A New Catalyst for a Pd Catalyzed Alder Ene Reaction. A Total Synthesis of (+)-Cassiol

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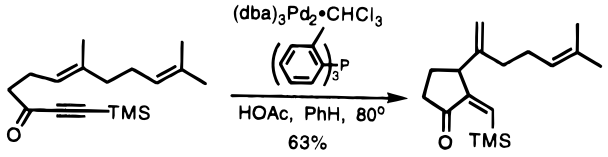
Abstract: The scope of the palladium catalyzed cycloisomerization of enynes in an Alder ene type fashion that led to a new catalytic system was explored in the context of a synthetic strategy to the antiulcerogenic agent (+)-cassiol. In a model study, the effect of six-membered ring formation, the presence of a carbonyl group in the tether, and the steric hindrance of the alkene conspire to prevent the cycloisomerization under the "standard" conditions. Two variables proved key in the development of a new catalytic system that has proven to be effective, the absence of traditional ligands and the choice of acid. An effective synthesis of (+)-cassiol was accomplished in which this new reaction played a key. A lipase served to introduce the chirality, and a palladium(0) catalyzed reaction was important in elaborating a side chain. The final adjustment of oxidation level made advantageous use of a platinum catalyzed enone hydrosilyation.

The Pd catalyzed Alder ene-type reaction constitutes a potentially powerful ring forming process.[1] While five-membered ring formation occurs smoothly with a broad array of substrates, six-membered ring formation appears less general, presumably because the higher entropy of cyclization to the six-membered ring allowed competing noncyclization reactions to predominate.[2] We therefore embarked on a program to examine the scope and limitations of the six-membered ring forming reaction in the context of a synthesis of (+)-cassiol **1**, a potent antiulcerogenic agent. Chinese cinnamon has long been used in traditional Chinese medicine as a diaphoretic, an antipyretic, and an analgesic. An aqueous extract from Cinnamomi Cortex (the dried stem bark of *Cinnamomum cassia* Blume) was reported to have potent antiulcerogenic activity.[3] The active ingredient proved to be cassioside (**2**) whose enzymatic hydrolysis product, cassiol (**1**), proved to be even more potent.[4]

The attractiveness of this interesting biological target which has been the subject of three syntheses to date[5] was the simplicity of the strategy outlined in Scheme 1 emanating from the employment of two Pd catalyzed reactions—allylic alkylation[6] and cycloisomerization.[1,2] By factoring the problem to a differentially dialkylated malonate as starting material, asymmetry could be introduced by an enzymatic hydrolysis which simultaneously chemodifferentiates the two esters in order to facilitate elaboration of one to the highly functional side chain of cassiol.[7]

The cycloisomerization step involves two significant methodological issues—the compatibility of a carbonyl group in the tether and the formation of a six-membered ring, especially considering the steric congestion associated with the quarternary carbon adjacent to the alkene requiring the intramolecular carbapalladation step occurring at a neopentyl center. Early work questioned the compatibility of a carbonyl group in the tether. Fortunately, in the context of a chokol C synthesis, although the presence of the carbonyl group proved nontrivial, the feasibility for cyclopentanone construction was established (eq 1).[1e] In this paper, we record our observations on the feasibility of the cycloisomerization for cyclohexanone synthesis, the development of a new catalyst system, and the applicability of this process to help create a synthetic strategy to (+)-cassiol.



(1)

A Model Study. The design of a meaningful model system required many of the structural issues of cassiol that would impact the effectiveness of the reaction, notably the steric hindrance. For this reason, the enyne **3** as illustrated in Scheme 2 was chosen. The 1,1-bishydroxymethyl segment was introduced using Pd(0) catalyzed allylic alkylation. Notably, both the regioselectivity and alkene geometry were completely controlled in this process. The polarity of the diol resulting from reduction of the diester with LAH made the workup of this reaction critical. Best results involved sequential addition of water, 10% aqueous sodium hydroxide, and finally saturated aqueous potassium fluoride. The addition of fluoride was necessary to liberate the diol from the aluminum salts which, by using this reagent, became quite granular and easily removed by filtration. This workup should prove generally useful for such polar products. Chemoselective hydroboration was readily accomplished with disiamylborane.[8] The remaining steps were uneventful. The model substrate was available in eight steps

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(5) Takemoto, T.; Fukaya, C.; Yokoyama, K. *Tetrahedron Lett.* **1989**, *30*, 723. Uno, T.; Watanabe, H.; Mori, K. *Tetrahedron* **1990**, *46*, 5563. Corey, E. J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611.

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(7) For reviews, see: Ohno, M.; Otsuka, M. *Org. Reactions* **1989**, *37*, 1. Enzyme Catalysis in Organic Synthesis; Drauz, K., Waldmann, H., Eds., VCH Verlagsgesellschaft mbH: Weinheim, 1995; Chapter B.1, pp 165−270.

(8) Leopold, E. J. *Org. Syn.* **1986**, *64*, 164.

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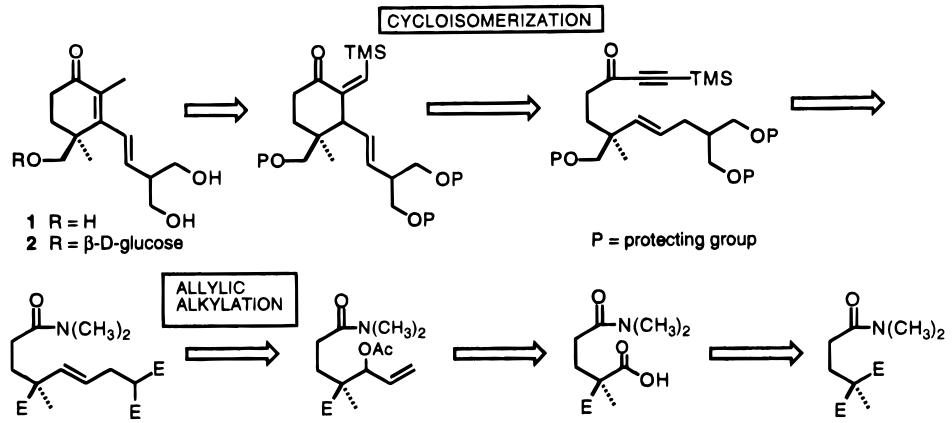
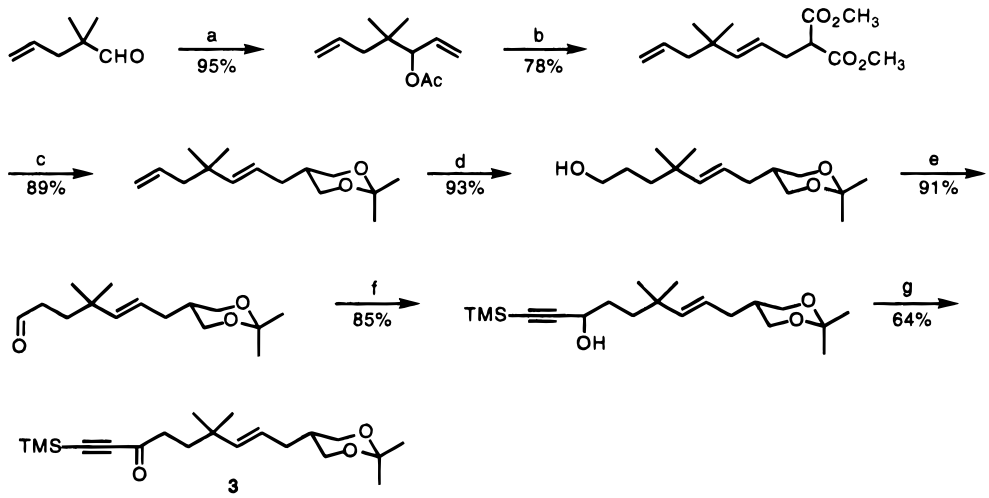
Scheme 1. A Retrosynthetic Analysis of (+)-Cassiol



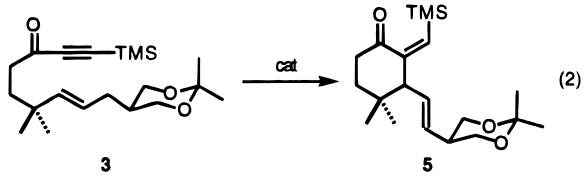
Scheme 2[a]



[a] (a) CH_2=$CHMgBr$, THF, 0 °C, then Ac_2O, room temperature. (b) $CH_2(CO_2CH_3)_2$, NaH, 2 mol% (η^3-$C_3H_5PdCl)_2$, 12 mol% Ph_3P, THF, room temperature. (c) (i) LAH, THF, reflux; (ii) $CH_3C(OCH_3)_2CH_3$, CH_3COCH_3, CSA, room temperature. (d) $[(CH_3)_2CHCH(CH_3)]_2BH$, THF, 0 °C, then NaOH, H_2O_2, room temperature. (e) PDC, CH_2Cl_2, room temperature. (f) TMS-C≡CH, *n*-C_4H_9Li, THF, −78 °C. (g) PDC, CH_2Cl_2, room temperature

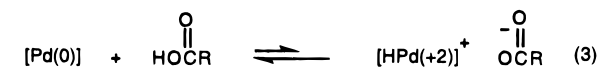
in 30% overall yield from 2,2-dimethyl-4-pentenal, the thermal adduct of allyl alcohol and isobutyraldehyde.[9]

Subjecting **3** to our preferred catalyst system, *N*,*N*-bisbenzylideneethylenediamine (BBEDA), $(dba)_3Pd{\cdot}CHCl_3$ (dba = dibenzylideneacetone, **4**), and acetic acid in 1,2-dichloroethane (DCE) at 60 °C [10] gave none of the desired cyclization product **5** (eq 2).



(2)

This failure led to a search for an effective catalyst system, a part of which is summarized in Table 1. As a perusal of the overall table reveals, the reaction appears plagued with low reactivity leading to recovered starting material or, if forced, to decomposition. Since it appears the reaction requires the substrate to function as a bidentate ligand to palladium, facilitating this coordination might increase this rate. We concluded that we required boosting the reaction rate so as to perform the reaction in as short a time period as possible to avoid product decomposition. Since the presence of ligands (entries 1,3−5) normally retards the rate by competing for coordination sites on the metal while prolonging catalyst lifetime, we focused efforts on performing the reaction in the absence of ligands (entries 2 and 7−15). The first sign of a trace of product occurred when the slightly stronger acid, benzoic acid (pK_a 4.19), replaced acetic acid (pK_a 4.75) (entry 10 vs 8). Using a bis-benzoic acid further increased the yield (entry 12) still requiring elevated temperatures (entry 11 vs 12). This trend suggested that shifting the equilibrium of eq 3 to the right helped increase the efficacy of the reaction. Stronger



(3)

acids should do so, however, previous experiences demonstrated too strong an acid caused decomposition. In seeking a balance, we turned to formic acid not only because of its somewhat higher acidity (pK 3.75) but also because it might prevent deleterious reactions that could be attributed to Pd(2+) catalysts (other than those of the type shown in eq 3) by reducing any such Pd(2+) complexes back to Pd(0). Indeed, with formic acid, the reaction now proceeded at room temperature (entry 13) but still somewhat slowly since somewhat higher temperatures did improve the yield (entry 14). Solvent choice played a significant role since switching to DCE (entry 15) from toluene gave the best result at room temperature. The structure of the product of the cycloisomerization is readily apparent from its spectroscopic properties. In the IR spectrum, the loss of the

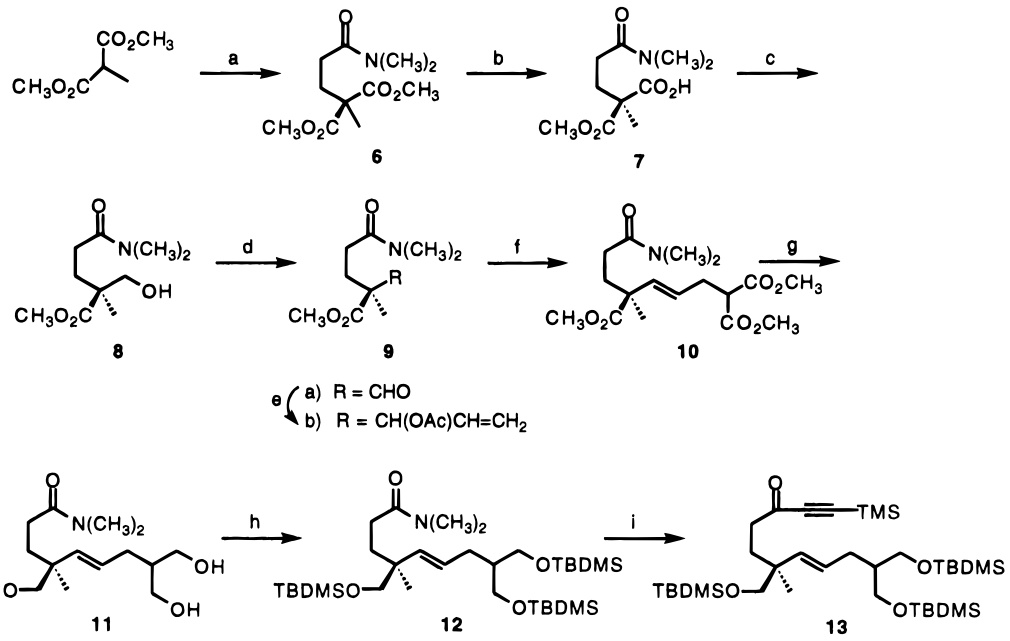
(9) Salomon, R. G.; Ghosh, S. *Org. Syn.* **1984**, *62*, 125.

Table 1. Catalyst Search for Cyclization of Enyne **3**

entry	Pd source[a]	ligand	acid	solv	temp °C[b,f]	result[c]
1	$Pd(OAc)_2$	BBEDA[d]	none	DCE[e]	60	S. M. + dec
2	$Pd(OAc)_2$	none	none	C_6D_6	80	S. M. + dec
3	**4**	BBEDA[d]	HOAc	DCE[e]	60	dec
4	**4**	$(o\text{-}CH_3C_6H_4)_3P$	HOAc	DCE[e]	60	S. M. + dec
5	**4**	Ph_3P	HOAc	DCE[e]	60	S. M. + dec
6	**4**	$(o\text{-}CH_3C_6H_4)_3P$	HCO_{2H}	DCE[e]	80	Dec.
7	**4**	none	HOAc	$PhCH_3$	rt	S. M. + dec
8	**4**	none	HOAc	$PhCH_3$	60	S. M. + dec
9	**4**	none	$PhCO_2H$	$PhCH_3$	rt	S. M. + dec
10	**4**	none	$PhCO_2H$	$PhCH_3$	60	**5** (*trace*)
11	**4**	none	1,1′-binaphthyl-2,2′-dicarboxylic acid	$PhCH_3$	rt	S. M. + dec
12	**4**	none	1,1′-binaphthyl-2,2′-dicarboxylic acid	$PhCH_3$	60	**5** (20%)
13	**4**	none	HCO_2H	$PhCH_3$	rt	**5** (40%)
14	**4**	none	HCO_2H	$PhCH_3$	60	**5** (50%)
15	**4**	none	HCO_2H	DCE[e]	rt	**5** (68%)

[a] **4** = $(dba)_3Pd_2{\cdot}CHCl_3$. Reactions run with 4 mol% of Pd source. [b] Bath temperature. [c] S.M. = starting material, dec = decomposition. [d] BBEDA = *N,N*′-bis(benzylidene)ethylenediamine. [e] DCE = 1,2-dichloroethane. [f] Room temperature = rt.

Scheme 3. The Cyclization Substrate for a (+)-Cassiol Synthesis[a]



[a] (a) 5% NaH, THF, room temperature. (b) PLE, phosphate buffer, pH 7, room temperature; 75% for two steps. (c) HOBT, DCC, THF, 0 °C, then $NaBH_4$, 64%. (d) DMSO, ClCOCOCl, CH_2Cl_2, $(C_2H_5)_3N$, −78 °C to room temperature. (e) $CH_2{=}CHMgBr$, THF, −78 °C, then Ac_2O; 76% for two steps. (f) $CH_2(CO_2CH_3)_2$, NaH, 2% $(\eta^3\text{-}C_3H_5PdCl)_2$, 12% Ph_3P, THF, 80%. (g) $NaBH_4$, THF−C_2H_5OH (10:1), 90%. (h) TBDMS-Cl, imidazole, DMF, 80 °C, 94%. (i) $TMSC{\equiv}CLi$, $BF_3{\cdot}$ether, 74%.

alkyne stretching vibration at 2156 cm^{-1} for **3** and the presence of bands for a conjugated cyclohexanone (1684, 1596 cm^{-1}) support the presence of the functional groups of **5**. The ^1H and ^{13}C NMR data indicate a single isomer. The Z-geometry of the trisubstituted double bond, suggested by the proposed mechanism, was supported by the olefinic H appearing at δ 5.77 (d, J = 1.8 Hz). The E-geometry of the disubstituted alkene is clearly indicated by the coupling pattern of the olefinic H (δ 5.50, ddd, J = 15.5, 8.6, 0.9 Hz, 1H and δ 5.21, dd, J = 15.5, 7.8 Hz, 1H).

A Synthesis of (+)-Cassiol. With the realization of the model cycloisomerization (eq 2), the stage was set for a synthesis of (+)-cassiol. Scheme 3 outlines the synthesis of the cyclization substrate. We envisioned introduction of the absolute stereochemistry by an enzymatic desymmetrization of a dialkylated malonate.[1,11] The choice of the Michael acceptor for the malonate was influenced by the effectiveness of addition of an alkynyllithium to a *N,N*-dimethyl carboxamide for the synthesis of the requisite alkynone.[1e] The conjugate addition of dimethyl methylmalonate to *N,N*-dimethylacrylamide did not proceed in methanol nor was catalyzed by $Ni(acac)_2$.[12] Use of stoichiometric amounts of strong base under nonprotic conditions gave oligomerization. Good results arose by use of only a catalytic amount of sodium hydride in the presence of a slight excess of the Michael donor. Since the NMR spectrum of the material upon workup showed it was virtually pure adduct **6**, it was subjected to enzymatic desymmetrization without any purification.

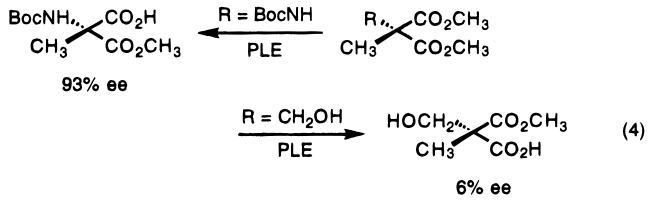
Among the various enzymes, pig liver esterase (PLE) has been used most extensively for the desymmetrization of disubstituted malonates.[11] Virtually all of the examples involve

(10) Trost, B. M.; Jebaratnam, D. J. *Tetrahedron Lett.* **1987**, *28*, 1611.

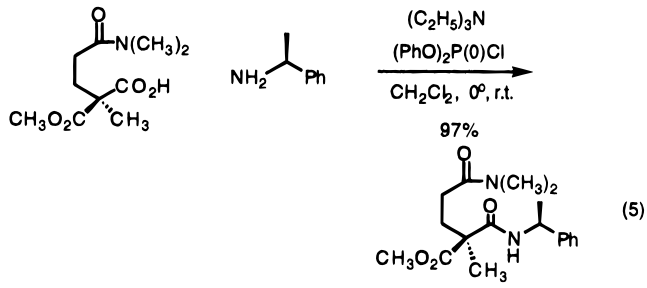
(11) Björkling, F.; Boutelje, J.; Gatenbeck, S.; Hult, K.; Norin, T.; Szmulik, P. *Tetrahedron* **1985**, *41*, 1347. Luyten, M.; Müller, S.; Herzog, B.; Keese, R. *Helv. Chim. Acta* **1987**, *70*, 1250. Toone, E. J.; Jones, J. B. *Tetrahedron: Asym.* **1991**, *2*, 1041.

(12) Nelson, J. H.; Howells, P. N.; De Lullo, G. C.; Landen, G. L.; Henry, R. A. *J. Org. Chem.* **1980**, *45*, 1246. Trost, B. M.; Quayle, P. *J. Am. Chem. Soc.* **1984**, *106*, 2469.

two different alkyl groups with enantioselectivities varying over a wide range. The effect of one of the two substituents being polar has been mixed as shown in eq 4.[13] These results make any predictions for the malonate **6** quite tenuous. Based upon the model put forth by Jones et.al.,[14] we felt that our substituent, if not too sterically bulky for the hydrophilic pocket occupied



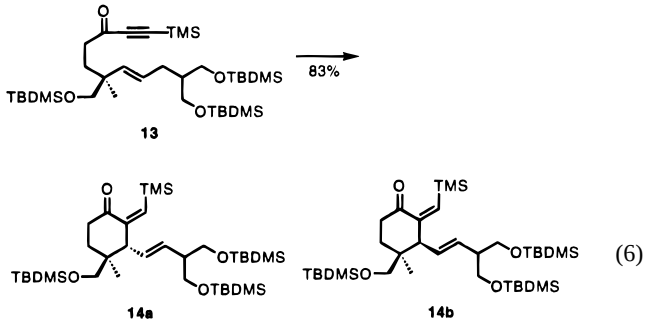
by the hydroxymethyl group in eq 4, would favor the *S* enantiomer **7** but may give low ee. Since chemoselective manipulation of either the acid or ester should be possible, either enantiomer was acceptable. In the event, PLE catalyzed hydrolysis proceeded nearly quantitatively (75% overall yield from dimethyl methylmalonate) to give the (−) enantiomer. The ee was established by conversion of the acid **7** to the amide with (*S*)-α-methylbenzylamine using diphenyl chlorophosphate (eq 5) which proceeded in >95% isolated yields and analysis



of the diastereomeric ratio by capillary gas chromatography. It proved to be 66% ee. Variation of buffer or pH had little effect, whereas addition of organic solvents decreased the ee. Use of different enzymes like *Candida cylindracea* lipase (CCL)[15a] and porcine pancreas lipase (PPL)[15] prove inferior. Fortunately, it was possible to crystallize the racemate from the major enantiomer. One recrystallization from ethyl acetate−ether gave **7** of 92% ee from the mother liquor . The absolute configuration was tentatively assigned as *S* as depicted but was not confirmed until completion of the synthesis.

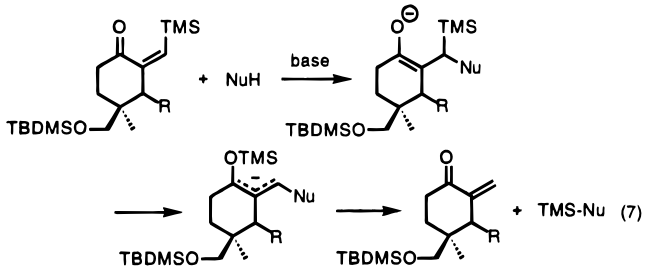
Chemoselective reduction of the carboxylic acid with borane leads to ester rather than carboxylic acid reduction.[16] On the other hand, chemoselective reduction of the acid was nicely accomplished via a protocol developed for our synthesis of merulidial[1d] involving activation of the carboxylic acid as its 3-hydroxybenztriazole derivative and *in situ* reduction with sodium borohydride to **8**. Oxidation with chromium based reagents or the Dess−Martin periodinane seemed plagued with cleavage. The Moffatt−Swern method however proved satisfactory to produce aldehyde **9a**. Addition of freshly prepared vinylmagnesium bromide and *in situ* capping with acetic anhydride provided the substrate **9b** for the first Pd catalyzed reaction which proceeded with excellent regioselectivity and geometrical control as in the model series to form triester **10**.

Chemoselective ester reduction to triol **11** occurs with sodium (not lithium) borohydride in a 10:1 THF:ethanol mixture.[13] The polarity of the product required minimization of water during workup. In this regard, the best protocol involved addition of methanol and acidification to pH 3 with amberlyst 15 followed by simple filtration, evaporation *in vacuo*, and column chromatography. On large scale, the quantity of amberlyst 15 required for the acidification makes the use of 1 N hydrochloric acid more convenient, but the yield drops from 90% to 60−70% as a result. Conversion of the amide **12** to the alkynyl ketone **13** requires addition of boron trifluoride to promote loss of the dimethylamino group rather than the alkynyl moiety during breakdown of the tetrahedral intermediate. The cyclization precursor was available in 18% overall yield in nine steps. With the requisite enyne in hand, the key cycloisomerization was attempted. Applying the "ligandless" conditions with formic acid as in the model series proceeded even better (83% yield) to give a 3:1 diastereomeric mixture (eq 6). Because the diastereoselectivity was irrelevant to the target, establishment



of the relative stereochemistry was not pursued. Simple steric considerations suggest **14a** may be the major diastereomer.

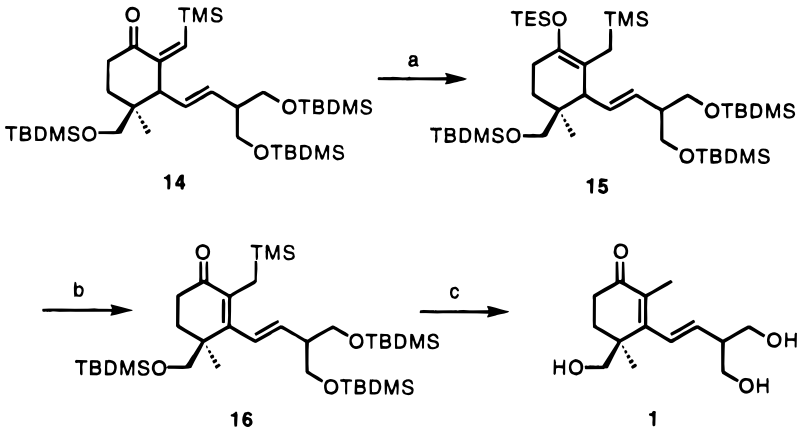
Double bond migration and desilylation of **14** are required to complete the synthesis of (+)-cassiol. Numerous acid and transition metal catalyzed processes were investigated to no avail. In one experiment with the model substrate **5**, aqueous hydrochloric acid appeared to achieve both transformations, but these conditions failed with the cassiol precursor **14** and could not be reproduced in the model series. Desilylation also proved troublesome. The usual fluoride methods normally left **14** untouched or decomposed. A Michael initiated desilylation as outlined in eq 7 wherein the nucleophile would also be a group



that can stabilize an adjacent carbanion did not come to fruition. A variation on this theme did succeed as outlined in Scheme 4. Conjugate reduction with triethylsilane catalyzed by Karstedt's platinum[17] catalyst generated the enol silyl ether **15**. Hydride abstraction of the bis-allylic hydrogen with DDQ gave the net double bond migrated product **16**. Complete O and C desilylation with TBAF gave (+)-cassiol whose spectral properties are in complete agreement with those previously recorded. The sequence was performed without purification of either **15** or **16** and gave a 42% overall yield for the three steps.

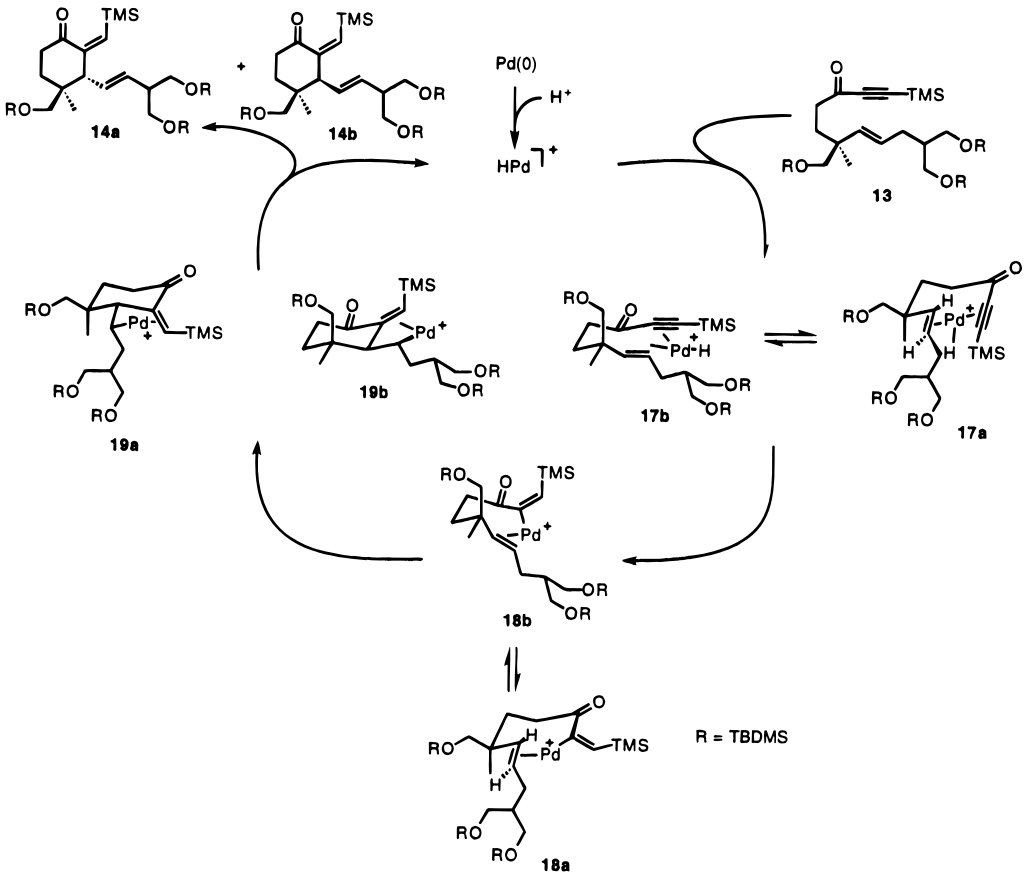
(13) Fukuyama, T.; Xu, L. *J. Am. Chem. Soc.* **1993**, *115*, 8449.
(14) Toone, E. J.; Werth, M. J.; Jones, J. B. *J. Am. Chem. Soc.* **1990**, *112*, 4946.
(15) (a) Kitazume, T.; Sato, T.; Ishikawa, N. *Chem. Lett.* **1984**, 1811; (b) Kitazume, T.; Sato, T.; Kobayashi, T.; Tain Lin, T. *J. Org. Chem.* **1986**, *51*, 1003.

Scheme 4. Final Stage of Synthesis of (+)-Cassiol[a]



[a] (a) $(C_2H_5)_3SiH$, $\{[CH_2{=}CHSi(CH_3)_2]_2O\}_2Pt$, $PhCH_3$, 70 °C. (b) DDQ, CH_2Cl_2, room temperature. (c) TBAF, THF, room temperature; 42% overall for three steps.

Scheme 5. A Mechanistic Rationale for the Cycloisomerization



Conclusions

The palladium catalyzed enyne cyclization represents an attractive strategy for ring construction. With the development of a new catalyst system, a so-called "ligandless" palladium catalyst in the presence of formic acid, a previously difficultly attainable ring system now becomes readily available. Application of this new catalyst system to other programs currently underway suggests it is generally effective. The fact that the reaction proceeds well even at room temperature is promising for high chemoselectivity. While five- and six-membered ring formation appears generally secure by this methodology, extension to other ring sizes must await further work. The nature of the tether substituents is broadened to include the carbonyl group. In this case where the carbonyl group is conjugated with the alkyne, the latter cannot be terminal (i.e., bearing H) since self-condensation dominates. Thus, the silylalkyne obviates such problems.

Scheme 5 outlines the proposed mechanism of the $Pd(0)/H^+$ version of the cycloisomerization.[2] The effectiveness of formic acid may be associated with helping to make the equilibrium between the precatalyst Pd(0) complex and the catalytically active HPd^+ species shift toward the latter (eq 3). In comparison to acetic acid, the higher acidity of formic acid should favor protonation. While stronger acids may further shift the equilibrium in the direction of HPd^+, lower chemoselectivity is experienced. The choice of acid must be a compromise between these two orthogonal effects. We suggest the key to the efficiency of the cycloisomerization is associated with the ability of the substrate to function as a bidentate ligand to palladium as in **17**. Thus, it is not surprising that a three atom tether which

leads to five membered ring formation is almost universally successful. Increasing tether length makes this bis-coordination less favorable. In such circumstances, reducing the presence of alternative ligands in the reaction medium then makes the palladium sufficiently coordinatively unsaturated it still recognizes the substrate as a bidentate ligand in which any strain in functioning as such is overcome by the enhanced bonding energy. Furthermore, the absence of bulky ligands coordinated to palladium also will decrease any unfavorable steric interactions especially in substrates like **3** and **13** which have neopentyl type alkenes. The higher reactivity of alkynes in *cis*-syn additions of palladium species leads to **18** whose intramolecular carbapalladation sets the diastereoselectivity of the reaction. The bulkiness of the siloxymethyl group should favor **18a** going to **19a** over **18b** going to **19b**—accounting for the modest diastereoselectivity observed. While this stereochemical issue was inconsequential for the current objective, the observed selectivity is a promising beginning in those applications where such control is needed. The efficacy of the palladium catalyzed cycloisomerization compared to thermal Alder ene reactions is apparent in this case since FVT at 500 °C generated only a trace of product. Of course, access to 1,3-dienes, not accessible by thermal methods, constitutes another important benefit of the palladium catalyzed process.[1,2]

The lipase technology to desymmetrize disubstituted malonates has been extended to a propionamide substituent. Using the Jones model, this substituent occupies the same hydrophilic pocket as a hydroxymethyl group meaning that pocket is capable of accommodating somewhat larger groups than his model depicts. No attempt was made to vary the amide substituent to further enhance the ee, a prospect that would be worthwhile to pursue.

The platinum catalyzed hydrosilylation of **14** highlights the effectiveness of this process. The unreactivity of the Michael system present in **14** toward many donors demonstrates the advantage of the transition metal catalyzed methodology. The ultimate result of these developments is an effective synthetic strategy to (+)-cassiol and analogues. More generally, a promising strategy for the synthesis of cyclohexanones and cyclohexenones has been demonstrated.

Experimental Section

Reactions were generally conducted under a positive pressure of dry nitrogen within glassware which had been flame-dried under a stream of nitrogen. Reaction flasks were sealed with red rubber septa and were, unless otherwise mentioned, magnetically stirred. Anhydrous solvents and reaction mixtures were transferred by oven-dried syringe or cannula. 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}). ^{1}H NMR spectra were obtained and recorded from Gemini GEM-200 (200 MHz), Gemini GEM-300 (300 MHz), or Varian XL-400 (400 MHz) instrument, in ppm from residual $CDCl_3$ (7.26 ppm), residual C_6D_6 (7.15 ppm), or from an internal *t*-BuOH standard (1.27 ppm) in D_2O. ^{13}C NMR spectra were recorded on a Gemini GEM-200 (50 MHz) or a Gemini GEM-300 (75 MHz) or a Varian XL-400 (100 MHz) instrument. Chemical shifts are reported in δ units, parts per million from the central peak of $CDCl_3$ ($\delta = 77.0$), or C_6D_6 (128.0) as an internal reference, or from an internal *t*-BuOH standard (32.10, 72.25) in D_2O. IR spectra were obtained using a Nicolet 205 FT-IR spectromer. Melting points were determined using Thomas-Hoover oil bath apparatus and were not corrected. Analytical gas chromatography was performed on a Varian 3700 gas chromatograph using a 25 m × 0.25 mm polydimethylsiloxane column from Alltech. Mass spectral analyses were performed by the NIH Mass Spectral Facility at the School of Pharmacy, University of California-San Francisco on a Kratos MS-90 instrument with an ionizing current of 98 mA and an ionizing voltage of 70 eV. Microanalyses were performed by M-H-W Laboratories, Phoenix, AZ.

Preparation of 3-Acetoxy-4,4-dimethyl-1,6-heptadiene. To 2,2-dimethyl-4-pentenal (11.22 g, 100 mmol) in dry THF (100 mL) at 0 °C was added dropwise a THF solution of vinylmagnesium bromide (1 M, 120 mL, 120 mmol). The mixture was stirred for 15 min at 0 °C and 1 h at room temperature. It was cooled to 0 °C, and acetic anhydride (28.3 mL, 300 mmol) was then introduced. The reaction was allowed to proceed for 30 min at 0 °C and for 12 h at room temperature. Water was added, and the resultant mixture was extracted with diethyl ether. The ethereal solution was washed (1 × $NaHCO_3$, 3 × H_2O), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was vacuum distilled (71−79 °C/18 mmHg) to afford the title compound (17.3 g, 95%) as a colorless liquid: IR (thin film) 3074, 2971, 1743, 1639, 1469, 1239 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.7−5.9 (m, 2H), 5.26 (m, 1H), 5.18−5.22 (m, 1H), 5.0−5.1 (m, 3H), 2.09 (s, 3H), 2.08 (m, 2H), 0.92 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.1, 134.4, 133.2, 118.3, 117.6, 80.6, 43.2, 36.9, 23.0, 22.7, 21.0. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.28; H, 10.15.

Preparation of Methyl (4*E*)-6,6-Dimethyl-2-(methoxycarbonyl)-4,8-nonadienoate. Dry THF (350 mL) was added to sodium hydride (6.68 g of 60% dispersion in mineral oil, 167 mmol), washed with dry hexanes (50 mL) twice, at which time dimethyl malonate (20 mL, 175 mmol) was slowly added by syringe at room temperature. The resulting sodium malonate THF solution was cannulated into a solution of π-allylpalladium chloride dimer (150 mg, 0.41 mmol), triphenylphosphine (1.29 g, 1.64 mmol), the above acetate (15.2 g, 83.5 mmol), and dry THF (50 mL) also at room temperature. The reaction mixture was then heated at reflux for 6 h, cooled, quenched with water (400 mL), and extracted with diethyl ether (2 × 400 mL). The organic layer was washed (2 × H_2O, 1 × brine), dried over $MgSO_4$, and evaporated. The residue was vacuum distilled (90−100 °C/0.5 mmHg) to obtain the title compound (13.59 g, 64%) as a colorless liquid. Performing this reaction on a 5.92 mmol scale of allyl acetate gave a 78% yield of the title compound: IR (thin film) 3074, 2959, 1741, 1638, 1439, 1344, 1233 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.8−5.6 (m, 1H), 5.50 (d, $J = 15.6$, 1H), 5.25 (dt, $J = 15.6$, 7.0, 1H), 4.9−5.02 (m, 2H), 3.72 (s, 6H), 3.41 (t, $J = 7.6$, 1H), 2.59 (td, $J = 7.3$, 1.1, 2H), 1.98 (d, $J = 7.4$, 2H), 0.93 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 143.5, 135.5, 121.2, 116.8, 52.3, 52.0, 47.1, 35.7, 32.0, 26.8. HRMS calcd for $C_{14}H_{22}O_4$ (M^+): 254.15189. Found: 254.1523.

Preparation of 2,2-Dimethyl-5-[(2′*E*)-4′,4′-dimethyl-2′,6′-heptadienyl]-1,3-dioxane. LAH (8.1 g, 213 mmol) was carefully added to 150 mL of dry THF at 0 °C and then heated to reflux for 40 min. After the suspension was cooled to 0 °C, the above malonate (13.45 g, 52.88 mmol) in 50 mL of THF was added by syringe over 40 min. After heating at reflux for 15 h, the reaction mixture was then cooled to rt and magnetic stirring was replaced with mechanical stirring. After addition of 150 mL of THF, the reaction was worked up by slow addition of water (8.1 mL), followed by 10% aqueous sodium hydroxide (16 mL) and saturated potassium fluoride solution (25 mL). The white solid, removed by filtration, was thoroughly washed with methylene chloride. The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to yield crude diol (12.2 g) as a colorless liquid which was directly used for the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66−5.81 (m, 1H), 5.46 (d, $J = 15.6$, 1H), 5.29 (dt, $J = 15.6$, 6.9, 1H), 4.94−5.04 (m, 2H), 3.80 (dd, $J = 10.8$, 4.0, 2H), 3.67 (dd, $J = 10.7$, 7.4, 2H), 1.96−2.06 (m, 4H), 1.78−1.94 (m, 1H), 0.97 (s, 6H).

To the mixture of the above crude diol (12.2 g, 52.88 mmol) and dimethoxypropane (30 mL, 244 mmol) in reagent grade acetone (50 mL) was added a catalytic amount of camphorsulfonic acid (200 mg, 0.86 mmol) at room temperature. After stirring 2 h at room temperature, anhydrous Na_2CO_3 was added, and the mixture was stirred for 4 h at room temperature. It was filtered through a silica gel plug and vacuum distilled (85−96 °C/2.5 mmHg) to afford the titled acetonide (11.17 g,

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89% for two steps) as a colorless liquid. IR (thin film) 3075, 2961, 1637, 1456, 1198, 1071 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.65−5.8 (m, 1H), 5.43 (d, $J = 15.6$, 1H), 5.21 (dt, $J = 15.6$, 6.7, 1H), 4.93−5.03 (m, 2H), 3.84 (dd, $J = 11.6$, 4.5, 2H), 3.57 (dd, $J = 11.9$, 9.0, 2H), 2.01 (d, $J = 7.3$, 2H), 1.8−1.95 (m, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 0.96 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.2, 135.6, 122.4, 116.7, 97.7, 64.6, 47.4, 35.8, 34.3, 32.1, 27.3, 27.1, 20.7. HRMS calcd for $C_{15}H_{26}O_2$ (M^+): 238.1933. Found: 238.1941.

Preparation of 2,2-Dimethyl-5-[(2′*E*)-4′,4′-dimethyl-7′-hydroxy-2′-heptenyl]-1,3-dioxane. 2-Methyl-2-butene (7.1 mL, 67 mmol)) was added to a THF solution of borane (1 M, 30 mL, 30 mmol) at −30 °C. The mixture was stirred at 0 °C for 2 h and then transferred to a THF solution (20 mL) of the above diene (4.77 g, 20 mmol) at 0 °C. The reaction was allowed to proceed for 1.5 h at 0 °C and then for 15 h at room temperature. After cooling to −10 °C, 10% aqueous sodium hydroxide (11 mL) followed by 30% aqueous hydrogen peroxide (11 mL, slow addition) was added, and the resultant mixture was stirred for 5 h at room temperature. The ethereal layer obtained by extraction was washed (2 × NH_4Cl, 1 × H_2O, 1 × brine), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was vacuum distilled (170−200 °C/2 mmHg) to give the title alcohol (4.77 g, 93%) as a colorless liquid. IR (thin film) 3420, 2950, 1656, 1455, 1371, 1198 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.38 (d, $J = 15.6$, 1H), 5.2 (dt, $J = 15.6$, 6.8, 1H), 3.83 (dd, $J = 12.0$, 4.3, 2H), 3.51−3.61 (m, 4H), 1.8−1.95 (m, 3H), 1.35−1.45 (m, 2H), 1.41 (s, 3H), 1.39 (s, 3H), 1.24−1.32 (m, 2H), 0.95 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.3, 122.3, 97.7, 64.4, 63.2, 38.8, 35.4, 34.2, 32.0, 28.0, 27.2, 27.0, 20.7. HRMS calcd for $C_{15}H_{28}O_3$(M^+): 256.2038. Found: 256.2018.

Preparation of 2,2-Dimethyl-5-[(2′*E*)-4′,4′-dimethyl-7′-oxo-2′-heptenyl]-1,3-dioxane. A mixture of the above alcohol (86.8 mg, 0.338 mmol) and PDC (191 mg, 0.508 mmol) in methylene chloride (4 mL) was stirred for 22 h at room temperature. Diethyl ether (10 ml) and anhydrous $MgSO_4$ was then added, and stirring was continued for 2 h. The solution was passed through a silica plug. Removal of solvents *in vacuo* afforded the title aldehyde (78.3 mg, 91%) as a colorless liquid. IR (thin film) 2993, 2961, 2863, 2712, 1456, 1370, 1198 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, $J = 1.4$, 1H), 5.19−5.39 (m, 2H), 3.85 (dd, $J = 1.20$, 4.5, 2H), 3.57 (dd, $J = 12.0$, 8.8, 2H), 2.33 (td, $J = 8.0$, 1.5, 2H), 1.94 (t, $J = 6.3$, 2H), 1.8−1.9 (m, 1H), 1.60 (t, $J = 7.9$, 2H), 1.43 (s, 3H), 1.41 (s, 3H), 0.98 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 141.0, 123.6, 97.6, 64.4, 39.8, 35.3, 34.1, 31.9, 27.0, 26.8, 20.8. HRMS calcd for $C_{14}H_{23}O_3$ ($M^+ - CH_3$): 239.1647 Found: 239.1638.

Preparation of 2,2-dimethyl-5-[(2′*E*)-4′,4′-dimethyl-7′-oxo-9′-trimethylsilyl-2′-nonen-8′-ynyl]-1,3-dioxane (3). To a trimethylsilylacetylene (74.8 mg, 0.762 mmol) solution in THF (0.5 mL) was added dropwise *n*-butyllithium in hexanes (1.55 M, 0.448 mL, 0.694 mmol) at −78 °C. After 30 min stirring, the above aldehyde (85 mg, 0.334 mmol) in THF (0.5 ml) was slowly added by syringe at −78 °C. The reaction was then allowed to slowly warm to room temperature, quenched with saturated ammonium chloride solution, and extracted with diethyl ether. The resultant ethereal solution was washed (1 × water, 2 × brine), dried over $MgSO_4$, and evaporated *in vacuo* to yield the corresponding alkynol (101.3 mg, 85%) as a slightly yellow liquid which was directly used for oxidation without purification.

The above alcohol (74 mg, 0.21 mmol) and PDC (118 mg, 0.315 mmol) in dry methylene chloride (1 mL) was stirred at room temperature for 40 h. Diethyl ether (8 mL) and $MgSO_4$ were then added, and the resultant mixture was stirred for 2 h. The solution was filtered through a Celite plug and evaporated *in vacuo*, and the residue was purified on silica gel (4:1, hexanes−diethyl ether) to afford ketone **3** (47 mg, 64%) as a colorless liquid. IR (thin film) 2963, 2156, 1681, 1455, 1369, 1253, 1198 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (d, $J = 15.7$, 1H), 5.25 (dt, $J = 15.6$, 6.4, 1H), 3.85 (dd, $J = 12.0$, 4.4, 2H), 3.58 (dd, $J = 12.0$, 8.8, 2H), 2.46 (t, $J = 8.0$, 2H), 1.95 (t, $J = 6.7$, 2H), 1.8−1.92 (m, 1H), 1.63 (t, $J = 8.0$, 2H), 1.43 (s, 3H), 1.41 (s, 3H), 0.98 (s, 6H), 0.25 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 188.0, 141.2, 123.5, 102.0, 97.8, 97.6, 64.5, 41.3, 36.0, 35.4, 34.3, 32.1, 27.2, 27.0, 20.9, −0.8. Anal. Calcd for $C_{20}H_{34}O_3Si$: C, 68.52; H, 9.98. Found: C, 68.60; H, 10.06.

Cycloisomerization of 3. Preparation of 5. Enyne **3** (35 mg, 0.1 mmol) in 1,2-dichloroethane (0.5 mL) followed by formic acid (3.5 μl, 0.1 mmol) was added to a solution of Pd_2dba_3·$CHCl_3$ and **4** (2 mg, 0.002 mmol) in 1,2-dichloroethane (0.5 mL) at room temperature. The reaction was stirred at room temperature for 9 h. Celite was then added, and the mixture was filtered through a silica plug. Purification by flash chromatography (3% diethyl ether in hexane) afforded the cyclized ketone **5** (24 mg, 68%) as a colorless liquid. IR (thin film) 2995, 2869, 1684, 1596, 1451, 1390, 1373, 1247, 1197, 1073 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (d, $J = 1.8$, 1H), 5.5 (ddd, $J = 15.5$, 8.6, 0.9, 1H), 5.21 (dd, $J = 15.4$, 7.8, 1H), 3.84 (dd, $J = 12.0$, 4.9, 2H), 3.72 (m, 2H), 2.76 (bro d, $J = 8.5$, 1H), 2.6 (m, 1H), 2.45 (t, $J = 7.2$, 2H), 1.6−1.8 (m, 2H), 1.45 (s, 3H), 1.42 (s, 3H), 0.99 (s, 3H), 0.93 (s, 3H), 0.09 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 153.5, 142.5, 131.5, 130.1, 97.5, 64.3, 59.9, 38.3, 37.1, 35.9, 33.8, 28.7, 27.6, 23.3, 20.4, −0.4. HRMS calcd for $C_{20}H_{34}O_3Si$ (M^+): 350.2277. Found: 350.2269.

Preparation of (*S*)-4-(*N*′,*N*′-Dimethylaminocarbonyl)-2-(methoxycarbonyl)-2-methylbutanoic Acid (7). To a suspension of sodium hydride (0.5 g of 60% dispersion in mineral oil, 12.5 mmol, washed with 35 mL pentane) in THF (150 mL) was added dimethyl methylmalonate (33.9 mL, 255 mmol) at room temperature. The mixture was stirred at room temperature for 30 min, and *N*,*N*-dimethylacrylamide (24.7 g, 250 mmol) in THF (120 mL) was added dropwise. After 2 h stirring, ethyl acetate (300 mL) was added. The solution was washed (NH_4Cl, H_2O, brine), dried ($MgSO_4$), and evaporated *in situ* to give the Michael adduct **6** (47.5 g, 194 mmol) as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 6H), 3.01 (s, 3H), 2.94 (s, 3H), 2.29−2.39 (m, 2H), 2.17−2.26 (m, 2H), 1.45 (s, 3H).

PLE (2000 units) was added to diester **6** (47.5 g, 194 mmol) in 0.03 M pH 7 phosphate buffer (1.5l) at room temperature. The pH of the solution was maintained at 7 by addition of 1 M aqueous sodium hydroxide through a pH-stat. More PLE, total 4000 units, was added as the reaction proceeded. The hydrolysis was stopped after 1 equiv of base was consumed (194 mL, in 9 days). The reaction mixture was frozen at −78 °C and then just thawed at which point a saturating amount of sodium chloride was added. The resulting solution had its pH adjusted to 13, was washed with ethyl acetate (2 × 50 mL), and was then acidified to pH 2 with 6 N aqueous hydrochloric acid. Extraction with ethyl acetate (2 × 1 mL) followed by evaporation of the dried ($MgSO_4$) ethyl acetate extracts yielded monoester acid **7** (43.4 g, 75.2%. 66% ee) as a white solid. Recrystallization was performed with ethyl acetate and diethyl ether. Racemic mixtures were crystallized out, and the mother liquor was enriched to provide pure **7** with 92% ee; mp 104−105 °C, $[\alpha]^{25}_D = -1.69°$ (*c* 2.45, CD_3OD). IR (KBr) 3430, 2925, 1731, 1669, 1463, 1259 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.08 (s, 3H), 2.96 (s, 3H), 2.38−2.6 (m, 2H), 2.1−2.28 (m, 2H), 1.48 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 175.0, 174.7, 174.2, 54.2, 52.9, 37.7, 35.8, 32.4, 29.8, 20.7. Anal. Calcd for $C_{10}H_{17}O_5N$: C, 51.94; H, 7.41; N, 6.06. Found: C, 52.12; H, 7.44; N, 6.21.

Determination of Enantiomeric Excess. To a solution of acid **7** (5.0 mg, 0.021 mmol), $[\alpha]^{25}_D = -1.69$ (*c* 2.45, $CDCl_3$), and triethylamine (9.0 μl, 0.07 mmol) in methylene chloride (0.5 mL) was added diphenyl chlorophosphate (6.1 μl, 0.027 mmol). After stirring at 0 °C for 15 min and at room temperature for 3 h, (*S*-α-methylbenzylamine (4.6 μl, 0.032 mmol) was added, and the reaction was stirred at room temperature overnight. Ethyl acetate (5 mL) was added, and the resulting organic layer was washed (1 × H_2O, 2 × $NaHCO_3$, 1 × brine), and dried ($MgSO_4$). Purification by silica gel chromatography (4% MeOH in CH_2Cl_2) afforded amide (7.0 mg, 97%) as a colorless syrup for which GC analysis shows 92% de. IR (thin film) 3323, 3010, 2978, 2943, 1736, 1635, 1530, 1454, 1405, 1262, 1117 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, $J = 7.2$, 1H), 7.33−7.30 (m, 5H), 5.08 (dq, $J = 6.2$, 1H), 3.75 (s, 3H), 2.88 (s, 3H), 2.76 (s, 3H), 2.22−2.0 (m, 4H), 1.48 (d, $J = 7.3$, 3H), 1.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 171.8, 169.9, 143.6, 128.6, 127.2, 126.0, 52.9, 52.7, 49.2, 37.0, 35.4, 33.2, 29.0, 22.0, 21.6 HRMS calcd for $C_{18}H_{26}O_4N_2$ (M^+): 334.1893. Found: 334.1899.

Preparation of (*S*)-*N*,*N*-Dimethyl-5-hydroxy-4-(methoxycarbonyl)-4-methyl pentanamide (8). A mixture of acid **7** (14.0 g, 60.6 mmol) and hydroxybenzotriazole hydrate (20 g, 118 mmol) in dry THF (250 mL) to which was added DCC (18.7 g, 90.8 mmol) at 0 °C was stirred at room temperature for 6 h. The mixture was filtered through Celite and washed with THF. The combined THF solution was cooled

to 0 °C, and sodium borohydride (4.6 g, 121 mmol) was slowly added after which stirring was continued at 0 °C for an additional 1.5 h. The reaction was then quenched with 1 N aqueous hydrochloric acid (3 mL, solution pH = 3) and water. The THF was removed *in vacuo*. A white solid was removed by filtration and washed with water. The combined aqueous layers were saturated with sodium chloride and extracted with ethyl acetate. After drying over $MgSO_4$, purification by flash chromatography (3% MeOH in CH_2Cl_2) afforded hydroxy ester **8** (8.36 g, 64%) as a colorless liquid; $[\alpha]^{25}_D = -4.22$ (*c* 2.08, $CDCl_3$). IR (thin film) 3410, 2951, 1737, 1645, 1505, 1403 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.59 (d, J = 11.7, 1H), 3.55 (d, J = 11.7, 1H), 3.01 (s, 3H), 2.95 (s, 3H), 2.34 (br t, J = 7.3, 2H), 1.91−2.04 (m, 2H), 1.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 173.0, 66.3, 51.9, 47.7, 37.2, 35.7, 29.3, 28.3, 20.5. HRMS calcd for $C_{10}H_{19}O_4N$ (M^+): 217.1314. Found: 217.1311.

Preparation of (4*S*)-*N,N*-dimethyl-5-acetoxy-4-(methoxycarbonyl)-4-methyl-5-heptenamide (9b). To a methylene chloride (10 mL) solution of oxalyl chloride (0.44 mL, 5.04 mmol) was slowly added DMSO (0.72 mL, 10.1 mmol) in methylene chloride (3 mL) at −78 °C. After 10 min stirring, alcohol **8** (0.731 g, 3.37 mmol) in methylene chloride (5 mL) was slowly added at the same temperature. The reaction mixture was stirred at −78 °C for 30 min at which point triethylamine (2.4 mL, 17.2 mmol) was introduced. The reaction temperature was kept at −78 °C for 1 h and then allowed to warm to room temperature. The reaction was quenched with water, dried over $MgSO_4$, and evaporated to give the crude aldehyde (0.672 g) as a liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1H), 3.74 (s, 3H), 2.97 (s, 3H), 2.91 (s, 3H), 2.05−2.35 (m, 4H), 1.32 (s, 3H).

To the crude aldehyde in dry THF (6 mL) was added vinylmagnesium bromide (1 M in THF, 4.68 mmol) slowly at −78 °C. After 2 h stirring, acetic anhydride (1.2 mL, 12.7 mmol) was introduced slowly. The reaction mixture was kept at −78 °C for 30 min and at room temperature for 8 h. Ethyl acetate (100 mL) was added. The reaction mixture was washed (2 × $NaHCO_3$, 2 × H_2O, 1 × brine), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on silica gel (CH_2Cl_2, then 2% MeOH in CH_2Cl_2) to afford the allylic acetate **9b** (0.733 g, 76% over two steps) as a mixture of two diastereomers in a ratio of 1.4 to 1. IR (thin film) 2995, 2946, 1740, 1650, 1646, 1400, 1236 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) major isomer, δ 5.70−5.8 (m, 1H), 5.54 (d, J = 6.5, 1H), 5.22−5.36 (m, 2H), 3.68 (s, 3H), 2.98 (s, 3H), 2.94 (s, 3H), 2.2−2.31 (m, 2H), 2.08 (s, 3H), 1.7−1.9 (m, 2H), 1.19 (s, 3H); minor isomer, 5.7−5.81 (m, 1H), 5.54 (d, J = 6.5, 1H), 5.22−5.36 (m, 2H), 3.67 (s, 3H), 2.98 (s, 3H), 2.94 (s, 3H), 2.2−2.31 (m, 2H), 2.03 (s, 3H), 1.7−1.9 (m, 2H), 1.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) major isomer, δ 174.5, 172.1, 169.7, 132.3, 119.1, 77.6, 51.9, 49.4, 37.1, 35.4, 30.7, 28.5, 20.9, 17.3; minor isomer, 174.8, 171.9, 169.5, 131.4, 120.1, 78.1, 51.9, 49.3, 37.1, 35.4, 30.7, 28.2, 20.9, 16.3. Anal. Calcd for $C_{14}H_{23}O_5N$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.71; H, 8.16; N, 4.76.

Preparation of (4*S*,5*E*)-*N,N*-Dimethyl-4,8-bis(methoxycarbonyl)-9-methoxy-4-methyl-9-oxo-5-nonenamide (10). Dimethyl malonate (0.44 mL, 3.85 mmol) was added to a THF (10 mL) suspension of sodium hydride (3.43 mmol) at room temperature. After 10 min stirring, it was cannulated into a THF (2 mL) solution of π-allylpalladium chloride dimer (18 mg, 0.049 mmol) and triphenylphosphine (103 mg, 0.393 mmol). After the solution was stirred for 20 min, allylic acetate **9b** (0.544 g, 1.91 mmol) in THF (3 mL) was added. The reaction was kept at 70 °C for overnight. Most THF was removed under vacuum, and the residue was dissolved in ethyl acetate (100 mL). The ethyl acetate solution was washed (1 × NH_4Cl, 1 × H_2O, 1 × brine), dried ($MgSO_4$), and evaporated *in vacuo*. Flash chromatography (2% MeOH in CH_2Cl_2) of the residue gave triester **10** (0.549 g, 80%) as an oil; $[\alpha]^{25}_D = -3.2$ (*c* 0.5, $CDCl_3$). IR (thin film) 2954, 1750, 1732, 1664, 1566, 1457, 1437, 1400, 1233, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (d, J = 15.7, 1H), 5.47 (dt, J = 15.7, 7.1, 1H), 3.70 (s, 6H), 3.65 (s, 3H), 3.41 (t, J = 7.5, 1H), 2.97 (s, 3H), 2.91 (s, 3H), 2.61 (t, J = 7.2, 2H), 2.22−2.18 (m, 2H), 2.02−1.8 (m, 2H), 1.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 172.3, 169.1, 136.3, 125.1, 52.4, 52.0, 51.6, 47.3, 37.1, 35.4, 34.1, 31.8, 28.7, 21.6. Anal. Calcd for $C_{17}H_{27}O_7N$: C, 57.13; H, 7.61; N, 3.92. Found: C, 57.33; H, 7.47; N, 4.06.

Preparation of (4*S*,5*E*)-*N,N*-Dimethyl-4,8-bis(hydroxymethyl)-9-hydroxy-4-methyl-5-nonenamide (11). Sodium borohydride (37 mg, 1 mmol) was added slowly to the triester **10** (35 mg, 0.098 mmol) in a solution of 10:1 THF:EtOH (2 mL). After heating at 80 °C for 2 days, the reaction was diluted with methanol (10 mL), and its pH was adjusted with Amberlyst 15:4. Filtration, evaporation *in vacuo* and purification on silica gel (5% MeOH in CH_2Cl_2 and then 10% MeOH in CH_2Cl_2) afforded triol **11** (24 mg, 90%) as a colorless syrup; $[\alpha]^{25}_D = +1.0$ (*c* 0.5, MeOH). Note: There are cases when palladium black appeared upon addition of sodium borohydride. In such cases, the reaction must be worked up with water to remove palladium or very low yields are observed. IR (thin film) 3375, 2925, 1623, 1513, 1403, 1038 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.36−5.47 (m, 2H), 3.6−3.8 (m, 4H), 3.30 (s, 2H), 3.01 (s, 3H), 2.94 (s, 3H), 2.2−2.32 (m, 2H), 2.04−2.1 (m, 2H), 1.6−1.85 (m, 3H), 0.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 137.3, 127.5, 69.5, 64.3, 64.1, 42.4, 41.0, 37.4, 35.7, 31.9, 31.7, 28.1, 21.0. Anal. Calcd for $C_{14}H_{27}O_4N$: C, 61.51; H, 9.95; N, 5.12. Found: C, 61.43; H, 10.08; N, 5.10.

Method B. Sodium borohydride (0.52 g, 13.7 mmol) was added slowly to the triester **10** (0.662 g, 1.85 mmol) in 10:1 THF:ethanol (10 mL). After 15 h at 60 °C, it was quenched with water, and the pH was adjusted to 2 with aqueous 2 N hydrochloric acid. It was thoroughly extracted with 5:2 chloroform:ethanol, and the organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give after purification on silica gel as above triol **11** (0.316 g, 63%).

Preparation of (4*S*,5*E*)-*N,N*-Dimethyl-4,8-bis(*tert*-butyldimethylsiloxymethyl)-9-(*tert*-butyldimethylsiloxy)-4-methyl-5-nonenamide (12). The mixture of the triol **11** (100 mg, 0.366 mmol), imidazole (177 mg, 2.6 mmol), and TBDMSCl (200 mg, 1.3 mmol) in dry DMF (5 mL) was kept at 70 °C overnight. It was then partitioned between diethyl ether and water. The ethereal solution was washed thoroughly with water, dried ($MgSO_4$), and evaporated. Purification on silica gel (diethyl ether) afforded **19** (214 mg, 94%) as a colorless liquid; $[\alpha]^{25}_D = -1.5^\circ$ (*c* 1.0, $CDCl_3$). IR (thin film) 2954, 2858, 1657, 1520, 1467, 1394, 1254, 1090 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.30−5.40 (m, 2H), 3.53 (d, J = 5.6, 4H), 3.35 (d, J = 9.5, 1H), 3.29 (d, J = 9.5, 1H), 2.98 (s, 3H), 2.93 (s, 3H), 2.18−2.26 (m, 2H), 2.01 (t, J = 6.3, 2H), 1.6−1.72 (m, 3H), 0.95 (s, 3H), 0.883 (s, 18H), 0.877 (s,. 9H), 0.025 (s, 12H), 0.014 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 137.0, 127.2, 70.9, 62.5, 62.3, 43.9, 40.7, 37.3, 35.4, 32.6, 31.3, 28.8, 25.9, 21.0, 18.3, −5.4, −5.5. Anal. Calcd for $C_{32}H_{69}O_4NSi_3$: C, 62.38; H, 11.29; N, 2.27. Found: C, 62.50; H, 11.24; N, 2.23.

Preparation of (6*S*,7*E*)-(6,10)-Bis(*tert*-butyldimethylsiloxymethyl)-11-(*tert*-butyldimethylsiloxy)-6-methyl-1-trimethylsilyl-7-undecen-1-yn-3-one (13). To trimethylsilylacetylene (126 μL, 0.89 mmol) in THF (2 mL) was added *n*-butyllithium (1.49 M, 0.77 mmol) at −78 °C. After 5 min, boron trifloride etherate (96 μL, 0.78 mmol) was added slowly, and, after another 15 min, amide **12** (344 mg, 0.558 mmol) in THF (3 mL) was added. After 2 h stirring, more boron trifloride etherate (100 μL) was added, followed by addition of acetic acid (100 μL) at −78 °C. The reaction was then allowed to warm to −20 °C and was quenched with saturated aqueous ammonium chloride solution. Extraction with diethyl ether, drying over $MgSO_4$, and evaporation *in vacuo* gave, after purification on silica gel (3% ether in hexanes) enyne **13** (276 mg, 74%) as a colorless liquid; $[\alpha]^{25}_D = -2.6$ (*c* 0.8 in hexanes). IR (thin film) 2957, 2858, 2154, 1681, 1472, 1253, 1094, 837 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.40−5.25 (m, 2H), 3.54 (d, J = 5.4, 4H), 3.31 (q, J = 9.5, 2H), 2.48 (t, J = 8.1, 2H), 2.02 (t, J = 6.4, 2H), 1.87−1.6 (m, 3H), 0.94 (s, 3H), 0.89 (s, 27H), 0.24 (s, 9H), 0.03 (s, 12H), 0.02 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 188.3, 136.5, 127.6, 102.1, 97.3, 70.8, 62.4, 46.8, 41.0, 40.6, 31.3, 31.2, 25.9, 21.0, 18.3, −0.7, −5.5, −5.4. HRMS calcd for $C_{31}H_{63}O_4Si_4$ ($M^+ - C_4H_9$): 611.3804. Found: 611.3794.

Preparation of 14. A toluene (1 mL) solution of Pd_2dba_3·$CHCl_3$, **4** (6.6 mg, 0.0064 mmol), formic acid (12 μL, 0.32 mmol), and enyne **13** (107 mg, 0.16 mmol) was stirred at room temperature for 35 h. Direct purification on silica gel (3% diethyl ether in hexanes) yielded **14** (89 mg, 83%) as an inseparable mixture of two diastereomers in a ratio of 3:1 as a colorless liquid. IR (thin film) 2955, 2858, 1690, 1583, 1470, 1254, 1095, 837 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) major δ 5.85 (d, J = 1.7, 1H); 5.40 (t, J = 7.8, 2H); 3.7−3.6 (m, 1H); 3.63 (d, J = 4.7, 2H); 3.55 (dd, J = 9.7, 5.5, 1H); 3.42 (d, J = 9.3, 1H); 3.26 (d, J = 9.4, 1H); 3.17 (dd, J = 7.7, 1.6, 1H); 2.5−2.4 (m, 2H);

2.4−2.3 (m, 1H); 2.05−1.9 (m, 1H); 1.67−1.57 (m, 1H); 0.88 (s, 27H); 0.84 (s, 3H); 0.09 (s, 9H), 0.04 (s, 6H); 0.03 (s, 6H); 0.01 (s, 6H). ^{13}C NMR (75 MHz, C_6D_6) major δ 201.3, 154.3, 124.7, 133.3, 130.2, 70.0, 63.5, 54.1, 48.5, 38.8, 36.7, 30.9, 26.2, 26.1, 19.0, 18.6, 18.5, 0.07, −5.2, −5.3, −5.4, −5.5. HRMS calcd for $C_{31}H_{63}O_4Si_4$ ($M^+ - C_4H_9$): 611.380. Found: 611.3757.

Preparation of (*S*)-2,4-Dimethyl-3-[(1′*E*)-4′-hydroxy-3′-hydroxymethyl-1′-butenyl]-2-cyclohexen-1-one [(+)-Cassiol] (1). Karstedt's catalyst[17] (25 μL) was added to triethylsilane (20 μL, 0.12 mmol) in toluene (0.2 mL) at room temperature. After the solution was stirred for 10 min, enone **14** (9.1 mg, 0.014 mmol) in toluene (0.3 mL) was added. The reaction mixture was kept at 70 °C for overnight, evaporated *in vacuo*, and passed through a florisil plug (rinsed with hexanes then 1% ether in hexanes) to give the crude triethylsilyl ether **15** (7.5 mg, 0.0096 mmol).

DDQ (5 mg, 0.022 mmol) was added to a methylene chloride (0.4 mL) solution of **15** at room temperature. After overnight stirring, the reaction was quenched with aqueous saturated sodium bicarbonate solution and extracted with diethyl ether. After washing (2 × $NaHCO_3$, 1 × brine) and drying ($MgSO_4$), the ethereal solution was evaporated *in vacuo*, and the residue was passed through a silica gel plug (3% ether in hexanes) to give enone **16** (4.1 mg, 0.0061 mmol).

TBAF (30 μL 1 M in THF, 0.03 mmol) was added to a THF (0.5 mL) solution of **16**. After overnight stirring, it was loaded on silica gel and eluted (5% MeOH in CH_2Cl_2) to yield cassiol (1.5 mg, 42%); $[\alpha]^{25}_D = +16.1$ (*c* 0.15 in MeOH). IR (thin film) 3376, 2927, 2874, 1648, 1589, 1462, 1357, 1038 cm^{-1}. ^{1}H NMR (400 MHz, D_2O) δ 6.30 (d, $J = 16.2$, 1H); 5.69 (dd, $J = 16.3$, 8.5, 1H); 3.80 (d, $J = 11.6$, 1H); 3.76 (ddd, $J = 11.1$, 6.0, 2.0, 2H); 3.68 (ddd, $J = 11.1$, 7.1, 1.3, 2H); 3.49 (d, $J = 11.5$, 1H); 2.4−2.5 (m, 3H); 2.25−2.15 (m, 1H); 1.83 (s, 3H); 1.82−1.7 (m, 1H); 1.14 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ 207.1, 164.7, 139.0, 134.2, 131.2, 70.4, 64.5, 50.1, 43.1, 35.8, 33.2, 22.9, 15.4. HRMS calcd for $C_{14}H_{22}O_4$ (M^+): 254.1518. Found: 254.1519.

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