-(trimethylsiloxy)non-1-en-4-one (12a). To a solution of *tert*-butyllithium (1.7 M in pentane, 2.27 mL, 3.85 mmol) in 8 mL of ether was added iodide racemic **11**[24] (623 mg, 1.94 mmol) in 2 mL of ether at −78 °C. After 1 h, this solution was added via cannula rapidly to a slurry of copper(I) cyanide (87.2 mg, 0.974 mmol) in 1 mL of ether. The slurry was allowed to warm to 0 °C. After 5 min, the cuprate was cooled to −78 °C and enone **10** (248 mg, 0.917 mmol) in 2 mL of ether was added. After 0.5 h, the mixture was poured into a cold stirring mixture of 10% ammonium hydroxide (25 mL), saturated ammonium chloride (25 mL), and ether (50 mL). The aqueous layer was extracted with ether (50 mL). The organic layers were washed with phosphate buffer (pH 6.88, 2 × 50 mL) and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated to an oil. Flash chromatography (11.5:1 hexanes/ether) afforded 458 mg of **12**, R_f 0.32 (9:1 hexanes/ether), contaminated with reduced starting iodide (isobutyl *p*-methoxybenzyl ether). The yield corrected for this impurity is 409 mg (88%), which was determined by integration of the ^1H NMR spectrum. The reduced iodide shows a heptet at δ 1.90 (isopropyl CH) and a singlet at δ 4.44 (OCH_2Ar). An analytical sample was obtained by rechromatography (12:1 hexanes/ethyl acetate). IR (neat): 1716 (m), 1614 (w), 1514 (m), 1463 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.20−7.28 (m, AA′XX′ 2 H), 6.83−6.90 (m, AA′XX′ 2H), 5.20 (t, J = 1.5 Hz, 1 H), 4.79 (br s, 1 H), 4.41 (s, 2 H), 4.26 (s, 1 H), 3.80 (s, 3 H), 3.27 (dd, ABX, J = 9.0, 6.1 Hz, 1 H), 3.19 (dd, ABX, J = 9.0, 6.7 Hz, 1 H), 2.38−2.55 (m, 2 H), 1.66−1.76 (m, 1 H), 1.30−1.65 (m, 3 H), 1.48 (d, AB, J = 13.9 Hz, 1 H), 1.36 (d, AB, J = 13.9 Hz, 1 H), 1.00−1.10 (m, 1 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.11 (s, 9 h), 0.026 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.6, 159.0, 151.0, 143.6, 130.8, 129.1 (2), 113.7 (2), 109.7, 82.6, 75.5, 72.6, 55.2, 35.3, 33.3, 33.1, 21.5, 21.01, 20.95, 17.0, −0.04, −1.27. Anal. Calcd for $C_{25}H_{44}O_4Si_2$: C, 64.60; H, 9.54. Found: C, 64.44; H, 9.45.

(+)-3-Hydroxy-9-(4-methoxybenzyloxy)-8(*R*)-methyl-2-((trimethylsilyl)methyl)non-1-en-4-one (12b). To a solution of diisopropylamine (0.0752 mL, 0.543 g, 5.37 mmol) in 30 mL of THF was added *n*-butyllithium (1.6 M in hexanes, 3.34 mL, 5.34 mmol) at 0 °C. The solution was cooled to −90 °C (internal temperature), and acrolein cyanohydrin silyl ether (1.00 mL, 0.854 g, 5.50 mmol) in 5 mL of THF was added over 5 min. The solution turned yellow-orange immediately. After 10 min, aldehyde **9** (0.745 g, 5.24 mmol) was added. The internal temperature throughout the reaction ranged from −88 to −92 °C. Concurrently, preparation of the cuprate was performed in a separate flask by adding iodide **11** (3.44 g, 10.7 mmol) in 9 mL of ether to a solution of *tert*-butyllithium (1.7 M in pentane, 12.6 mL, 21.5 mmol) in 25 mL of ether at −78 °C. After 1 h, this mixture was added via cannula rapidly into a slurry of copper(I) cyanide (0.481 g, 5.37 mmol) in 5 mL of ether. The cuprate was allowed to

(47) Trost, B. M.; Miller, M. L. *J. Am. Chem. Soc.* **1988**, *110*, 3687.

warm to 0 °C, then immediately cooled to −78 °C. The cuprate was then quickly added via cannula to the enone at −90 °C. The final pot temperature after the cuprate addition was −70 °C. After 30 min at −70 °C, the mixture was allowed to gradually warm to −60 °C and then poured into a cold, vigorously stirred mixture of 10% ammonium hydroxide (20 mL), saturated ammonium chloride (100 mL), and hexanes (50 mL). The aqueous layer was extracted with ether (100 mL). The organic layers were washed with phosphate buffer (pH 6.88, 2 × 50 mL) and brine, dried over sodium sulfate, filtered, and concentrated to 3.51 g of an oil. The oil was diluted with 12 mL of THF, and 1.8 mL of 10% aqueous sulfuric acid was added. After 1 h, the solution was partitioned between ether (100 mL) and saturated sodium bicarbonate (50 mL). The aqueous layer was extracted with ether (50 mL). The organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography (4:1 hexanes/ether) afforded 1.15 g (56%) of **12b** as a colorless oil, R_f 0.22 (4:1 hexanes/ether), with $[\alpha]^{25}_D$ +2.42 (*c* 2.8, $CHCl_3$). IR (neat): 3300−3600 (m), 1714 (s), 1633 (m), 1614 (s), 1587 (w), 1514 (s), 1463 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 5.05 (s, 1 H), 4.91 (s, 1 H), 4.48 (d, J = 4.0 Hz, 1 H), 4.41 (s, 2 H), 3.88−3.94 (m, 1 H), 3.80 (s, 3 H), 3.18−3.28 (m, 2 H), 2.35−2.60 (m, 2 H), 1.45−1.80 (m, 3 H), 1.35−1.45 (m, 1 H), 1.41 (d, AB, J = 13.8 Hz, 1 H), 1.24 (d, AB, J = 13.8 Hz, 1 H), 1.03−1.14 (m, 1 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.036 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.6, 159.0, 144.6, 130.7, 129.1, 113.9, 113.7, 82.3, 75.3, 72.6, 55.2, 37.5, 33.2, 33.1, 21.2, 21.1, 16.9, −1.08. Anal. Calcd for $C_{22}H_{36}O_4Si$: C, 67.30; H, 9.24. Found: C, 67.44. H, 9.00.

3-Acetoxy-9-(4-methoxybenzyloxy)-8(*R*)-methyl-2-((trimethylsilyl)methyl)non-1-en-4-one (12c). The three-component coupling was conducted as above with diisopropylamine (1.48 g, 14.6 mmol) in 85 mL of THF, *n*-butyllithium (1.6 M in hexanes, 9.10 mL, 14.6 mmol), acrolein cyanohydrin silyl ether (2.33 g, 15.0 mmol) in 5 mL of THF, and aldehyde **19** (2.03 g, 14.3 mmol). The cuprate was generated with iodide (*R*)-**11** (9.37 g, 29.3 mmol) in 30 mL of ether, *tert*-butyllithium (1.7 M in pentane, 34.4 mL, 58.5 mmol) in 85 mL of ether, and copper(I) cyanide (0.481 g, 5.37 mmol) in 20 mL of ether. Aqueous workup as described above afforded a yellow oil, which was passed through a 4 in. plug of silica (10:1 hexanes/ether) to remove the polar byproducts. The oil was diluted with 30 mL of THF, and 10.3 mL of 10% aqueous sulfuric acid was added. After 1 h, the solution was partitioned between ether (150 mL) and saturated sodium bicarbonate (100 mL). The aqueous layer was extracted with ether (100 mL). The organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford *ca*. 10 g of material which is primarily alcohol **12b** and isobutyl *p*-methoxybenzyl ether. To a solution of this oil and acetic anhydride (2.89 g, 28.4 mmol) in 14 mL of pyridine was added DMAP (173 mg, 1.42 mmol) at 0 °C. The mixture was allowed to warm to rt, and after 1.5 h, 10 mL of methanol was added. The mixture was partitioned between ether (150 mL) and aqueous 10% sodium bisulfate (200 mL). The aqueous layer was extracted with ether (100 mL). The organic layers were washed with 10% sodium bisulfate (3 × 100 mL) and phosphate buffer (pH 7, 50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography (8:1 hexanes/ethyl acetate) afforded 3.29 g (53%) of **12c** as a colorless oil, R_f 0.23 (9:1 hexanes:ethyl acetate), with $[\alpha]^{25}_D$ +2.52 (*c* 8.2, $CHCl_3$). IR (neat): 1747 (s), 1731 (s), 1634 (w), 1614 (m), 1587 (w), 1514 (s), 1372 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.21−7.28 (m, AA′XX′ 2 H), 6.83−6.90 (m, AA′XX′ 2 H), 5.32 (s, 1 H), 5.09 (s, 1 H), 4.94 (s, 1 H), 4.42 (s, 2 H), 3.80 (s, 3 H), 3.27 (dd, ABX, J = 9.1, 6.2 Hz, 1 H), 3.21 (dd, ABX, J = 9.1, 6.6 Hz, 1 H), 2.35−2.48 (m, 2 H), 2.15 (s, 3 H), 1.3−1.8 (m 6 H), 1.02−1.15 (m, 1 H), 0.91 (d, J = 6.9 Hz, 3 H), 0.056 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.4, 170.0, 159.0, 140.0, 130.8, 129.1, 114.6, 113.7, 82.9, 75.4, 72.6, 55.2, 38.1, 33.3, 33.0, 22.3, 20.8, 20.7, 16.9, −1.28. Anal. Calcd for $C_{24}H_{38}O_5Si$: C, 66.32; H, 8.81. Found: C, 66.21; H, 8.63.

(+)-3-Acetoxy-9-hydroxy-8(*R*)-methyl-2-((trimethylsilyl)methyl)-non-1-en-4-one and Its Racemate (13). To a solution of PMB ether **12c** (5.37 g, 12.36 mmol) in 1.1 mL of water and 31 mL of dichloromethane was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 3.37 g, 14.8 mmol). The mixture turned from orange to green immediately. After 45 min, the mixture was partitioned between ether (100 mL) and water (50 mL). The aqueous layer was extracted with ether (2 × 50 mL). The organic layers were washed with brine (2 × 25 mL), dried over magnesium sulfate, filtered, and concentrated to a dark solid. Flash chromatography (2:1 hexanes:ethyl acetate) afforded 3.62 g (93.1%) of **13** as a colorless oil, R_f 0.23 (3:1 hexanes:ethyl acetate), with $[\alpha]^{25}_D$ +13.80 (*c* 8.0, $CHCl_3$). In an identical manner, **(±)-12c** (2.20 g, 5.07 mmol) and DDQ (1.38 g, 6.08 mmol) in 0.46 mL of water and 20 mL of dichloromethane afforded 1.49 g (94%) of **(±)-13**. IR (neat): 3150−3650, 1747 (s), 1730 (s), 1634 (w), 1373 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.31 (s, 1 H), 5.08 (s, 1 H), 4.94 (s, 1 H), 3.36−3.52 (m, 2 H), 2.35−2.60 (m, 2 H), 2.14 (s, 3 H), 1.45−1.80 (m, 6 H), 1.30−1.42 (m, 1 H), 1.00−1.15 (m, 1 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.038 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.5, 170.13, 170.09, 139.9, 114.77, 114.73, 82.9, 67.8, 37.9, 35.5, 32.2, 22.2, 20.7, 20.5, 20.4, 16.43, 16.36, −1.29 (3 extra signals due to diastereomers). HRMS Calcd for $C_{14}H_{28}O_3Si$ ($M^+ - CH_2CO$): 272.1808. Found: 272.1805.

3-Acetoxy-8-methyl-9-oxo-2-((trimethylsilyl)methyl)non-1-en-4-one (14). Method B (Racemic). To a solution of oxalyl chloride (0.894 g, 7.05 mmol) in 25 mL of dichloromethane was added a solution of DMSO (1.00 g, 12.8 mmol) in 4.0 mL of dichloromethane at −78 °C. A solution of **13** (2.02 g, 6.41 mmol) in 6.0 mL of dichloromethane was added, the solution was stirred for 20 min, and then triethylamine (2.41 g, 17.1 mmol) was added. The cloudy white mixture was allowed to warm to −20 °C, whereupon the mixture was poured into a vigorously stirred mixture of water (80 mL), ether (40 mL), and hexanes (40 mL). The organic layer was extracted with ether (40 mL). The organic layers were washed with aqueous 10% sodium bisulfate (2 × 40 mL) and brine (40 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 1.91 g (95.5%) of racemic **14** as a light yellow oil.

Method B (Scalemic 8-*R*). To a slurry of Dess−Martin periodinane (4.29 g, 10.1 mmol) and sodium bicarbonate in 35 mL of dichloromethane was added alcohol **13** (2.45 g, 7.78 mmol) in 15 mL of dichloromethane at 0 °C. The mixture was allowed to warm to rt and stirred for 0.5 h, whereupon the mixture was added to a solution of ether (100 mL) and phosphate (pH 7) followed by extraction with ether (2 × 50 mL). The organic layers were washed with saturated sodium thiosulfate (3 × 25 mL) and brine (2 × 25 mL), dried over sodium sulfate, filtered, and concentrated. Flash chromatography (7:1 hexanes:ethyl acetate) afforded 2.02 g (83.3%) of **14** as a colorless oil, $[\alpha]^{25}_D$ −2.12 (*c* 11.0, $CHCl_3$). IR (neat): 1746 (s), 1728 (s), 1634 (w), 1373 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.582 (d, J = 2 Hz, 1 H), 5.28 (s, 1 H), 5.07 (s, 1 H), 4.92 (s, 1 H), 2.42−2.58 (m, 2 H), 2.25−2.35 (m, 1 H), 2.12 (s, 3 H), 1.50−1.75 (m, 3 H), 1.52 (d, AB, J = 14.5 Hz, 1 H), 1.48 (d, AB, J = 14.5 Hz, 1 H), 1.24−1.36 (m, 1 H), 1.07 (d, J = 7.1 Hz, 3 H), 0.026 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.6, 203.8, 170.0, 139.9, 114.6, 82.8, 46.1, 37.5, 29.6, 22.3, 20.67, 20.60, 20.54, 13.2, −1.33. HRMS Calcd for $C_{14}H_{26}O_3Si$ ($M^+ - CH_2CO$): 270.1651. Found: 270.1658.

Methyl (−)-9-Acetoxy-2-(phenylsulfonyl)-4(*R*)-methyl-8-oxo-10-((trimethylsilyl)methyl)undeca-2,10-dienoate and Its Racemate (18). To a mixture of aldehyde **14** (1.41 g, 4.51 mmol), methyl (phenylsulfonyl)acetate (1.16 g, 5.41 mmol), and powdered 3A molecular sieves (0.70 g, 50% weight of starting material) in 15 mL of acetonitrile were added, sequentially, piperidine (96.0 mg, 1.13 mmol) and glacial acetic acid (67.8 mg, 1.13 mmol) at 0 °C. The mixture was allowed to warm to rt and, after 3 h, was filtered through Celite. The latter was then rinsed with 1:1 ether/hexanes (*ca*. 100 mL). The filtrate was partitioned with water (40 mL), and the aqueous layer was extracted with ether (40 mL). The organic layers were washed with 10% sodium bisulfate, filtered, and concentrated, and the residue was purified via flash chromatography (4:1 hexanes:ethyl acetate) to afford 2.14 g (85.3%) of (−)-**18** as a colorless oil, R_f 0.28 (4:1 hexanes:ethyl acetate), with $[\alpha]^{25}_D$ −7.90 (*c* 2.89, $CHCl_3$). In an identical manner, **(±)-14** (367 mg, 1.17 mmol), methyl (phenylsulfonyl)acetate (282 mg, 1.29 mmol), powdered molecular sieves (183 mg), piperidine (24.9 mg, 0.292 mmol), and acetic acid (17.5 mg, 0.292 mmol) in 5.8 mL of acetonitrile afforded 457 mg (77%) of **(±)-18**. IR (neat): 1739−1745 (s), 1732 (s), 1633 (m), 1448 (m), 1436 (m), 1322 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.85−7.92 (m, 2 H), 7.57−7.63 (m, 1 H), 7.48−7.56 (m, 2 H), 7.34

(dd, J = 10.7, 1.4 Hz, 1 H), 5.28 (d, J = 2.1 Hz, 1 H), 5.08 (s, 1 H), 4.93 (d, J = 1.2 Hz, 1 H), 3.69 (s, 3 H), 3.00−3.12 (m, 1 H), 2.38−2.55 (m, 2 H), 2.14 (s, 3 H), 1.3−1.6 (m, 6 H), 1.10 (d, J = 6.7 Hz, 3 H), 0.048 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.8, 170.0, 161.9, 160.1, 140.2, 139.9, 134.7, 133.3, 128.8, 128.3, 114.7, 114.6, 82.8, 52.3, 37.3, 35.6, 34.6, 34.5, 22.3, 21.02, 20.98, 20.7, 19.4, −1.28. Anal. Calcd for $C_{25}H_{36}O_7SSi$: C, 59.03; H, 7.13. Found: C, 59.03; H, 7.11.

Methyl 9-Acetoxy-2-(methoxycarbonyl)-4-methyl-8-oxo-10-((trimethylsilyl)methyl)undeca-2,10-dienoate (19). Method A (Racemic). To a mixture of aldehyde **14** (90.0 mg, 0.288 mmol), dimethyl malonate (41.9 mg, 0.317 mmol), and powdered 3A molecular sieves (45 mg) in 6 mL of acetonitrile were added piperidine (6.1 mg) and acetic acid (4.3 mg, 0.072 mmol). After 1 day at rt, the mixture was partitioned between ether (20 mL) and phosphate buffer (pH 6.9, 20 mL). The aqueous layer was extracted with ether (30 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. Flash chromatography (88:12 hexanes:ethyl acetate) afforded 91.6 mg (79.0%) of (±)-**19** as an oil, R_f 0.44 (4:1 hexanes:ethyl acetate). IR (neat): 1744 (s), 1739 (s), 1732 (s), 1634 (w), 1437 (m), 1372 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 8.6 Hz, 1 H), 5.28 (s, 1 H), 5.08 (s, 1 H), 4.93 (s, 1 H), 4.75−4.85 (m, 1 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 2.37−2.57 (m, 3 H), 2.13 (s, 3 H), 1.43−1.60 (m, 3 H), 1.22−1.42 (m, 2 H), 1.03 (d, J = 6.6 Hz, 3 H), 0.04 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.0, 170.0, 165.9, 164.3, 154.5, 139.9, 131.5, 126.9, 114.62, 114.58, 82.8, 52.3, 52.2, 37.4, 35.5, 34.62, 34.57, 22.3, 21.0, 20.9, 20.7, 19.8, −1.3. HRMS: Calcd for $C_{21}H_{34}O_7Si$ (M^+): 426.2074. Found: 426.2079. Anal. Calcd for $C_{21}H_{34}O_7Si$: C, 59.13; H, 8.03. Found: C, 59.33; H, 7.88.

Method B (Scalemic (+)-19, R = H, R^1 = CH$_3$). Titanium tetrachloride (2.7 M in CCl_4, 3.87 mL, 10.4 mmol) was added to THF at 0 °C, forming a cloudy orange solution, and then a solution of aldehyde **14** (1.47 g, 4.72 mmol) and dimethyl malonate (0.685 g, 5.19 mmol) in 9 mL of THF was added. After 20 min, a solution of pyridine (1.64 g, 20.8 mmol) in 4 mL of THF was added, and the reaction mixture turned very dark. After the solution was warmed to rt and stirred for 1.5 h, ether (50 mL) was added, and the mixture was decanted through Celite. To the remaining solid, phosphate buffer (pH 7, *ca.* 20 mL) and ether were added, forming a slurry which was filtered through Celite. The filtrates were partitioned with 10% aqueous sodium bisulfate (50 mL). The aqueous layer was extracted with ether. The organic layers were washed with phosphate buffer (pH 7, 50 mL) and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography (10:1 hexanes:ethyl acetate, 500 mL, followed by 4:1 hexanes:ethyl acetate, 500 mL) afforded 1.42 g (71%) of (+)-**19** (R = H, R^1 = CH$_3$) as a colorless oil with $[\alpha]^{25}_D$ +0.89 (*c* 11.0, $CHCl_3$). This material was identical spectroscopically to the material above.

Cyclization of (±)-18. To a mixture of cyclization substrate **18** (458 mg, 0.900 mmol), trimethyltin acetate (10.0 mg, 0.0450 mmol), and 3A powdered molecular sieves (114 mg) in 7 mL of toluene was added 2 mL of a toluene solution containing palladium acetate (5.05 mg, 0.0225 mmol) and triisopropyl phosphite (28.1 mg, 0.135 mmol). The mixture was heated at 105−110 °C for 3 h, whereupon the mixture was filtered through a plug of silica gel. The filtrate was concentrated and purified via flash chromatography (5:4:1 ether/hexanes/benzene) to afford 144 mg (42.5%) of **20** and 135 mg (39.8%) of a mixture of **20**, **21**, and **22**. Cycloadduct **21** was only characterized by ^{1}H NMR spectroscopy in this mixture, and **22** was characterized subsequently (*vide infra*). Partial ^{1}H NMR (300 MHz, $CDCl_3$) for **21**: δ 7.87−7.96 (m, AA′XX′, 2 H), 7.63−7.81 (m, 1 H), 7.50−7.60 (m, AA′XX′, 2 H), 5.00 (d, J = 2 Hz, 1 H), 4.88 (d, J = 2 Hz, 1 H), 3.95 (br d, J = 9.8 Hz, 1 H), 3.71 (s, 3 H), 3.40 (dq, J = 17.7, 2.2 Hz, 1 H), 3.30 (dd, J = 9.8, 5.5 Hz), 3.16 (d, J = 17.7 Hz), 2.46 (t, J = 6.8 Hz, 2 H), 1.02 (d, J = 7.2 Hz, 3 H).

Data for **20** (recrystallized from ether/hexanes): mp 103−104 °C. IR (neat): 1742 (s), 1709 (s), 1447 (m), 1309 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88−7.96 (m, AA′XX′ 2 H), 7.62−7.72 (m, 1 H), 7.50−7.60 (m, AA′XX′ 2 H), 4.98 (s, 1 H), 4.79 (s, 1 H), 3.78−3.85 (m, 1 H), 3.78 (s, 3 H), 2.87−2.97 (m, 1 H), 2.83 (dd, J = 10.4, 9.1 Hz, 1 H), 2.50−2.65 (m, 3 H), 2.29 (d, J = 14.8 Hz, 1 H), 1.99−2.12 (m, 1 H), 1.75−1.99 (m, 2 H), 1.38−1.52 (m, 1 H), 1.30 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.6, 167.8, 141.1, 138.8, 133.9, 130.4, 128.5, 111.6, 79.1, 59.4, 53.1, 52.7, 46.3, 43.0, 36.9, 35.6, 21.9, 21.0. HRMS: Calcd for $C_{19}H_{21}O_4S$ (M^+ − OCH_3): 345.1161. Found: 345.1160. Anal. Calcd for $C_{20}H_{24}O_5S$: C, 63.81; H, 6.43. Found: C, 64.00; H, 6.40.

Methyl (−)-1(*R*),8(*S*),8a(*R*)-3,8-Dimethyl-4-oxo-1-(phenylsulfonyl)-4,5,6,7,8,8a-hexahydro-2*H*-azulene-1-carboxylate (22). To a mixture of (−)-**18** (1.08 g, 2.13 mmol), trimethyltin acetate (23.8 mg, 0.107 mmol) and powdered 3A molecular sieves (217 mg) in 17 mL of toluene was added 4.0 mL of a toluene solution containing palladium acetate (12.0 mg, 0.0533 mmol) and triisopropyl phosphite (66.6 mg, 0.320 mmol). The mixture was heated at 105−110 °C for 3 h, DBU (64.9 mg, 0.427 mmol) was added, and the mixture heated at 50−55 °C for 1 h. The greenish suspension was filtered through Celite and rinsed with 1:1 ether/hexanes (100 mL). The filtrate was washed with 1% sodium bisulfate (30 mL), phosphate buffer (pH 6.9, 30 mL), and brine (30 mL), dried over magnesium sulfate, filtered, and concentrated. Flash chromatography (1:1 ether/hexanes) afforded 458 mg (57%) of (−)-**22** as a light yellow-brown solid, mp 114−115 °C (ether/hexanes) and R_f 0.22 (1:1 ether/hexanes), with $[\alpha]_D$ −0.26 (*c* 2.1, $CHCl_3$). IR (neat): 1738 (s), 1685 (s), 1625 (s), 1584 (w), 1448 (m), 1435 (m), 1309 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86−7.92 (m, AA′XX′ 2 H), 7.62−7.69 (m, 1 H), 7.50−7.57 (m, AA′XX′ 2 H), 3.83 (s, 3 H), 3.71 (dd, dt, J = 7.1, 1.6 Hz, 1 H), 3.52 (dd, J = 20.1, 1.5 Hz, 1 H), 3.03 (d, J = 20.1 Hz, 1 H), 2.54−2.64 (m, 1 H), 2.32 (ddd, J = 12.5, 8.0, 1.5 Hz, 1 H), 1.72−1.92 (m, 2 H), 1.81 (s, 3 H), 1.52−1.72 (m, 2 H), 1.39−1.49 (m, 1 H), 1.07 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0, 167.1, 150.7, 136.6, 134.7, 134.2, 130.6, 128.7, 82.3, 56.9, 52.9, 44.7, 40.7, 33.2, 29.2, 19.0, 18.5, 15.7. HRMS: Calcd for $C_{19}H_{21}O_4S$ (M^+ − OCH_3): 345.1161. Found: 345.1161. Anal. Calcd for $C_{20}H_{24}O_5S$: C, 63.81; H, 6.43. Found: C, 64.01, H, 6.62.

Dimethyl (±)-3a(*R),8(*R**),8a(*S**)-8-Methyl-3-methylene-4-oxo-1,2,4,5,6,7,8,8a-octahydroazulene-1,1-dicarboxylate (23).** To a mixture of malonate (±)-**19** (50.3 mg, 0.118 mmol), trimethyltin acetate (2.6 mg, 0.012 mmol), and 3A powdered molecular sieves (25 mg) in 0.7 mL of toluene was added 0.5 mL of a toluene solution containing palladium acetate (1.3 mg, 0.0059 mmol) and triisopropyl phosphite (3.7 mg, 0.018 mmol). The mixture was heated at reflux for 2 h and then passed through a plug of silica gel. Flash chromatography (15:4:1 hexanes/ether/benzene) afforded 17.5 mg (50%) of (±)-**23** as an oil, R_f 0.44 (1:1 ether/hexanes). IR (neat): 1715−1747 (vs), 1666 (w), 1436 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.15 (br s, 1 H), 4.78 (br s, 1 H), 3.76 (s, 3 H), 3.73 (s, 3 H), 3.70−3.80 (m, 1 H), 3.07 (d, J = 15.5 Hz, 1 H), 2.78 (dq, J = 15.5 Hz, 2.7 Hz, 1 H), 2.45−2.62 (m, 2 H), 2.44 (t, J = 11.0 Hz, 1 H), 1.72−2.11 (m, 4 H), 1.10−1.21 (m, 1 H), 0.97 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.6, 172.0, 170.5, 144.9, 110.3, 62.1, 57.9, 56.8, 52.7, 52.2, 45.0, 43.6, 37.5, 21.6, 21.0. HRMS: Calcd for $C_{16}H_{22}O_5$ (M^+): 294.1467. Found: 294.1469.

Dimethyl 3,8-Dimethyl-4-oxo-4,5,6,7,8,8a-hexahydro-2*H*-azulene-1,1-dicarboxylate. Method A (Racemic 24). A solution of **(±)-23** (41.2 mg, 0.143 mmol) and DBU in 1.4 mL of toluene was heated at 60 °C for 1 h. The solution was partitioned between ether (40 mL) and 1% sodium bisulfate (20 mL). The organic layer was washed with brine (2 × 10 mL), dried over magnesium sulfate, filtered, and concentrated. Flash chromatography (7:3 hexanes/ether) afforded 30 mg (73%) of **(±)**-24 as an oil, R_f 0.21 (7:3 hexanes/ether). IR (neat): 1733 (vs), 1683 (m), 1627 (m), 1435 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 6 h), 3.67 (d, J = 8.5 Hz, 1 H), 3.39 (d, J = 18.6 H, 1 H), 2.87 (d, J = 18.6 Hz, 1 H), 2.72 (dt, J = 12.8, 9.5 Hz, 1 H), 2.35 (ddd, J = 12.8, 7.8, 2.1 Hz, 1 H), 2.10 (s, 3 H), 1.80−2.00 (m, 2 H), 1.57−1.72 (m, 2 H), 1.44 (dq, J = 10.2, 4.3 Hz, 1 H), 1.01 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.6, 172.3, 170.5, 149.7, 136.0, 62.6, 56.7, 53.0, 52.5, 46.3, 41.4, 31.2, 30.9, 19.4, 18.5, 16.2. HRMS: Calcd for $C_{16}H_{22}O_5$ (M^+): 294.1467. Found: 294.1473. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29, H, 7.53. Found: C, 65.06; H, 7.65.

Method B (Scalemic (+)-24). To a suspension of **(+)-19** (1.98 g, 4.63 mmol), trimethyltin acetate (51.6 mg, 0.232 mmol), and powdered 3A molecular sieves (0.40 g) in 40 mL of toluene was added a catalyst solution consisting of palladium acetate (26.0 mg, 0.116 mmol) and

triisopropyl phosphite (145 mg, 0.694 mmol) in 5 mL of toluene. The mixture was heated at reflux for 3 h, the bath temperature was changed to 90 °C, and DBU (0.176 g, 1.16 mmol) was added. After 2 h, the mixture was filtered through Celite (with 50 mL ether). The filtrate was partitioned with aqueous 2% sodium bisulfate (50 mL). The aqueous layer was extracted with ether (50 mL). The organic layers were washed with phosphate buffer (pH 7, 25 mL) and brine (25 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography (4:1 hexanes:ethyl acetate) afforded 0.970 g (71.3%) of **(+)-24** as an oil with $[\alpha]_D$ +67.58 (*c* 7.6, $CHCl_3$). This material was identical spectroscopically to the material above.

Methyl (−)-1(*R*),8(*S*),8a(*R*)-3,8-Dimethyl-4-(2,4,6-triisopropylbenzenesulfonylhydrazido)-1-(phenylsulfonyl)-4,5,6,7,8,8a-hexahydro-2*H*-azulene-1-carboxylate (38). To a solution of enone (−)-**22** (64.3 mg, 0.0.171 mmol) and trisylhydrazine (56.1 mg, 0.188 mmol) in 2.7 mL of methanol was added 1.24 M hydrochloric acid/methanol (0.145 mL, 0.179 mmol). After 16 h at rt, the mixture was concentrated and chromatographed directly (7:3 hexanes:ethyl acetate) to afford 70.1 mg (63%) of **38** as a white solid. A small portion was recrystallized from methanol/ether for characterization, mp 160−163 °C and R_f 0.39 (9:9:2 ether/hexanes/benzene), with $[\alpha]_D$ −0.85 (*c* 4.00, $CHCl_3$). IR (neat): 1738 (s), 1600 (m), 1564 (w), 1307 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.93 (s, 1 H), 8.00−8.10 (m, AA′XX′, 2 H), 7.63−7.71 (m, 1 H), 7.50−7.60 (m, AA′XX′ 2 H), 7.16 (s, 2 H), 4.31 (septet, J = 6.7 Hz, 2 H), 3.70 (s, 3 H), 3.43 (br d, AB, J = 18.6 Hz, 1 H), 3.25 (d, AB, J = 18.6 Hz, 1 H), 3.13 (br d, J = 6.6 Hz, 1 H), 2.90 (septet, J = 6.9 Hz, 1 H), 2.54−2.64 (m, 1 H), 2.18−2.28 (m, 1 H), 1.59 (s, 3 H), 1.45−1.70 (m, 4 H), 1.15−1.38 (m, 19 H), 0.56 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 167.5, 152.8, 152.7, 151.4, 138.1, 135.3, 134.3, 132.3, 131.5, 129.9, 128.6, 123.7, 82.0, 57.4, 52.7, 42.2, 36.2, 35.1, 34.1, 33.4, 29.8, 25.0, 24.9, 23.6, 21.1, 20.8, 14.2. Anal. Calcd for $C_{35}H_{48}N_2O_6S_2$: C, 64.00; H, 7.36; N, 4.26. Found: C, 63.83; H, 7.18; N, 4.19.

Methyl (+)-1(*R*),8(*S*),8a(*R*)-3,8-Dimethyl-1-(phenylsulfonyl)-1,2,6,7,8,8a-hexahydroazulene-1-carboxylate (39). A mixture of **38** (62.7 mg, 0.0954 mmol) and lithium hydride (3.8 mg, 0.477 mmol) in 8 mL of toluene and 0.5 mL of diglyme was heated at reflux for 4 h. The solution was partitioned between ether/phosphate buffer (pH 6.9, 20:20 mL), washed with brine, dried over magnesium sulfate, filtered, and concentrated to an oil. Flash chromatography (4:1 hexanes:ethyl acetate) afforded 30 mg (87%) of **39** as a colorless oil, R_f 0.25 (4:1 hexanes:ethyl acetate), with $[\alpha]_D$ +3.19 (*c* 1.8, $CHCl_3$). IR (neat): 1737 (s), 1733 (s), 1619 (w), 1584 (w), 1447 (m), 1308 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (m, AA′XX′ 2 H), 7.55−7.64 (m, 1 H), 7.45−7.53 (m, AA′XX′ 2 H), 5.65−5.75 (m, 2 H), 3.84 (s, 3 H), 3.49−3.56 (m, 1 H), 3.48 (d, J = 18.8 Hz, 1 H), 2.83 (d, J = 18.8 Hz, 1 H), 2.42 (br dd, J = 19.0, 12.1 Hz, 1 H), 2.06 (br dt, J = 18.9 Hz, 6.0 Hz, 1 H), 1.88−1.98 (m, 1 H), 1.78−1.88 (m, 1 H), 1.36−1.46 (m, 1 H), 1.22 (s, 3 H), 0.99 (d, J = 6.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 137.7, 133.7, 133.6, 133.0, 132.8, 130.3, 128.3, 123.6, 82.4, 60.5, 52.8, 43.4, 33.2, 32.5, 24.4, 19.6, 13.3. Anal. Calcd for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.71. Found: C, 66.74, H, 6.57.

(+)-1(*S*),8(*S*),8a(*R*)-3,8-Dimethyl-1-(phenylsulfonyl)-1,2,6,7,8,8a-hexahydroazulene (40). A mixture of **39** (30 mg, 0.0832 mmol), sodium iodide (37.4 mg, 0.250 mmol), and sodium bicarbonate (28.0 mg, 0.333 mmol) in 1.0 mL of DMF was heated at 145 °C for 3 h. The mixture was partitioned between ether (20 mL) and water (20 mL). The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated. Flash chromatography (4:1 hexanes/ether) afforded 20.4 mg (81.1%) of **40** as a colorless oil, R_f 0.31 (7:3 hexanes/ether), with $[\alpha]_D$ +1.40 (*c* 0.5, $CHCl_3$). IR (neat): 1661 (m), 1611 (m), 1585 (m), 1447 (s), 1260−1340 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.84−7.92 (m, AA′XX′ 2 H), 7.58−7.65 (m, 1 H), 7.48−7.56 (m, AA′XX′ 2 H), 5.87 (dd, ABX, J = 11.0, 2.9 Hz, 1 H), 5.75 (ddd, ABX, J = 10.9, 7.6, 3.2 Hz, 1 H), 3.39 (dt, J = 8.5 Hz, 1.8 Hz, 1 H), 3.06 (br d, J = 10.3 Hz, 1 H), 2.86 (br dd, J = 18.5, 8.8 Hz, 1 H), 2.66 (d, J = 18.7 Hz, 1 H), 2.30−2.45 (m, 1 H), 1.99 (dt, J = 17.3, 7.3 Hz, 1 H), 1.77−1.91 (m, 1 H), 1.62−1.77 (m, 1 H), 1.49 (s, 3 H), 1.40−1.52 (m, 1 H), 0.92 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 135.5, 133.4, 133.1, 132.4, 128.9, 128.8, 124.4, 67.6, 55.4, 37.7, 36.6, 34.5, 23.7, 20.0, 13.6. HRMS: Calcd for $C_{18}H_{22}O_2S$ (M^+): 302.1341. Found: 302.1348.

(+)-*ent*-Isoclavukerin A (41). A suspension of sulfone **40** (19.9 mg, 0.0658 mmol), sodium amalgam (126 mg, 0.329 mmol), and sodium dihydrogen phosphate (38.6 mg, 0.322 mmol) in 1.0 mL of methanol was stirred for 6 h. The suspension was partitioned between cold pentane (20 mL) and 1% sodium bisulfate. The organic layer was washed with brine (2 × 10 mL), dried over magnesium sulfate, filtered, and concentrated. Flash chromatography (100% pentane) afforded 6.2 mg (57.9%) of isoclavukerin A with $[\alpha]_D$ +33 (*c* 0.6, $CHCl_3$), which exhibited a ^1H NMR and IR spectrum identical to the literature, except for the optical rotation (*vide infra*).[13]

Dimethyl (+)-8(*R*),8a(*S*)-3,8-Dimethyl-4-(2,4,6-triisopropylbenzenesulfonylhydrazido)-4,5,6,7,8,8a-hexahydro-2*H*-azulene-1,1-dicarboxylate (48). To a mixture of enone **24** (325 mg, 1.81 mmol) and 2,4,6-triisopropylbenzenesulfonyl)hydrazine (395 mg, 2.17 mmol) in 3.5 mL of methanol was added 0.48 mL of 2.4 M concentrated hydrochloric acid in methanol solution (1.12 mmol) at 0 °C. The solution was allowed to warm to room temperature and stirred for 12 h. The solution was concentrated and chromatographed directly (4:1 hexanes:ethyl acetate) to afford 630 mg (100%) of **48** as a white crystalline solid, mp 135−137 °C, after recrystallization from ethyl acetate/hexanes, R_f 0.31 (4:1 hexanes/ethyl acetate, with $[\alpha]_D$ +84.91 (*c* 3.0, $CHCl_3$). IR (neat): 1726 (s), 1600 (m), 1561 (w), 1432 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.49 (br s, 1 H), 7.16 (s, 2 H), 4.31 (heptet, J = 6.7 Hz, 2 H), 3.80 (s, 3 H), 3.73 (s, 3 H), 3.32 (br d, J = 16.0 Hz, 1 H), 3.01 (br s, 1 H), 2.90 (hepet, J = 6.9 Hz, 1 H), 2.61 (d, J = 16.7 Hz, 1 H), 2.35−2.45 (m, 1 H), 2.20−2.30 (m, 1 H), 1.35−1.75 (m, 4 H), 1.55 (s, 3 H), 1.20−1.30 (m, 19 H), 0.75 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 170.2, 154.5, 152.7, 151.3, 136.1, 132.1, 131.5, 123.6, 63.6, 57.1, 53.3, 52.4, 44.2, 35.9, 34.1, 32.6, 29.8, 25.0, 23.6, 21.4, 14.5. HRMS: Calcd for $C_{31}H_{46}N_2O_6S$ (M^+): 574.3079. Found: 574.3082. Anal. Calcd for $C_{31}H_{46}N_2O_6S$: C, 64.78; H, 8.07; N, 4.87. Found: C, 64.69; H, 7.82; N, 4.81.

Dimethyl (−)-8(*R*),8a(*S*)-3,8-Dimethyl-6,7,8,8a-tetrahydro-2*H*-azulene-1,1-dicarboxylate (49). A suspension of **48** (0.867 g, 1.51 mmol) and lithium hydride (48.0 mg, 6.04 mmol) in 15 mL of diglyme was heated at 130 °C for 1 h. The mixture was partitioned between ether (100 mL) and phosphate buffer (pH 7, 50 mL), and the latter was extracted with ether (50 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The diglyme was removed by Kugelrohr distillation (80 °C, <1 Torr). Flash chromatography (5.7:1 hexanes/ether) afforded 358 mg (85%) of **49** as a white solid, mp 57−58 °C (after recrystallization from ether/hexanes) and R_f 0.33 (5.7:1 hexanes/ether), with $[\alpha]_D$ −39.67 (*c* 1.02, $CHCl_3$). IR (neat): 1732 (s), 1434 (w), 1249 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.09 (br d, J = 11.1 Hz, 1 H), 5.72 (ddd, J = 10.5, 6.9, 3.6 Hz, 1 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 3.50 (d, J = 9.4 Hz, 1 H), 3.26 (d, J = 16.8 Hz, 1 H), 2.74 (d, J = 16.8 Hz, 1 H), 2.35−2.48 (m, 1 H), 1.95−2.10 (m, 2 H), 1.80−1.88 (m, 1 H), 1.68 (s, 3 H), 1.38−1.48 (m, 1 H), 0.91 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 171.4, 134.6, 132.4, 131.8, 124.0, 63.2, 60.1, 52.7, 52.2, 45.1, 34.8, 31.5, 25.2, 20.4, 14.0. HRMS: Calcd for $C_{16}H_2O_4$ (M^+): 278.1518. Found: 278.1510.

Methyl (−)-1(*R*),8(*R*),8a(*R*)-3,8-Dimethyl-1,2,6,7,8,8a-hexahydroazulene-1-carboxylate (50). A mixture of **49** (105 mg, 0.377 mmol), sodium iodide (170 mg, 1.13 mmol), and sodium bicarbonate (127 mg, 1.51 mmol) in 3 mL of DMF was heated at 160 °C for 5 h. The mixture was partitioned between ether (20 mL) and water (20 mL), and the aqueous layer was extracted with ether (20 mL). The organic layers were washed with water (20 mL) and brine (20 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography afforded 79 mg (95%) of **50** as a colorless oil, R_f 0.52 (9:1 hexanes/ether), with $[\alpha]_D$ −43.67 (*c* 1.5, $CHCl_3$). IR (neat): 1739 (s), 1733 (s), 1435 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.18 (d, J = 11.6 Hz, 1 H), 5.71 (dt, J = 11.1, 5.6 Hz, 1 H), 3.69 (s, 3 H), 2.82−2.92 (m, 1 H), 2.60−2.78 (m, 2 H), 2.30−2.50 (m, 2 H), 2.00−2.12 (m, 1 H), 1.70−1.80 (m, 1 H), 1.72 (s, 3 H), 1.45−1.60 (m, 1 H), 1.35−1.45 (m, 1 H), 0.96 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 135.2, 134.5, 130.5, 124.1, 58.4, 51.7, 47.7, 41.4, 39.4, 36.0, 27.7, 21.1, 14.2. HRMS: Calcd for $C_{14}H_{20}O_2$ (M^+): 220.1463. Found: 220.1457.

(−)-1(*R*),8(*R*),8a(*R*)-3,8-Dimethyl-1,2,6,7,8,8a-hexahydroazulene-1-carboxylic acid (51). Method A (from Ester 50). A solution of **50** (79 mg, 0.36 mmol) and lithium hydroxide hydrate (75 mg, 1.8 mmol) in 3 mL of methanol and 0.5 mL of water was stirred at rt for 20 h. The solution was partitioned between ether (20 mL) and 1% aqueous sodium bisulfate (20 mL), and the aqueous layer was extracted with ether. The organic layers were washed with brine (10 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography (2:1 hexanes/ether) afforded 72 mg (97%) of **51** as an off-white solid, mp 61−63 °C, with $[\alpha]_D$ −38.17 (*c* 2.0, $CHCl_3$). IR (neat): 2500−3400, 1704, 1423, 1296 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.18 (d, J = 11.7 Hz, 1 H), 5.72 (dt, J = 11.1, 5.6 Hz, 1 H), 2.85−2.95 (m, 1 H), 2.67−2.80 (m, 2 H), 2.45−2.60 (m, 1 H), 2.32−2.42 (m, 1 H), 2.00−2.10 (m, 1 H), 1.75−1.85 (m, 1 H), 1.72 (s, 3 H), 1.50−1.62 (m, 1 H), 1.36−1.48 (m, 1 H), 1.20−1.30 (m, 1 H), 1.02 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.5, 135.2, 134.3, 130.8, 124.2, 58.4, 47.6, 41.1, 39.3, 35.9, 27.3, 21.2, 14.2. HRMS: Calcd for $C_{13}H_{18}O_2$ (M^+): 206.1307. Found: 206.1307.

Method B (from Trisylhyrazone 48). A suspension of trisylhydrazone **48** (108 mg, 0.188 mmol) and lithium hydride (6.0 mg, 0.755 mmol) in 1.9 mL of diglyme was heated at 130 °C for 1.5 h, sodium iodide (84.5 mg, 0.564 mmol) was added, and the suspension was heated at 160 °C for 3 h. The mixture was cooled to rt, and lithium hydroxide hydrate (31.6 mg, 0.752 mmol), 1.9 mL of methanol, and 0.38 mL of water were added. The suspension was stirred at room temperature for 16 h and then heated at 50 °C for 4 h. The mixture was partitioned between ether (30 mL) and 10% sodium bisulfate (30 mL), and the aqueous layer was extracted with ether (30 mL). The organic layers were washed with brine (2 × 10 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The remaining diglyme was evaporated via Kugelrohr distillation (80 °C, <1 Torr). Flash chromatography (1:1 hexanes/ether) afforded 18 mg (46.4%) of pure acid **51**, plus an additional 6 mg (15.5%) of the desired acid which contains *ca*. 20% impurities.

(−)-Isoclavukerin A (2). To a solution of acid **51** (88.0 mg, 0.427 mmol), DMF (15.6 mg, 0.213 mmol), and pyridine (67.5 mg, 0.853 mmol) in 1.5 mL of toluene and 2.0 mL of benzene was added oxalyl chloride (86.7 mg, 0.663 mmol) slowly, at 0 °C, followed by the addition of 1.0 mL of benzene. The mixture was allowed to warm to room temperature and was filtered through cotton, under nitrogen. Solvents were removed under reduced pressure, using a Teflon-coated, air-driven pump. To the crude acid chloride and 2-mercaptopyridine *N*-oxide sodium salt (76.4 mg, 0.512 mmol, azeotropically dried in benzene) in 4.3 mL of benzene was added DMAP (12.5 mg, 0.102 mmol). After 0.5 h, *tert*-butyl thiol (384 mg, 4.27 mmol) was added, and the reaction flask was irradiated with a 150 W light bulb, approximately 1−2 in. from the side of the flask. Nitrogen was gently blown through the flask to remove the bulk of the *tert*-butyl thiol, and then the reaction mixture was partitioned between pentane (25 mL) and water (25 mL). The aqueous layer was extracted with pentane (25 mL). The organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated at atmospheric pressure. Flash chromatography (pentane) afforded 39.4 mg (57%) of **2** as a colorless liquid, R_f 0.65 (hexanes), with $[\alpha]_D$ −99.90 (*c* 2.02, $CHCl_3$) [lit.[13] $[\alpha]_D$ −100 (*c* 1.0, $CHCl_3$)]. IR (neat): 1646 (w), 1606 (w), 1456 (m), 1440 (m), 1376 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.24 (br d, J = 11.8 Hz, 1 H), 5.61−5.69 (m, 1 H), 2.20−2.42 (m, 4 H), 2.00−2.18 (m, 2 H), 1.74 (s, 3 H), 1.68−1.78 (m, 1 H), 1.28−1.42 (m, 3 H), 0.96 (d, J = 6.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 136.6, 129.2, 124.2, 55.6, 39.9, 36.72, 36.67, 30.3, 29.3, 22.0, 14. HRMS: Calcd for $C_{12}H_{18}$ (M^+): 162.1414. Found: 162.1409.

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Supporting Information Available: Experimental procedures for **15**, **17**, **25**−**28**, **30b**, **43**, **44** (6 pages). See any current masthead page for ordering and Internet access instructions.

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