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Ketyl−Allene Cyclizations Promoted by Samarium(II) Iodide†

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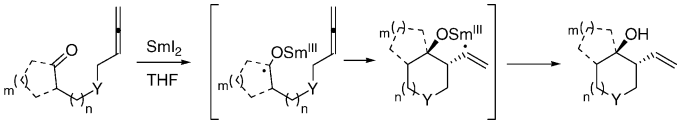

Samarium(II) iodide has proven to be an effective reagent for intramolecular reductive coupling reactions. Previous investigations of intramolecular ketyl−olefin coupling reactions provided carbocycles in excellent yield and good diastereoselectivity. This method has been extended to ketyl cyclizations with allenes. Substrates leading to both carbocycles and heterocycles in a selective manner are explored.

Introduction

Carbon radicals are reliable and efficient intermediates for the selective construction of carbon−carbon bonds. As a result of their demonstrated synthetic utility, the use of carbon radicals in contemporary organic chemistry has received much attention. Our group has focused upon the samarium diiodide (SmI_2)[1] promoted intramolecular reductive coupling reactions of ketyl radicals with unsaturated systems, such as alkenes,[2] alkynes,[3] and nitriles.[4] These reductive cyclizations generate functionalized carbocycles containing tertiary alcohols.

Recently, an influx of research concerning the formation of homoallylic alcohols via palladium-, rhodium-, and nickel-catalyzed carbonyl-allene cyclizations has appeared in the literature.[5] Allenyl ketone and aldehyde cyclizations utilizing electrolysis,[6] photochemistry,[7] and dissolving metals[8] were reported nearly two decades ago, proceeding through a ketyl radical intermediate. The reaction of allenes with ketyl radicals generated from SmI_2 was first reported by Gillmann some years ago on a single intramolecular ketyl-allene system.[9] More recently, Reissig communicated his results of the intermolecular reaction of aldehydes and ketones with methoxyallene as an acrolein equivalent.[10] To expand upon the aforementioned chemistry, intramolecular cyclizations onto allenes were investigated. A thorough investigation

† Dedicated to Professor Iwao Ojima on the occasion of his 60th birthday.

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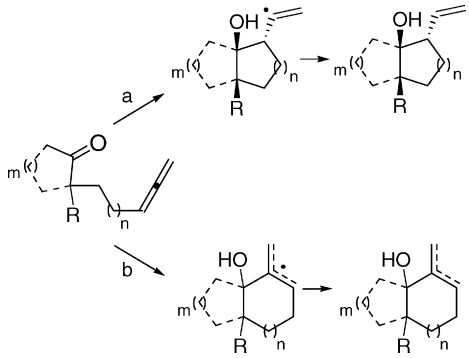
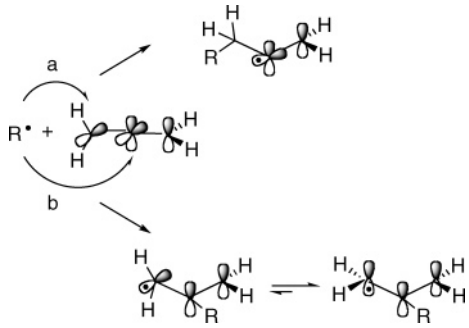
SCHEME 1



SCHEME 2

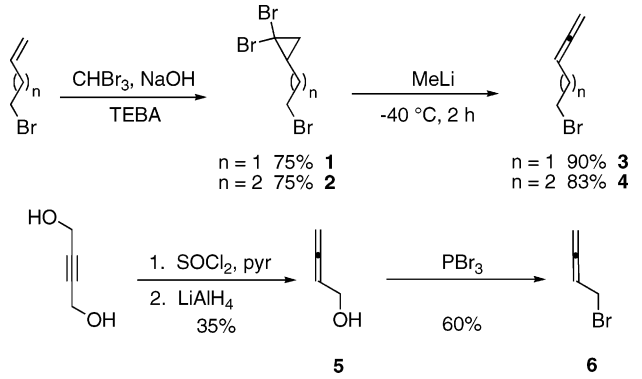


on the regioselectivity, stereoselectivity, and scope of the cyclization process was conducted to exploit this chemistry to the fullest extent. Our focus was on processes that provided high selectivity for addition to the proximal sp^2 center (Scheme 1, pathway a) avoiding regio- and stereoisomeric product mixtures in anticipation of effecting sequential reactions.

Regioselectivities of free-radical additions to allenes range from complete terminal attack to exclusive central carbon addition depending on the reaction conditions.[11] At first glance, the allylic radical resulting from radical addition to the central carbon may appear to be a more favorable pathway owing to resonance delocalization. However, the radical intermediate initially generated lacks allylic stabilization because the adjacent π bond is orthogonal to the singly occupied p orbital and a rotation is necessary to realize allylic stabilization (Scheme 2).[12]

Crandall demonstrated that alkyl radicals generated from tributyltin hydride cyclize onto both the proximal and central carbon of the allene.[13a,b] In this case, 5-*exo* cyclization to the proximal sp^2 center competes with radical addition to the central sp carbon. Extension of the chain length preferentially leads to cyclization onto the sp^2 carbon to furnish the 6-*exo* product. Hart[13c] and

SCHEME 3



Renaud[13d−f] have reported tin-induced cyclizations of alkyl radicals onto the sp and sp^2 carbon of the allene, respectively. Pattenden first presented the electrochemically promoted allenyl ketone cyclization in an *exo* fashion preferentially forming five-membered rings via addition to either center.[6] Likewise, Gillmann utilized SmI_2 for ester-substituted allenyl aldehydes.[9] Additionally, dissolving metal reduction of a carbonyl to the ketyl radical was reported to furnish homoallylic carbocycles as the major product via addition to the proximal carbon of the allene.[8] Reissig has demonstrated SmI_2-promoted intermolecular couplings of ketones with diphenylallene, methoxyallene and benzyloxyallene with addition to both the central and terminal carbons, respectively.[10]

The ketyl−allene coupling reaction promoted by SmI_2 would provide ready access to stereocontrolled, highly functionalized carbocycles and heterocycles. Additionally, our interest is to utilize the intermediate vinyl radical as a vehicle for sequential radical processes. Alkenyl radicals have a reasonably long lifetime when generated under SmI_2-promoted conditions. Reduction to the corresponding alkenyl anion is very slow under the mild reducing conditions, and thus the major reactive pathway is hydrogen abstraction from THF or related hydrogen atom sources.[14] In the absence of such hydrogen atom donors, the vinyl radicals are relatively persistent, making them ideal for sequential reactions.

Results and Discussion

To explore the scope of the samarium diiodide promoted reductive coupling of carbonyls and allenes, both cyclic and acyclic substrates were synthesized. Successful execution of the cyclization protocol would provide ready access to highly functionalized five- and six-membered carbocycles and heterocycles. Excellent stereochemical control was anticipated based upon previous reductive cyclizations. Experiments were conducted to determine the range of carbonyls that might eventually be applicable to the intramolecular cyclization reactions.

A series of acyclic and cyclic allenyl ketones were synthesized from common precursor bromoallenes **3**, **4**, and **6** (Scheme 3). Synthesis of these allenes commenced with the formation of the 1,1-dibromocyclopropanes via a dibromocarbene addition to the alkene.[15] Reaction of

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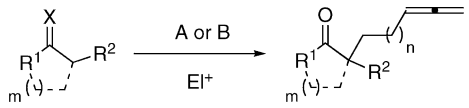
TABLE 1. Synthesis of Carbocyclic and Acyclic Substrates



Method

A: X = O, R^2 = CO_2Me, CO_2Et; NaH, bromoallene

B: X = $NN(CH_3)_2$ R^2 = H; i) LDA, bromoallene; ii) Amberlyst resin

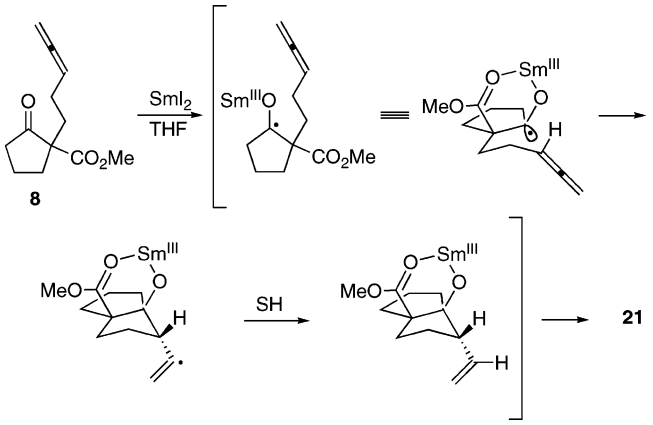
R^1	R^2	El^+	m	n	method	product	yield (%)
$-CH_2-$	CO_2Me	**6**	1	0	A	**7**	94
$-CH_2-$	CO_2Me	**3**	1	1	A	**8**	58
$-CH_2-$	CO_2Me	**4**	1	2	A	**9**	61
$-CH_2-$	CO_2Et	**3**	2	1	A	**10**	57
$-CH_2-$	H	**6**	1	0	B	**11**	70
$-CH_2-$	H	**3**	1	1	B	**12**	85
$-CH_2-$	H	**4**	1	2	B	**13**	94
$-CH_2-$	H	**3**	2	1	B	**14**	60
$-CH_2-$	H	**4**	2	2	B	**15**	65
Me	CO_2Me	**3**		1	A	**16**	60
Me	H	**3**		1	B	**17**	31
H	H	**3**		1	B	**18**	24
Me	H	**4**		2	B	**19**	30
H	H	**4**		2	B	**20**	27

the *gem*-dibromocyclopropane with methyllithium leads to cyclopropylidenes that rearrange to the desired allenes.[16] Evidently, when $n = 0$, the trihalide will not furnish the desired allene.[17] Therefore, bromoallene **6** was prepared from 1,4-dihydroxybutyne. The diol was converted to the monochloride, and then reduced using lithium aluminum hydride to afford allenyl alcohol **5**. The hydroxyl group was converted to the bromide using phosphorus tribromide to afford bromoallene **6**. With an arsenal of bromoallenes in hand, the various substrates could be readily constructed.

Allenyl β-keto esters were prepared by deprotonation of the corresponding β-keto esters with sodium hydride followed by alkylation with the allenyl bromides to provide substrates **7**−**10** and **16** in 57−94% yield (Table 1, method A). Allenyl ketones **11**−**15** and **17**−**20** were prepared via alkylation of the corresponding hydrazones (method B).[2c] The crude allenyl hydrazones were deprotected to afford the allenyl carbocycles in 24−94% yield. Attenuated isolated yields were attributed to the volatility of the low molecular weight compounds.

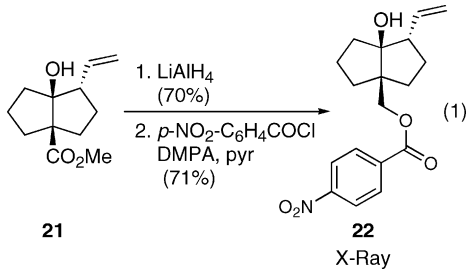
Initial studies were performed to determine the optimum reaction conditions for the SmI_2-mediated cyclization of allenyl ketones. Treatment of β-keto ester **8** with 2.2 equiv of SmI_2 and 2.0 equiv of *t*-BuOH at −78 °C gave a 4:1 mixture of cyclized product **21** (40% yield) and uncyclized alcohol, derived from reduction of the carbonyl moiety (10% yield). In an attempt to diminish this side reaction, *t*-BuOH was replaced with MeOH as an additive. This variation of the hydrogen donor did not significantly decrease the amount of the reduced starting material produced. In the absence of an additive, the amount of uncyclized reduced product decreased. However, the reaction did not proceed to completion. Addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone

SCHEME 4



(DMPU),[18] a coordinating solvent, with 2.5 equiv of SmI_2 at room temperature produced the desired cyclized product in 83% yield in 36 h. HMPA[19] proved to be a more efficient cosolvent to afford **21** in 68% yield (>95:5 ds) with a ratio of 9:1 of cyclized to uncyclized products in 4 h at ambient temperature.

High diastereoselectivities have been ascribed to a favorable secondary orbital overlap interaction between the developing vinyl radical and the adjacent alkyl substituent in the transition state.[7,20] Important electrostatic interactions may also contribute to formation of the *trans* product.[21] The samarium and its associated ligands are quite bulky and preferentially occupy the equatorial position (Scheme 4). The expected stereochemistry was confirmed by X-ray crystallographic analysis of the *p*-nitrobenzoyl derivative of **21** (eq 1).



The reaction pathway depicted in Scheme 4 proceeds by reduction of the carbonyl to a ketyl radical. The samarium oxyanion forms a six-membered chelate with the oxygen on the methyl ester to provide a template for the reaction pathway. The ketyl radical preferentially adds to the proximal sp^2 carbon of the allenyl moiety to afford the alkenyl radical. It has been previously established that vinyl as well as aryl radicals are not reduced to organosamarium reagents but rather abstract a hydrogen from the solvent.[14]

Reactions of carbocyclic compounds to form carbobicycles were explored (Table 2). The formation of 5,5-ring systems (Table 2, entries 1 and 5) was achieved in good

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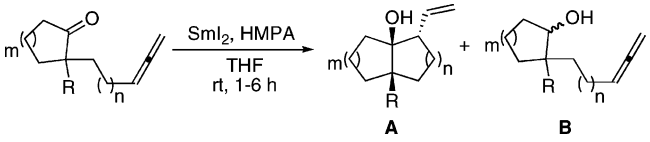
TABLE 2. Cyclization of Carbocyclic Compounds



entry	substrate	m	n	R	product	yield (%) (ds)	ratio (**A/B**)[a]
1	**8**	1	1	CO_2Me	**21**	68 (>95:5)	90:10
2	**9**	1	2	CO_2Me	**23**	27	93:7
3	**10**	2	1	CO_2Et	**24**	20	42:58
4	7	1	0	CO_2Me		complex mixture[b]	
5	**12**	1	1	H	**25**	67 (>95:5)	
6	**13**	1	2	H	**26**	72 (>95:5)	
7	**14**	2	1	H	**27**	87 (>95:5)	
8	**15**	2	2	H	**28**	15 (88:12)	44:56
9	**11**	1	0	H		complex mixture[c]	

[a] Ratio was determined by ^1H NMR of the crude reaction mixture. [b] Trace amounts of bicyclo[3.3.0]octane double bond isomers were obtained via addition to the center sp carbon of the allene. [c] Trace amounts of bicyclo[3.2.0]heptane homoallylic alcohol and bicyclo[3.3.0]octane double-bond isomers were obtained.

yields and high regio- and stereoselectivities. We observed addition exclusively to the proximal sp^2 carbon, and carbocycle **25** was accessed in much higher yield in comparison to electrochemical and sodium naphthalenide conditions.[6] Although both β-keto ester and isolated ketone functionality were successful components in cyclizations affording 5,5-ring systems, low yields were observed in the creation of 5,6-ring systems with β-keto ester substrates (entries 2 and 3). By contrast, the analogous isolated ketones provided good yields of the corresponding 5,6-ring systems with high diastereoselectivity (entries 6 and 7). In many cases, the uncyclized reduced starting material, a secondary alcohol, was observed as a byproduct in the reaction mixtures (entries 1−3, 8). The construction of a 6,6-ring system was achieved in low yield with good selectivity. In attempts to access 4,5-ring systems (entries 4 and 9) only trace amounts of product were isolated.

As mentioned above, the presence of acyclic alcohol was ubiquitous for the β-keto ester substrates, and thus in general β-keto esters **7**−**10** cyclized in lower yields than the corresponding ketones **11**−**15**. Initially, this result was not anticipated because chelation of the samarium(II) species to the ketone carbonyl and ester carbonyl moieties dramatically increases the rate of carbonyl reduction.[22] Consequently, reduction of β-keto esters is more facile than that of isolated ketones. However, the rate- and product-determining step in the process is not the reduction, but is likely to be the cyclization event. In this regard, the singly occupied molecular orbital (SOMO) of the β-keto ester ketyl radical anion is lower in energy relative to the SOMO of an isolated ketone ketyl radical anion. This has the effect of increasing the SOMO−LUMO gap in the β-dicarbonyl intermediates, thus inhibiting their transformation to product and resulting in uncyclized alcohol byproducts.

Acyclic carbonyl compounds were synthesized in a fashion similar to the allenyl carbocycles starting with

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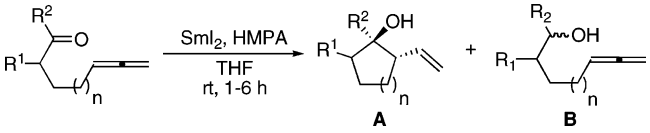
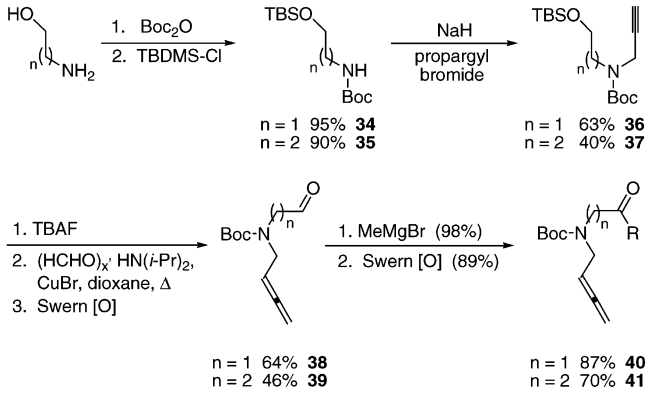
TABLE 3. Cyclization of Acyclic Compounds



entry	sub-strate	*n*	R^1	R^2	product	yield (%) (ds)	ratio (**A/B/SM**)[a]
1	**16**	1	CO_2Me	Me	**29**	56 (dr 73:20:7:−)	
2	**17**	1	H	Me	**30**	87 (94:6)	92:8:−
3	**18**	1	H	H	**31**	70 (>95:5)	70:26:4
4	**19**	2	H	Me	**32**	51 (>95:5)	65:35:−
5	**20**	2	H	H	**33**	30 (89:11)	52:36:11

[a] Ratio was determined by ^1H NMR of the crude reaction mixture.

SCHEME 5



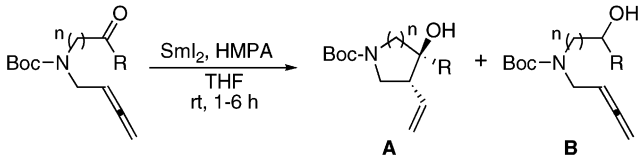
the hydrazones of acetone and of acetaldehyde (Table 1). For the acyclic substrates five-membered ring cyclization proceeded more efficiently than six-membered ring formation (Table 3). Aldehydes gave lower yields of the desired product than their methyl ketone analogues.

Acyclic amino compounds (**38**−**41**) were synthesized to extend the method to the formation of heterocycles (Scheme 5). Starting from the amino alcohol, the amine was protected as the Boc-carbamate followed by silylation of the hydroxyl group. Alkylation of the carbamate nitrogen with propargyl bromide afforded alkynylamines **36** and **37** in moderate yields. Treatment with TBAF unveiled the hydroxyl group that was subsequently subjected to a one-carbon homologation mediated by copper(I) bromide to form the allenyl moiety. The resulting allenylamine was oxidized using standard Swern conditions to produce the requisite amino aldehydes **38** and **39**. The aldehydes were suitable substrates for the reaction and were also further elaborated to ketones **40** and **41**.

Amino aldehyde **38** cyclized in good yield and diastereoselectivity to afford the five-membered hydroxyl heterocycle **42**. Pyrrolidine **43** was obtained from amino ketone **40** within 1 h with excellent yield and diastereoselectivity (98%, 95:5 ds). The *trans* configuration of the hydroxyl group in relation to the vinyl group was confirmed by X-ray crystallographic analysis of the TFA salt of the free amine. Formation of six-membered heterocycles was achieved in moderate yields along with reduced uncyclized product.

In conclusion, the SmI_2-mediated radical cyclization of the allenes with ketones and aldehydes proceeds well to afford highly functionalized carbocycles and heterocycles

TABLE 4. Cyclization of Amino Compounds



entry	substrate	*n*	R	product	yield (%) (ds)	ratio (**A/B**)[a]
1	**38**	1	H	**42**	77 (92:8)	
2	**40**	1	Me	**43**[b]	98 (95:5)	
3	**39**	2	H	**44**	43[c]	4:1
4	**41**	2	Me	**45**	68[d]	2.4:1

[a] Ratio was determined by ^{1}H NMR of the crude reaction mixture. [b] The free amine TFA salt of **43** confirmed the relative stereochemistry via X-ray crystallographic analysis. [c] Calculated yield based on an isolated mixture of **A/B** in a ratio of 4:1. [d] Calculated yield based on isolated mixture of **A/B** in a ratio of 3.5:1.

in fair to excellent yield and excellent stereochemical control. The reactions proceed via a chairlike transition state governed by the samarium alkoxide occupying the pseudoequatorial position to achieve high diastereoselectivity. Two adjacent stereocenters are created as well as the hydroxyl group and alkene moiety that serve as handles for further elaboration.

The reactions proceed best when HMPA is used as an additive. When the toxicity of HMPA is a concern, DMPU can be used; however, extended reaction times must be employed.

Five-membered ring formations proceed more efficiently than six-membered rings. Allenyl carbocycles cyclize to provide bicycles in good yield for 5,5-ring systems. Simple ketones furnish bicyclo[4.3.0]nonanes in good yield and excellent diastereoselectivity. Acyclic compounds react to afford carbocycles in moderate yield and good diastereoselectivity. Incorporation of a heteroatom within the substrate provided a reliable means for the diastereoselective construction of pyrrolidines. Piperidines are also assembled in a similar fashion, albeit with lower yield and selectivities. Methyl ketones formed carbocycles in higher yields than the analogous aldehydes (Table 4).

Extension of the ketyl-allene coupling to sequential reactions is being explored. The resulting intermediate vinyl radical is highly reactive and might be harnessed to trap suitable radicophiles. Typically, the sp^2 radical abstracts a hydrogen atom from the solvent, tetrahydrofuran. In the absence of such a hydrogen donor, vinyl radicals are reasonably persistent, making them ideal for sequential reactions. The development of the tandem radical process will be the focus of future work.

Experimental Section

Reagents. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium and benzophenone under a nitrogen atmosphere. Samarium metal (99.9%, ~40 mesh) was purchased from a commercial supplier and stored in an inert atmosphere. Diiodomethane was distilled under nitrogen, stored over copper beads, and protected from light. HMPA was distilled under nitrogen and stored over 4 Å molecular sieves in a Schlenk flask. *CAUTION*: HMPA is a cancer suspect agent and should be handled with discretion. Standard flash chromatography procedures were followed using 32−63 μm silica gel.[23] The residual $CHCl_3$ was applied as an internal standard (δ = 7.27 ppm) for ^{1}H spectra while the $CDCl_3$ signal served as internal standard (δ = 77.00) for ^{13}C spectra. Standard benchtop techniques were employed for handling air-sensitive reagents.[24]

General Procedure for the Ketyl−Allene Cyclization Reactions Using Samarium(II) Iodide.

(3*R, 3a*R**) 3-Vinyloctahydroinden-3a-ol (27).** To a vigorously stirred suspension of Sm metal (211 mg, 1.4 mmol) in dry THF (13 mL) under N_2 was added diiodomethane (335 mg, 1.25 mmol). The resultant mixture was stirred for a minimum of 2 h at ambient temperature and protected from light to afford a deep blue solution To this solution was added HMPA (1.74 mL, 10 mmol), changing the reagent color to purple, followed by dropwise addition of a 0.1 M solution of **14** (82 mg, 0.5 mmol) via cannula in THF (5 mL). The reaction mixture was stirred for 0.5−4 h until completion (determined by TLC or GC) and quenched with an aqueous solution of Rochelle's salt[25] (potassium sodium tartrate) and extracted with Et_2O (4 × 6 mL). The combined organic layers were then washed with H_2O (5 × 3 mL) and with brine, then dried over $MgSO_4$. ^{1}H NMR spectra of the crude material was used to determine diastereoselectivity. The product was purified by flash chromatography (20% Et_2O in hexanes) to afford 73 mg (87%, >95:5 ds) of **27** as a clear, colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddd, J = 17.1, 10.3, 8.3 Hz, 1H), 5.10−5.04 (m, 2H), 2.42 (ddd, J = 9.4, 9.4, 9.4 Hz, 1H), 2.00−1.95 (m, 1H), 1.96−1.83 (m, 1H), 1.71−1.46 (m, 9H), 1.38−1.31 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 117.2, 79.9, 57.0, 44.9, 30.1, 26.6, 25.1, 24.6, 22.0, 21.2; IR (neat) 3395, 2930, 1639 cm^{-1}; HRMS calcd for $C_{11}H_{18}O$ (M^+) 166.1358, found 166.1359.

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

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