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Convergent, Enantioselective Syntheses of Guanacastepenes A and E Featuring a Selective Cyclobutane Fragmentation[1]

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Abstract: The evolution of a convergent strategy that led to efficient, enantioselective syntheses of both natural (+)- and unnatural (−)-guanacastepene E and formal total syntheses of (+)- and (−)-guanacastepene A is described. A union of five- and six-membered ring intermediates by an efficient π-allyl Stille cross-coupling reaction was followed by an intramolecular enone-olefin [2 + 2] photocycloaddition and a stereoelectronically controlled, reductive fragmentation of the resulting cyclobutyl ketone. The latter two transformations enabled controlled formation of the C-11 quaternary stereocenter and the central seven-membered ring of the guanacastepenes. An enantiospecific synthesis of the functionalized five-membered ring vinyl stannane from the monoterpene *R*-(−)-carvone featuring a carbon−carbon bond forming ring contraction was also developed.

Introduction

Strain-releasing fragmentations of small rings were among the earliest reports of free radical rearrangements in organic chemistry. In 1950, two laboratories proposed a free radical chain mechanism and a selective fragmentation of a cyclobutyl carbinyl radical to explain the reaction of β-pinene with trichloromethyl radical (Scheme 1).[2] In this transformation, the strain intrinsic to a four-membered ring drives the conversion of one tertiary radical intermediate into another.[3,4]

Strained rings flanked by carbonyl groups can also be fragmented under reducing conditions.[5] The tactic of generating angular methyl groups by selective reductive cleavage of the cyclopropane ring of conjugated cyclopropyl ketones has been known for more than 40 years and is often utilized in organic synthesis.[6] Interesting reductive ring openings, such as the one shown in Scheme 2, led to the generalization that the cyclopropane bond that is cleaved is the one possessing the maximum overlap with the π-orbital system of the carbonyl group.[6d,e] The rigid structure of carone is such that the internal cyclopropane C−C bond is oriented to permit very little overlap with the π-system of the carbonyl group, whereas the external C−C bond enjoys excellent overlap. The external bond is thus predisposed toward fragmentation; it is the bond that fragments selectively in the presence of reducing metals.

Our laboratory was drawn to this and related examples of stereoelectronically controlled strained ring fragmentations[5,6] and to the possibility that conjugated cyclobutyl ketones might undergo analogous reductive ring openings[7,8] as we began to contemplate a strategy for synthesizing the unique molecular

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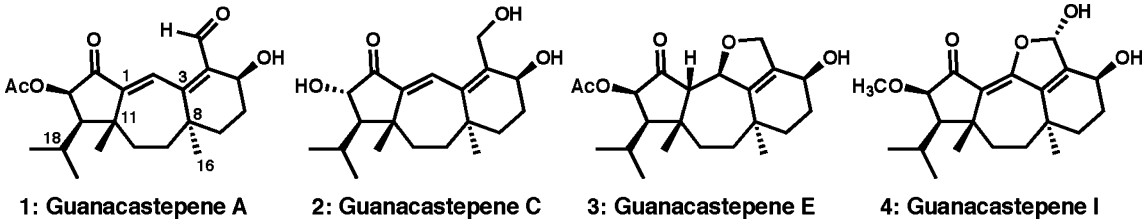
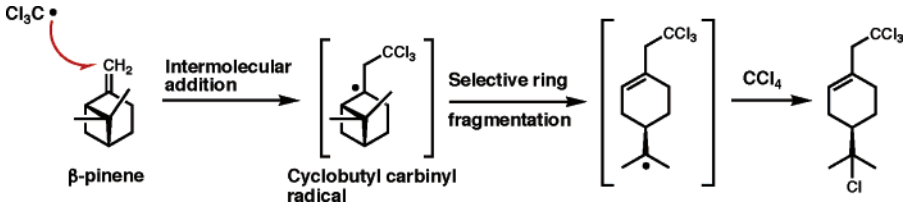
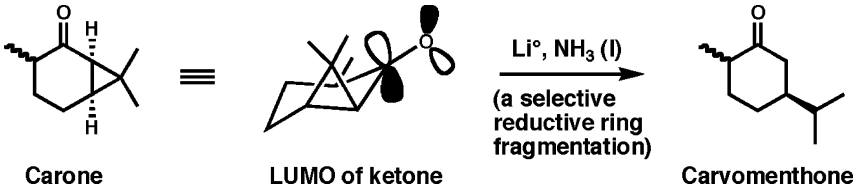


Figure 1. Selected members of the guanacastepene family of natural products.

Scheme 1. An Early Example of a Strain-Releasing Fragmentation of the Pinene System



Scheme 2. Lithium Metal Reduction of Carone to Carvomenthone (+ Its Methyl Epimer) by the Groups of Norin[6d] and Dauben;[6e] the Bond that Cleaves Is the One Having the Maximum Overlap with the π-Orbital System of the Carbonyl Group



architecture of the guanacastepene diterpenes. The guanacastepenes are produced by a previously unknown endophytic fungus that was discovered in the Guanacaste Conservation Area in Costa Rica.[9] Using NMR spectroscopic and X-ray crystallographic methods, Clardy and co-workers revealed the diverse and complex structures of the guanacastepenes. These compounds represented a new diterpene structural type and were shown to possess an interesting 5−7−6 tricyclic carbon skeleton with an oxidized, polar face and a hydrophobic face. Figure 1 shows the structures of four members of this family of natural products.

The realization that the guanacastane diterpene architecture was novel, combined with the discovery that two members of the family, guanacastepenes A (**1**) and I (**4**), are potent inhibitors of drug resistant strains of *Staphylococcus aureus* and *Enterococcus faecalis*,[10,11] stimulated great interest in these natural products as objectives for chemical synthesis. The reaction of the chemical community to research opportunities provided by the guanacastepenes was seemingly undiminished by the report that guanacastepenes A (**1**) and I (**4**), the two members of the class with promising antibacterial properties, also damage the delicate membranes of human red blood cells.[10] In addition to the creative synthesis of guanacastepene A in racemic form by Danishefsky and co-workers[12] and the subsequent formal total syntheses by the groups of Snider[13] and Hanna,[14] more than 10 distinct designs for synthesizing the guanacastepenes have been reported.[15] Recently, a synthesis of racemic guanacastepene C (**2**) was described by Mehta and co-workers,[16] and an enantioselective route to guanacastepene A was published by the Danishefsky group.[17]

Our laboratory viewed the guanacastepene architecture as a challenging context for the development of a concise synthesis of the 5−7 hydroazulane carbon framework based on a selective cyclobutane fragmentation.[15h] In this article, we describe how this approach to the seven-membered ring problem paved the way for convergent, asymmetric syntheses of (+)-guanacaste-

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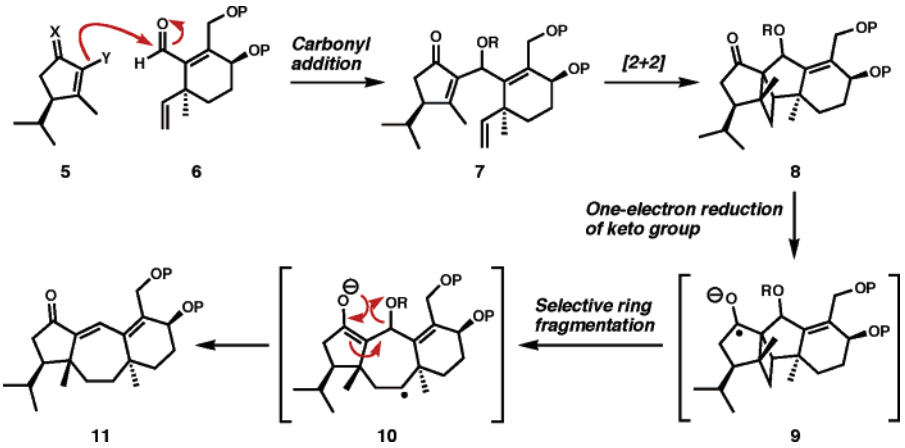
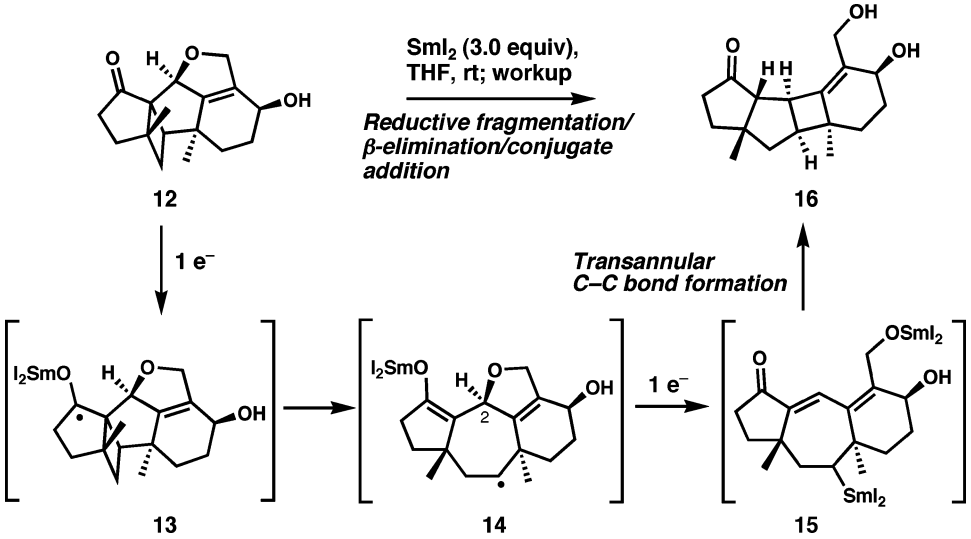
Scheme 3. An Approach Initiated by an Intermolecular Carbonyl Addition Reaction[a]



[a] X = a carbonyl surrogate; Y = metal; P = unspecified protecting group. The metal counterions in intermediates **9** and **10** are not shown.

Scheme 4. Formation of Tetracycle **16** from Compound **12**



pene E (**3**) and its enantiomer as well as the direct precursor of naturally occurring (+)-guanacastepene A (**1**).

Results and Discussion

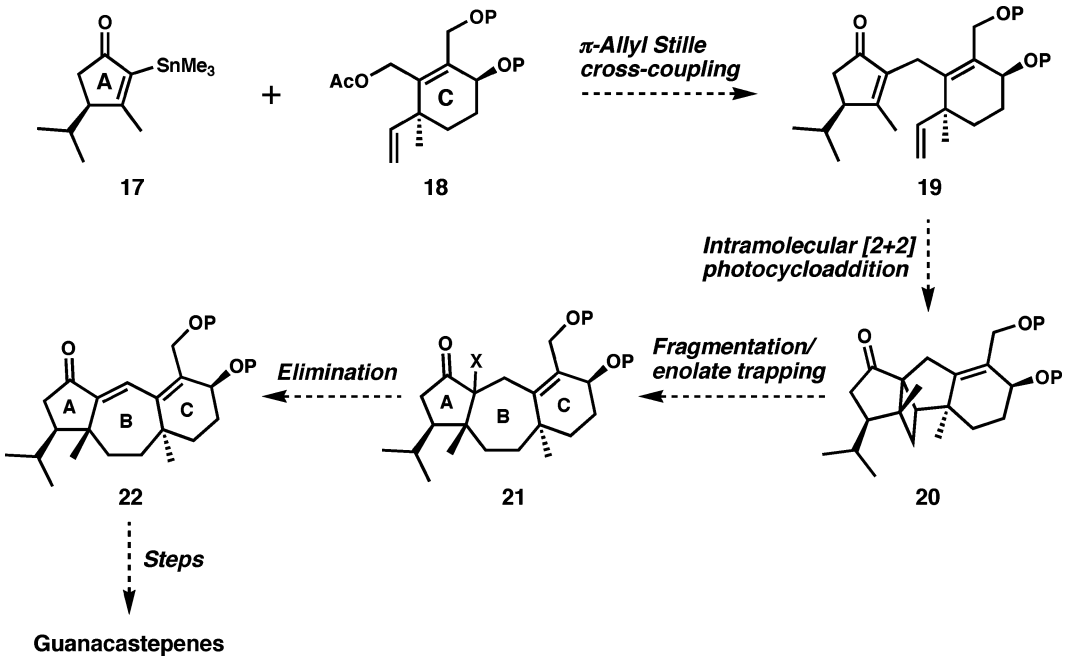
1. An Approach for Synthesis Based on a Selective Cyclobutane Ring Cleavage. To achieve a convergent synthesis of the guanacastane molecular architecture, we would attempt a carbonyl addition of a cyclopentenyl organometallic reagent such as **5**, wherein Y is a metal and X is a suitable surrogate for a ketone carbonyl group, to the aldehyde function of **6**. This union would establish a needed carbon−carbon bond and create a favorable setting for a key intramolecular enone-olefin [2 + 2] photocycloaddition.[18] A diastereoface-selective [2 + 2] cycloaddition of the ethenyl side chain of **7** to the underside of the cyclopentenone ring would generate a rigid, cyclobutyl ketone of type **8** with the desired configuration at the methyl-bearing C-11 quaternary stereocenter (Scheme 3).

An analysis of a molecular model of tetracycle **8** revealed that the cyclobutane bond that is exocyclic to the five-membered ring is nearly parallel to the π-orbital system of the adjacent carbonyl group. Owing to this circumstance, we reasoned that this bond would fragment selectively in the course of a one-electron reduction of the keto group in **8**. The pivotal transformation in our approach to the guanacastane architecture would be a stereoelectronically controlled cyclobutane ring cleavage in the context of a ketyl radical anion such as **9**. If successful, this selective ring fragmentation would leave in its wake a reactive species **10** having the desired 5−7−6 tricyclic skeleton and a β-alkoxy enolate system, which would be expected to collapse to a guanacastepene-like enone. We hoped that this β-elimination reaction and a reduction of the putative secondary carbon radical intermediate would afford the advanced guanacastepene structural type **11**. From this vantage point, the prospects for achieving syntheses of various members of the guanacastepene family seemed excellent.

In the course of investigating this strategy, we synthesized the complex pentacyclic ketone **12** (Scheme 4) by a reaction sequence involving an intermolecular carbonyl addition reaction and an intramolecular enone olefin [2 + 2] photocycloaddition.[15h] While this structure lacked the isopropyl group that is a conspicuous feature of many of the guanacastepenes, it seemed to provide an ideal context for probing the feasibility of some of the key ideas outlined in Scheme 3. When a solution of ketone **12** in THF at room temperature was treated with 3 equiv of the powerful reducing agent samarium diiodide, a new, structurally

(18) For a comprehensive review of enone olefin [2 + 2] photochemical cycloadditions, see: Crimmins, M. T.; Reinhold, T. L. *Org. React.* **1993**, *44*, 297−588.

Scheme 5. An Approach Initiated by a Stille Cross-Coupling Reaction[a]



[a] P = Unspecified protecting group.

complex cyclobutane-containing compound having the structure **16** was formed.[19] This outcome was encouraging because it suggested that the strained cyclobutane ring of compound **12** did, in fact, fragment in the desired and expected fashion. Moreover, the dihydrofuran ring was opened, almost certainly via the anticipated β-elimination. However, the supposition that the putative carbon radical arising from the reductive cleavage of **12** would simply convert itself to a methylene group and not bring about undesired chemistry proved to be the weakness of our initial plan. We assume that the guanacastepene-like enone system in intermediate **15** exists only transiently in this process and undergoes a transannular addition of either a neutral secondary carbon radical or a samarium(III) carbanion as implied in Scheme 4. Fortunately, this outcome suggested a means by which to alter the synthesis in order to obtain the desired 5−7−6 tricyclic ring system. The oxidation state at C-2 simply had to be reduced to prevent β-elimination, since that event led to the irreversible and undesired transannular carbon−carbon bond formation. The manner in which this was accomplished is described below.

2. A Strategy Featuring an Efficient π-Allyl Palladium Stille Cross-Coupling Reaction. Having demonstrated the susceptibility of the "exocyclic" cyclobutane bond toward a reductive fragmentation, we felt comfortable with the foundation of our approach to the synthesis of the guanacastepenes. We next directed our attention to the problem of synthesizing a fragmentation substrate, such as **20**, wherein a β-elimination at C-2 during the reductive fragmentation of the cyclobutane ring would not be a possibility (Scheme 5).

To reach compound **20**, we envisioned a reaction sequence wherein two building blocks, a vinylstannane **17** and an allylic acetate **18** representing the A and C rings of the guanacastepenes, respectively, would be joined through a π-allyl Stille cross-coupling reaction.[15h,20,21] This method for achieving the crucial fragment coupling held at least one important advantage over the carbonyl addition strategy: there would be no complications arising from the production of diastereoisomeric secondary alcohols at C-2. A synthesis of a compound of type **19** would be followed by an intramolecular [2 + 2] photocycloaddition reaction to fashion conjugated cyclobutyl ketone **20**. Once again, we hoped to effect a reductive fragmentation of only one of the cyclobutyl bonds in **20** to yield the seven-membered B ring characteristic of the guanacastepenes. One of the nice features of this fragmentation strategy is that the putative samarium(III) enolate formed in the process would be regiodefined. It would thus be possible, at least in principle, to make use of that regiodefined enolate ion in a controlled synthesis of the needed double bond between C-1 and C-2. Our new goal was to carry out a tandem reductive fragmentation/enolate trapping sequence, followed by a heteroatom elimination reaction to produce the guanacastepene architecture **22**.

In a previous publication,[15h] we described the successful application of this general design to a racemic synthesis of the 5−7−6 ring framework of the guanacastepenes lacking a C-12 isopropyl group. It was now required that we construct and use an A ring domain containing the required isopropyl group and that the overall synthesis be rendered enantioselective. Since our synthesis would employ a convergent Stille cross-coupling step, we needed to obtain the A ring and C ring building blocks in enantiomerically pure form.

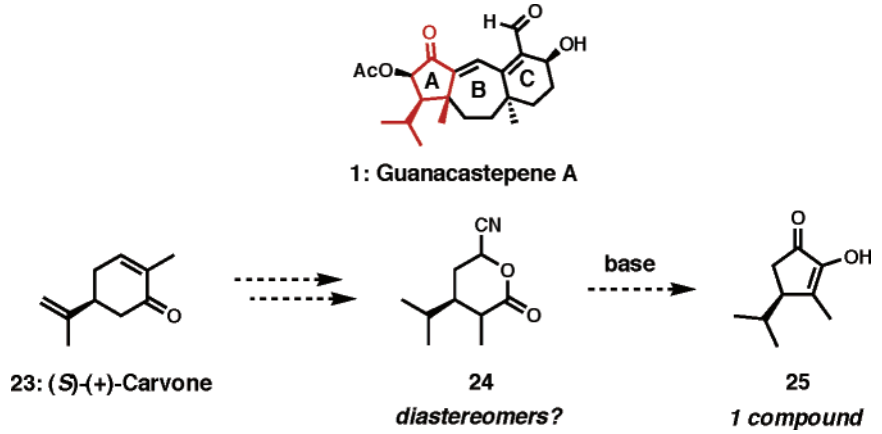
3. Asymmetric Synthesis of an A Ring Fragment. After considering several ideas for mastering the relative and absolute stereochemistry of the rather densely substituted five-membered ring domain of guanacastepene A (**1**) (colored in red, Scheme 6), we decided to turn to a useful building block from the chiral

(19) For excellent discussions of the chemistry of samarium diiodide, see: Molander, G. A. *Org. React.* **1994**, *46*, 211−367.

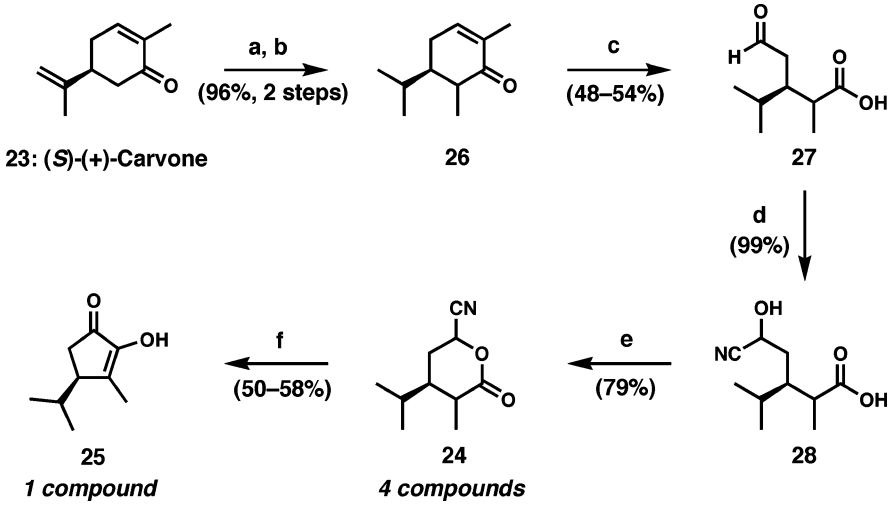
(20) For an excellent review of the Stille reaction, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652.

(21) For an example of a π-allyl Stille coupling reaction to achieve a merger of complex fragments from our laboratory, see: Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2004**, *125*, 5393−5407.

Scheme 6. Strategy for an Asymmetric Synthesis of an A-Ring Fragment

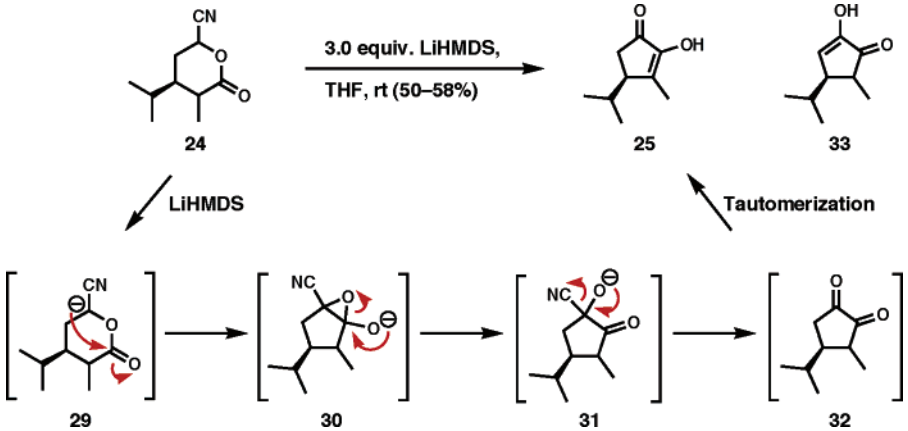


Scheme 7. Synthesis of Keto Enol **25**[a]



[a] (a) 0.2 mol % PtO_2, H_2, rt, 23 h, 100%. (b) LDA, THF, −78 °C → 0 °C; then MeI, 0 °C → rt, 17 h, 96% as a 5.5:1 mixture of diastereoisomers. (c) O_3, EtOAc, −78 °C, 90 min; then H_2, Pd/C, rt, 17 h, 48−54%. (d) NaCN, *p*-TsOH, THF·H_2O, rt, 14 h, 99%. (e) EDCI, 0 °C → rt, CH_2Cl_2, 7 h, 79%. (f) 3.0 equiv of LiHMDS, THF, rt, 2 h; then 1 N aq. HCl, 50−58%. LDA = lithium diisopropylamide; *p*-TsOH = *para*-toluenesulfonic acid; EDCI = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; rt = room temperature; LiHMDS = $LiN(SiMe_3)_2$.

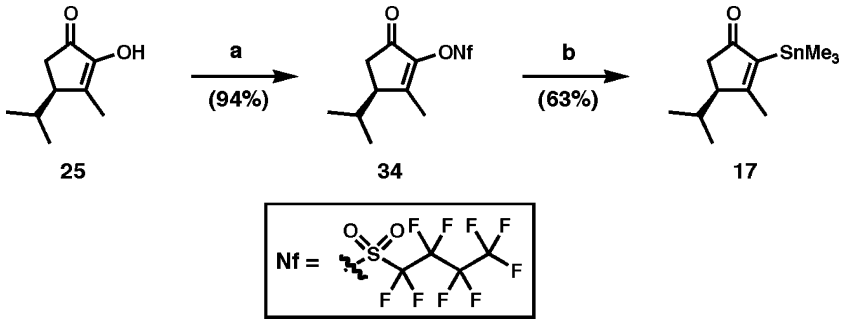
Scheme 8. Proposed Mechanism of the Base-Induced Ring Contraction of Compound **24**[a]



[a] LiHMDS = $LiN(SiMe_3)_2$; rt = room temperature.

pool. The choice of (*S*)-(+)-carvone (**23**) as a starting material arose in part from the fact that it already contains an isopropenyl substituent with the same stereochemical configuration as the isopropyl group of the guanacastepenes; a simple hydrogenation of carvone's isopropenyl group would afford the isopropyl function. Of course, a commitment to (*S*)-(+)-carvone meant that we would, at some point, be required to effect a one-atom ring contraction to access the five-membered guanacastepene A ring. This objective led us to consider the suitability of α-acyloxy nitrile **24** (a cyanohydrin lactone) as an advanced intermediate en route to A-ring surrogate **25**. Even if compound **24** was constructed as a mixture of diastereoisomers, we were

Scheme 9. Synthesis of Vinylstannane **17**[a]



[a] (a) Et_3N, NfF, CH_2Cl_2, rt, 14 h, 94%. (b) $Pd(dppf)Cl_2$, $Me_3SnSnMe_3$, NMP, 60 °C, 8 h, 63% of **17**, 11% of **34**, 16% of **25**. NMP = 1-methyl-2-pyrrolidinone; rt = room temperature; dppf = 1,1′-bis(diphenylphosphino)ferrocene.

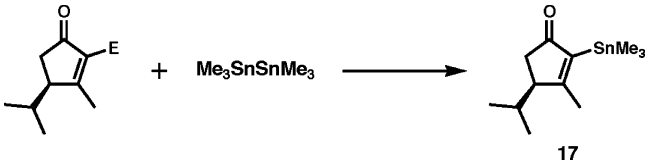
drawn to the possibility that this substance might undergo conversion to a single 1,2-diketone (or its enol tautomer **25**) on treatment with a strong, non-nucleophilic base. It was always our intention to attempt an introduction of the A-ring acetoxy group at a late stage in the synthesis.

From (*S*)-(+)-carvone (**23**), the synthesis began with the selective hydrogenation of the less hindered olefin (Scheme 7). This known transformation could be carried out with either platinum(IV) oxide (Adams' catalyst)[22] or tris(triphenylphosphine)rhodium chloride (Wilkinson's catalyst);[23] however, we found that both the platinum-catalyzed hydrogenation was more reliable and the isolation of the product in that case was much simpler. The resulting dihydrocarvone did not require purification and was directly employed in the base-induced α-methylation;[24] this sequence afforded compound **26** in excellent yield after distillation as a 5.5:1 mixture of diastereoisomers. This mixture was carried forward, as the configuration of the newly formed stereocenter would be of no consequence. Reductive ozonolysis[22c] of enone **26** resulted in the excision of two carbon atoms and yielded the linear aldehyde carboxylic acid **27**, which was easily converted to the cyanohydrin **28** by treatment with sodium cyanide and *p*-toluenesulfonic acid. Lactonization of the mixture of cyanohydrin carboxylic acids with EDCI yielded the α-acyloxy nitriles **24** as a mixture of four diastereoisomers. When this mixture was treated with lithium bis(trimethylsilyl)-amide (LiHMDS), keto enol **25** emerged as a single compound from the reaction mixture in 50−58% yield.[25−27]

One possible mechanism by which this interesting and potentially general cyclic 1,2-diketone synthesis could occur is shown in Scheme 8. Deprotonation of **24** with LiHMDS could generate the nitrile-stabilized anion **29**, which might undergo intramolecular addition to the lactone carbonyl. The intermediacy of epoxy alkoxide ion **30** would be brief, for it would be expected to rapidly open to the isomeric alkoxide ion **31**. Collapse of the latter species with expulsion of cyanide ion would then give rise to the five-membered ring 1,2-diketone **32**. 1,2-Dicarbonyl compounds frequently exist as their enol tautomers. However, in the case of compound **32**, the tautomerization could take place in two directions. In early experiments, a single equivalent of base was used to effect the contraction of compound **24**. In these instances, comparable yields of the ring-contracted carbocyclic products were attained, but the less substituted tautomer **33** was found to be a minor product in these reactions. Increasing the amount of base to 3.0 equiv altogether prevented the formation of this undesired tautomer.

The conversion of keto enol **25** to the desired A-ring vinylstannane **17** was expected to be straightforward (Scheme 9). In fact, the formation of vinyl nonafluorobutanesulfonate

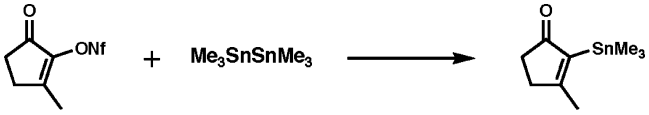
Table 1. Selected Reaction Conditions Screened for the Wulff−Stille Synthesis of Vinylstannane **17**[a]



entry	−E	catalyst	solvent	temp (°C)	time (h)	% yield
1	−OTf	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	THF	60	20	34
2	−ONf	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	THF	60	20	44
3	−ONf	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	NMP	60	8	63[b]

[a] NMP = 1-methyl-2-pyrrolidinone; dppf = 1,1′-bis(diphenylphosphino)ferrocene; dba = *trans*,*trans*-dibenzylideneacetone; rt = room temperature. [b] 474 mg of **17** produced.

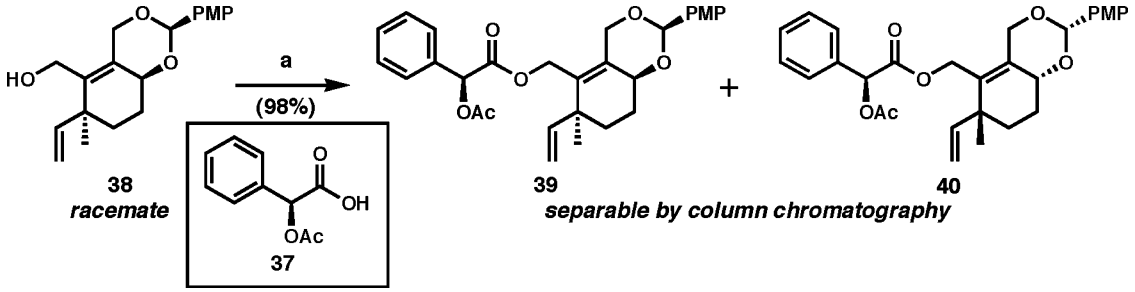
Table 2. Wulff−Stille Coupling of Hexamethylditin and Nonaflate **35**



entry	catalyst	additives	solvent	temp (°C)	time (h)	% yield
1	Pd_2dba_3	dppf	THF	65	36	90
2	Pd_2dba_3	dppf	THF	70	8	83
3	Pd_2dba_3		NMP	rt	24	85

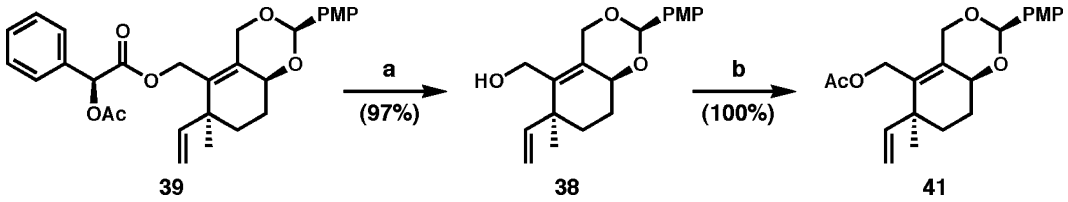
(22) (a) Kitahara, T.; Kurata, H.; Matsuoka, T.; Mori, K. *Tetrahedron* **1985**, *41*, 5475−5485. (b) Paquette, L. A.; Dahnke, K.; Doyon, J.; He, W.; Wyant, K.; Friedrich, D. *J. Org. Chem.* **1991**, *56*, 6199−6205. (c) Deslongchamps, P.; et al. *Can. J. Chem.* **1990**, *68*, 127−152.
(23) Ireland, R. E.; Bey, P. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 459.
(24) Hua, D. H.; Takasu, K.; Huang, X.; Millward, G. S.; Chen, Y.; Fan, J. *Tetrahedron* **2000**, *56*, 7389−7398.
(25) For studies on the use of protected cyanohydrins as acyl carbanion equivalents, see: (a) Zervos, M.; Wartski, L.; Seyden-Penne, J. *Tetrahedron* **1986**, *42*, 4963−4973. (b) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207−3233. (c) Ferrino, S. A.; Maldonado, L. A. *Synth. Commun.* **1980**, *10*, 717−723. (d) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1974**, *96*, 5272−5274. (e) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1971**, *93*, 5286−5287. (f) Jacobson, R. M.; Lahm, G. P.; Clader, J. W. *J. Org. Chem.* **1980**, *45*, 395−405.
(26) For an investigation of the trapping of α-acyloxy nitrile carbanions with aldehydes and Michael acceptors, see: Kraus, G. A.; Dneprovskaia, E. *Tetrahedron Lett.* **2000**, *41*, 21−24.
(27) Recently, a method has been described for the synthesis of α-keto esters involving the rearrangement of aromatic cyanohydrin carbonate esters using LDA: Thasana, N.; Prachyawarakorn, V.; Tontoolarug, S.; Ruchirawat, S. *Tetrahedron* **2003**, *44*, 1019−1021.

Scheme 10. Classical Resolution of the C-Ring Alcohol **38**[a]



[a] (a) **37**, DMAP, DCC, CH_2Cl_2, 0 → rt, 90 min, 98%. DMAP = 4-dimethylaminopyridine; DCC = dicyclohexylcarbodiimide; PMP = *p*-methoxyphenyl.

Scheme 11. Synthesis of Enantiopure Allylic Acetate **41**[a]

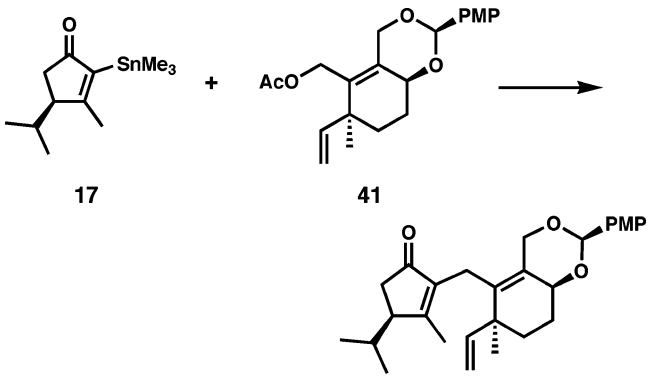


[a] (a) K_2CO_3, MeOH, rt, 30 min, 97%. (b) Ac_2O, DMAP, pyridine, rt, 15 min, 100%. DMAP = 4-dimethylaminopyridine; rt = room temperature; PMP = *p*-methoxyphenyl.

(nonaflate) **34** from **25** was quite smooth;[28] however, efforts to transform the nonaflate to vinylstannane **17** repeatedly failed.[29] It was not until many sets of reaction conditions were tested,[30] three of which are shown in Table 1, that an acceptable yield of stannane **17** was attained. The critical modification was the use of [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium-(II) as the catalyst. Attempts to form this catalyst in situ from tris(dibenzylideneacetone)dipalladium(0) and 1,1′-bis(diphenylphosphino)ferrocene ligand never led to success.[29] Some **34** and **25** were always recovered from the reaction mixture along with the product stannane and were recycled.

It is not entirely clear why we faced so much resistance in the conversion of vinyl sulfonates (nonaflates or triflates) to vinylstannane **17**. It seemed that the mere addition of an isopropyl group on the far side of the five-membered ring had shut down the reaction under nearly all conditions tested.[29] To properly test that notion, we synthesized compound **35** (Table 2), a nonaflate lacking an isopropyl group, from the corresponding commercially available 1,2-diketone. The Wulff−Stille reaction consistently succeeded under conditions identical to those which had failed in the isopropyl-containing system, without the need to resort to the bis(diphenylphosphino)-ferrocene dichloropalladium catalyst.[31] This observation indicates that it is the isopropyl group that necessitates the use of a more active catalyst.

Table 3. Some Conditions Screened for the π-Allyl Stille Cross-Coupling of **17** and **41**



entry	catalyst	additives	solvent	temp (°C)	time (h)	% yield
1	Pd_2dba_3	$AsPh_3$	NMP	150	18	0
2	$Pd(PPh_3)_4$	CuCl, LiCl	DMSO	rt, 60	1, 20	91[a]
3	$Pd(PPh_3)_4$	CuCl, LiCl	DMSO	rt, 60	1, 15	87[b]

[a] 86 mg of **42** produced. [b] 221 mg of **42** produced.

4. Classical Resolution of the C-Ring Fragment. The relative stereochemistry of the cyclohexenyl domain of the guanacastepenes was established at an early stage of the project via an efficient intermolecular Diels−Alder reaction between dimethyl acetylenedicarboxylate and a cross-conjugated silyl enol ether.[15h] Seeing no simple way to render this process asymmetric, we resorted to a classical resolution as a means to obtain an enantiopure C-ring precursor that could be elaborated to an allylic acetate of the type **18** (Scheme 5). To this end, we chose an approach that involved the formation of an ester with one of our alcohol intermediates and the *O*-acetate of inexpensive (*S*)-(+)-mandelic acid (compound **37**, Scheme 10).[32] Racemic allylic alcohol **38**,[33] an advanced intermediate in our synthesis, was reacted with *O*-acetyl (*S*)-(+)-mandelic acid **37** in the presence of a dehydrating agent; this union afforded a

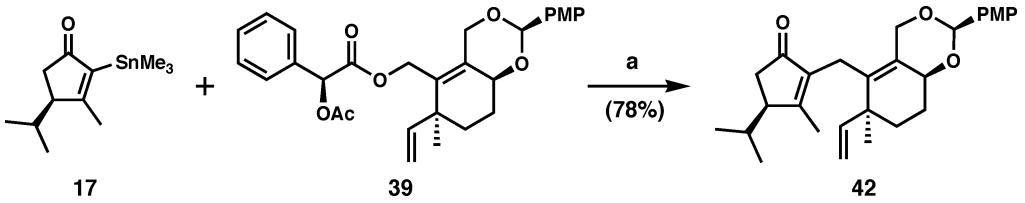
(28) Commercially available nonafluorobutanesulfonyl fluoride is a stable and easily handled liquid. Obtained from the electrochemical fluorination of 2,5-dihydrothiophene 1,1-dioxide, this compound is cheaper than triflic anhydride, see: Lyapkalo, I. M.; Webel, M.; Reissig, H.-U. *Eur. J. Org. Chem.* **2002**, 1015−1025.

(29) See Table 1 in the Supporting Information for a summary of our observations on the synthesis of compound **17**.

(30) (a) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277−279. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033−3040.

(31) We knew from previous chemistry that the Wulff-Stille reaction to convert a vinyl iodide to a vinylstannane in the absence of an isopropyl group was a smooth process (see ref 15h). However, this new two-step synthesis of vinylstannane **36** was actually an improvement on the α-iodination/Wulff−Stille sequence developed earlier in terms of both yield and ease of execution.

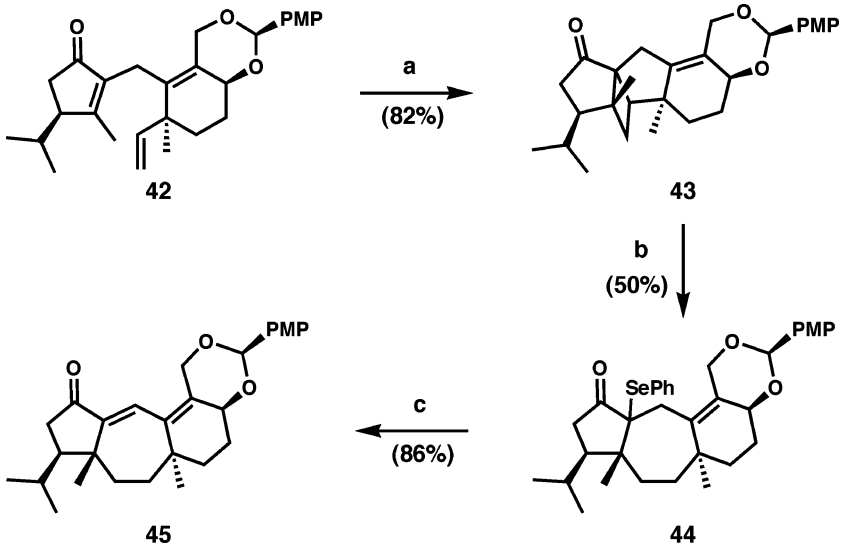
Scheme 12. A Palladium-Catalyzed Coupling of Vinyl Stannane **17** with Allylic Mandelate Ester **39**[a]



17 39 42

[a] (a) LiCl, CuCl, $Pd(PPh_3)_4$, DMSO, rt → 60 °C, 78%. PMP = *p*-methoxyphenyl.

Scheme 13. Synthesis of Tricyclic Dienone **45**[a]



42 43 44 45

[a] (a) *hν* , *i*-Pr_2NEt (0.5 equiv), Et_2O, 3 h, 82%. (b) SmI_2 (2.5 equiv), HMPA (10 equiv), THF, rt, 15 min; then PhSeBr, 50%. (c) *m*CPBA, CH_2Cl_2, −78 °C, 10 min, 86%. HMPA = hexamethylphosphoramide; *m*CPBA = 3-chloroperoxybenzoic acid; PMP = *p*-methoxyphenyl.

1:1 mixture of diastereoisomers **39** and **40** that could be separated by flash column chromatography on silica gel.[34]

In our synthesis of a guanacastepene-like tricycle, racemic allylic acetate **41** performed very well in π-allyl Stille cross-coupling reactions with five-membered ring vinyl stannanes.[15h] Owing to this experience, we opted to transform mandelate ester **39** to allylic alcohol **38**, after which a simple acetylation of the hydroxyl group afforded enantiopure allylic acetate **41** in 97% overall yield (Scheme 11).

5. An Enantioselective Formal Synthesis of Guanacastepene A. With routes to optically active ester **41** and the chiral pool derivative **17** in place, we were in a position to test the feasibility of the general strategy outlined previously in Scheme 5. The first hurdle was the projected π-allyl Stille coupling,[15h,20,21] and having already faced a steep challenge in the formation of vinylstannane **17** by a Wulff−Stille coupling, we cautiously proceeded using the reaction conditions that had worked well in our prior model study. To our great dismay, the desired fragment coupling failed. All aspects of the new reaction were identical to the model, except for the presence of an isopropyl group on the vinyl stannane component. We once again set about surveying conditions described in the literature for hindered Stille cross-couplings; three of the reactions we carried out and their outcomes are shown in Table 3. With this problem, there was no such thing as a partial success. Only when we implemented the outstanding procedure developed by the Corey laboratory for achieving cuprous-chloride-accelerated Stille couplings (entries 2 and 3) could this critical merger be achieved.[35,36] As advertised, this procedure can be uniquely effective at joining sterically crowded vinyl stannanes with organic electrophiles.

We also discovered that allylic mandelate ester **39**, which was synthesized for the sole purpose of achieving a resolution of stereoisomers, is a good substrate for the π-allyl Stille coupling (Scheme 12). This approach obviated the transformations shown in Scheme 11, and the overall yield of the three-step process (~84%) only slightly exceeded the 78% yield achieved in this single reaction.

Having now been thwarted twice by the presence of the isopropyl group during key reactions, it was with some anxiety that we embarked on the construction of the C-11 quaternary carbon center and seven-membered B ring. Fortunately, these fears proved groundless, as irradiation of compound **42** with a 450 W Hanovia mercury vapor lamp effected a [2 + 2] photocycloaddition that was more facile and efficient than in

(32) For classical resolution of mandelic esters, see: Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548−3551. For classical resolution of *O*-acetyl mandelic esters, see: Breitholle, E. G.; Stammer, C. H. *J. Org. Chem.* **1974**, *39*, 1311−1312.

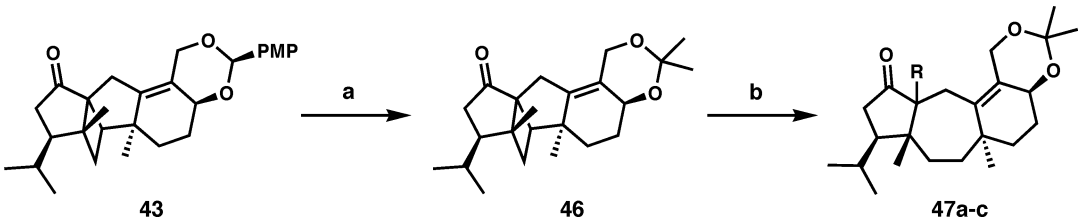
(33) A Diels−Alder cycloaddition between dimethylacetylene dicarboxylate and the cross-conjugated trimethylsilyl enol ether derived from 3-methyl cyclohexenone and a regiospecific Baeyer−Villiger oxidation were key steps in our previously published synthesis of racemic allylic alcohol **38** (see Supporting Information and ref 15h). The configuration of the *p*-methoxyphenyl-bearing stereogenic center in optically active **38** (see Scheme 11) was determined by an NOE experiment.

(34) Over 20 solvent systems were screened before one was found that satisfactorily separated the mandelic esters on TLC (49% CH_2Cl_2/49% toluene/2% Et_2O). Without recourse to HP silica gel, the diastereoisomers could be separated with an efficiency of 40−60% (60−40% remained a mixture and was recycled).

(35) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600−7605.

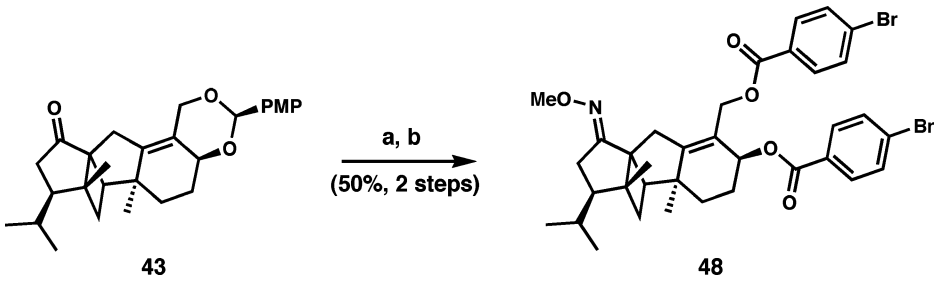
(36) See Table 3 in the Supporting Information for a summary of our observations on the Stille coupling of compounds **17** and **41**.

Scheme 14. Reductive Fragmentations Mediated by Lithium Metal[a]



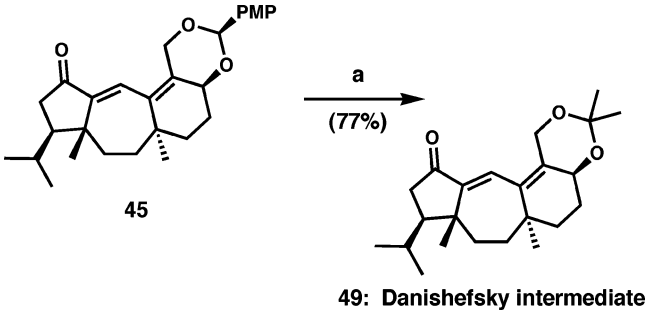
[a] (a) PPTS, cat. MeOH, 2,2-dimethoxypropane, 60 °C, 17 h, 75%. (b) Li°, NH_3(l), *t*-BuOH, THF, −78 °C; then trapping agent. Trapping agent, −R, yield: a −MeOH, −H, 63%. b −TMSCl, −H, 64%. c −PhSeBr, −SePh, 46%. PMP = *p*-methoxyphenyl.

Scheme 15. Synthesis of Crystalline Diester **48**[a]



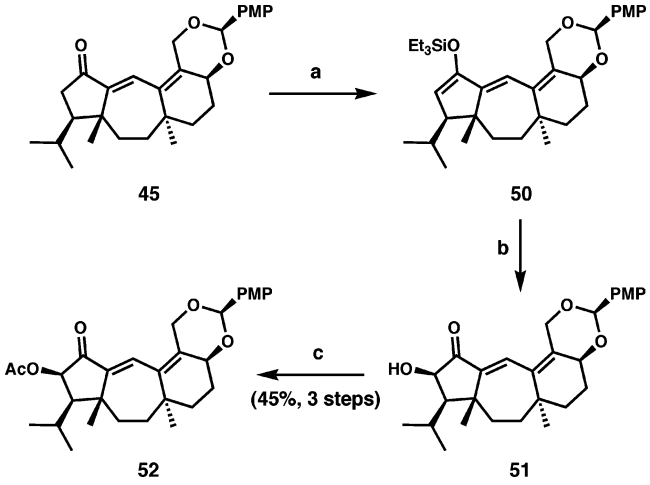
[a] (a) $H_2NOMe{\cdot}HCl$, pyridine, MeOH, rt, 3 h, 77%. (b) 4-Bromobenzoyl chloride, DMAP, pyridine, rt, 2 h, 65%. DMAP = 4-dimethylamino pyridine; PMP = *p*-methoxyphenyl.

Scheme 16. Synthesis of Known Compound **49** and Completion of a Formal Synthesis of (+)-Guanacastepene A[a]



[a] (a) PPTS (0.2 equiv), 2,2-dimethoxypropane, 60 °C, 20 h, 77%. PPTS = pyridinium *p*-toluenesulfonate; PMP = *p*-methoxyphenyl.

Scheme 17. Rubottom-Type α-Acetoxylation[a]



[a] (a) Et_3N, Et_3SiOTf, CH_2Cl_2, −78 °C, 15 min. (b) *m*CPBA, CH_2Cl_2, −78 °C, 5 min. (c) Ac_2O, DMAP, pyridine, rt, 30 min, 45%, 3 steps. DMAP = 4-dimethylamino pyridine; PMP = *p*-methoxyphenyl.

any model system (Scheme 13). Previously, we had observed outstanding diastereofacial selectivity in model systems with this intramolecular reaction.[37] The presence of the isopropyl group on the cyclopentenone ring reinforced that selectivity. Treatment of ketone **43** with samarium diiodide[19] accomplished a selective, reductive fragmentation of the cyclobutane ring, after which trapping of the putative samarium enolate with phenylselenenyl bromide gave rise to organoselenide **44** as a mixture of diastereoisomers. Elimination of the selenoxide[38] formed by oxidation of **44** with *m*CPBA generated the complete tricyclic [5−7−6] ring system of the guanacastepenes.

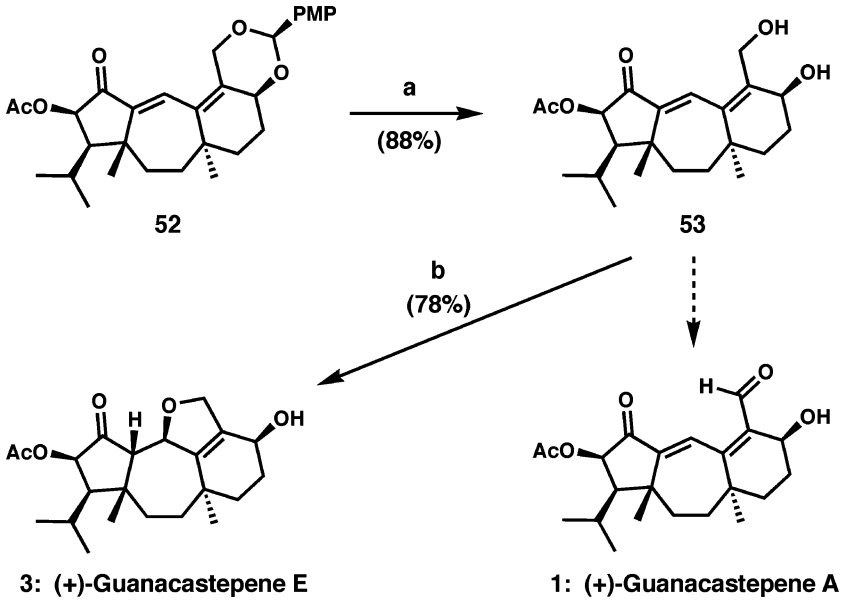
In an attempt to improve the yield of the samarium-diiodide-mediated reductive fragmentation/enolate trapping sequence, we explored reductions with lithium metal in liquid ammonia (Scheme 14). The aromatic benzylidene acetal protecting group was clearly incompatible with these conditions, so we replaced it with an isopropylidene ketal in a single reaction (**43** → **46**). In the fragmentation reaction, attempted enolate trapping with chlorotrimethylsilane[39] gave the same product as the methanol quench control reaction after workup. Trapping with phenylselenenyl bromide afforded **47c** in 46% yield, which was not an improvement over the samarium diiodide approach.

At this point in our work, we wished to confirm that the relative and absolute stereochemistry were as we believed them to be. To that end, we sought a crystalline intermediate for an X-ray crystal structure determination. Previously, we had managed to obtain a crystal from a rigid, pentacyclic methoxime derivative.[15h] We therefore chose to derivatize cyclobutyl ketone **43** as a methoxime (Scheme 15). Under the conditions of this reaction, the benzylidene acetal was also cleaved, and it was possible to advance the resulting diol to the crystalline diester **48** by straightforward acylations. An X-ray crystallographic analysis of this compound confirmed its complex structure.[40]

(37) Inspection of molecular models showed a significant steric interaction between the C16 methyl group and the vinyl C17 methyl group in the transition state that would lead to addition on the undesired face.

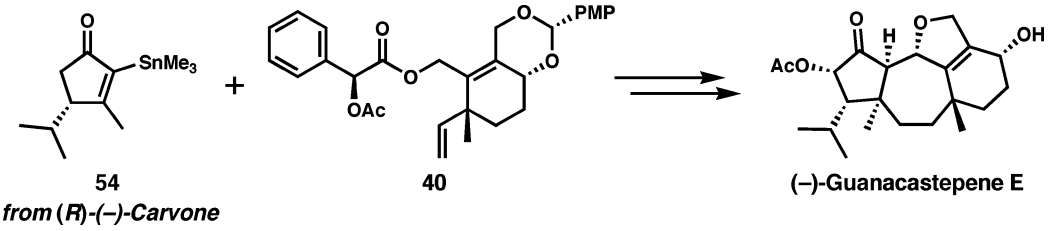
(38) (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697−2699. (b) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813−5815. (c) Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Product Synthesis*; CIS, Inc.: Philadelphia, PA, 1984.

Scheme 18. Synthesis of (+)-Guanacastepene E (**3**)[a]



[a] (a) PPTS (0.25 equiv), MeOH, 70 °C, 30 min, 88%. (b) SiO_2, CH_2Cl_2, rt, 36 h, 78%. PPTS = pyridinium *p*-toluenesulfonate.

Scheme 19. Synthesis of Unnatural (−)-Guanacastepene E



Proof that the reductive ring fragmentation had actually accomplished cleavage of the desired cyclobutyl bond was also sought. This was done in a single experiment by synthesizing an advanced intermediate in the Danishefsky[12,17] and Snider[13] routes to (±)-guanacastepene A. Warming of a solution of compound **45** in 2,2-dimethoxypropane containing 0.2 equiv of pyridinium *p*-toluenesulfonate transformed the benzylidene acetal ring to the isopropylidene ketal of **49** (Scheme 16). The ^{1}H NMR spectrum of this substance exactly matched the one published by the Snider group.[13] With this result, we too could claim a formal total synthesis of guanacastepene A.

6. A Synthesis of (+)-Guanacastepene E. After several original strategies for installing the C-13 acetoxy group found in guanacastepenes A and C were observed to be unsatisfactory, we resorted to a three-step α-acetoxylation approach analogous to the one employed by the Danishefsky group on their acetonide-containing intermediate **49**.[41] Formation of the triethylsilyl enol ether **50** from **45** occurred smoothly, and the crude material was subsequently treated with *m*CPBA to effect a net α-hydroxylation (Scheme 17).[42] Wary of the potential instability of α-hydroxy ketone **51**, we immediately produced acetate ester **52** by acetylation of the hydroxyl group. Our ^{1}H NMR spectrum of **52** showed a vicinal coupling constant of 6.0 Hz between the methine protons on the five-membered ring (C-12 and C-13), indicating a *cis* relationship between them and, thus, a highly stereoselective α-hydroxylation. This is in accord with observations on coupling constants made by Danishefsky's group on the acetoxylation of their acetonide-containing system.[43]

From compound **52**, the paths to guanacastepenes A and E were direct (Scheme 18). Acid-catalyzed methanolysis of the benzylidene acetal in **52** afforded diol **53** in 88% yield. The latter substance was previously converted to guanacastepene A (**1**) by a selective oxidation of the primary alcohol,[12,17] although we found this transformation to be challenging owing to the proclivity of **53** toward an intramolecular conjugate addition reaction.[15h] Nevertheless, this conjugate addition reaction was welcome, for it gave rise to (+)-guanacastepene E (**3**) as a single diastereoisomer. We were pleased with this result, since no synthesis of the tetracyclic natural product **3** has been reported. The formation of compound **3** in this manner was best achieved by stirring a solution of diol **53** and silica gel in diethyl ether

(39) (a) Stork, G.; Uyeo, S.; Wakamatsu, T.; Grieco, P.; Labovitz, J. *J. Am. Chem. Soc*. **1971**, *93*, 4945−4947. (b) Batey, R. A.; Motherwell, W. B. *Tetrahedron Lett*. **1991**, *32*, 6649−6652.

(40) We are grateful to Dr. Doug Ho, director of the X-crystallographic facility in the Chemistry Department at Princeton University, for performing the X-ray crystallographic analysis of compound **48**.

(41) We sincerely thank Professor Samuel Danishefsky and members of his group for providing us with unpublished procedures and data for the late stages of their synthesis.

(42) We noted that the two-step yield was somewhat low; thus dimethyldioxirane was employed as an oxidant. Danishefsky's group observed a high-yielding conversion to the α-hydroxylated compound using this reagent. In our case, however, with a benzylidene acetal as a protective group, much decomposition was quickly seen by TLC and the yield of **51** was very low.

(43) The stereoselectivity of the oxidation of **50** may be sensitive to temperature; in one reaction run at 0 °C (rather than −78 °C), the cis/trans ratio was nearly 1:1.

for 36 h at room temperature.[44] The ^{1}H NMR spectrum of our synthetic (+)-guanacastepene E (**3**) was identical to that supplied by the Clardy group.[9b]

7. Synthesis of Unnatural (−)-Guanacastepene E. Naturally, half of the material that had been elaborated to the stage of the classical resolution had the incorrect absolute stereochemistry (compound **40**, Scheme 19) for a synthesis of natural (+)-guanacastepene E. However, we were able to make productive use of this material in a synthesis of unnatural (−)-guanacastepene E. When coupled with vinylstannane **54** derived in eight steps from (*R*)-(−)-carvone, we had, in a sense, a completely reliable model system since it differed from the real system only in absolute configuration. In fact, much of the chemistry described above was developed using this material.

Conclusions

Three reactions, an efficient π-allyl Stille cross-coupling, an intramolecular [2 + 2] photocycloaddition, and a stereoelectronically controlled reductive fragmentation of a conjugated cyclobutyl ketone, enabled a convergent synthesis of the complex, tricyclic guanacastane molecular architecture and asymmetric total syntheses of both (+)- and (−)-guanacastepene E. Formal asymmetric syntheses of (+)- and (−)-guanacastepene A were also achieved. Our synthesis of the A-ring cyclopentenone building block from carvone led to the development of a novel ring contraction that affords cyclic 1,2-diketones. The synthesis of the C-ring cyclohexene domain featured a Diels−Alder/Baeyer−Villiger/methanolysis sequence[15h] that provided efficient access to the desired relative stereochemistry. The convergent strategy described herein gives rise to guanacastepene E in 28 steps with a longest linear sequence of 20 steps.

(44) We observed an analogous cyclization in a model system lacking the C13 acetoxy and C12 isopropyl groups (see ref 15h).

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Supporting Information Available: Experimental procedures and characterization data for all compounds and a complete listing of authors for ref 22c. This material is available free of charge via the Internet at http://pubs.acs.org.

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