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Enantioselective Total Synthesis of Guanacastepene N Using an Uncommon 7-Endo Heck Cyclization as a Pivotal Step

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Abstract: A convergent, enantioselective total synthesis of (+)-guanacastepene N was developed that features a 7-endo Heck cyclization as the key step. In the course of this synthesis, short syntheses of the enantiomerically pure cyclopentenone and cyclohexene building blocks **5** and **6**, which constitute A and C ring fragments of guanacastepene N, were developed. These fragments were linked by a challenging conjugate addition reaction that also generated the C11 quaternary carbon stereocenter. Regioselective 7-endo Heck cyclization gave rise to a tricyclic intermediate, which was elaborated to complete the first total synthesis of guanacastepene N and the second enantioselective total synthesis of a guanacastepene natural product.

Introduction

The Heck reaction is recognized as being among the most powerful and reliable C−C bond forming processes.[1] In particular, the intramolecular variant has found widespread application for the assembly of natural products and other molecules containing complex ring systems.[2] Regioselection in intramolecular Heck reactions is generally controlled by the nature of the tether separating the reactive sites, rather than by the substituents on the C−C double bond. When the tether length is short, exo-mode cyclization is highly favored, with 5- and 6-exo cyclizations dominating over the 6- and 7-endo counterparts.[2] 7-Endo cyclizations are extremely rare,[2] being seen only when the 6-exo cyclization leads to an intermediate that lacks β-hydrogens,[3] or when an eclipsed insertion topography[4] is disfavored in a 6-exo cyclization by virtue of the ring system.[5] In a few cases, the nature of the catalyst, particularly the absence of phosphine ligands and the presence of an inorganic base,[6] is reported to favor the 7-endo pathway.[3d,7]

The guanacastepene diterpenes attracted our attention as challenging synthetic targets that present the opportunity to further explore the utility of rare 7-endo Heck cyclizations in total synthesis. A unique tricyclotetradecane ring system composed of fused five-, six-, and seven-membered rings is the signature structural motif of this diterpene family (Figure 1).[8] The guanacastepenes were isolated by Clardy and co-workers from an endophytic fungus growing on the tree *Daphnosis americana* in the Guanacaste Conservation Area in Costa Rica.[8] Structures of the guanacastepenes were established by X-ray crystallography, with the absolute configuration of two members of this set, guanacastepenes E and L, being determined by anomalous dispersion from their C5 *p*-bromobenzoyl derivatives.[8b] The guanacastepene tricyclic skeleton is roughly planar; NMR spectra of guanacastepene A suggest the existence of two low-energy conformers resulting from torsion about the C9−C10 σ-bond of the central seven-membered ring.[8a]

The unique molecular architecture of the guanacastepenes, along with the initial report of their antibacterial activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-

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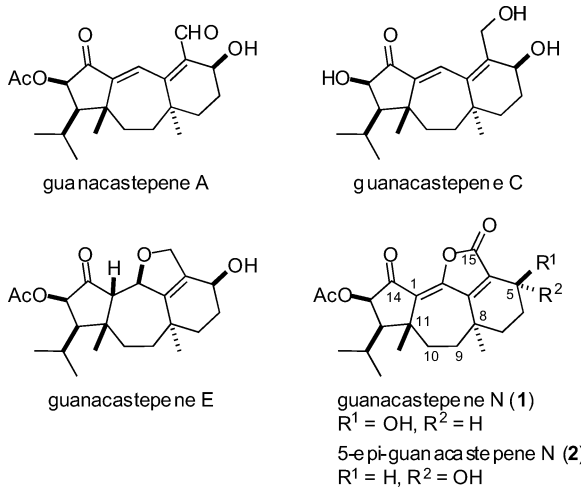


Figure 1. Structures of selected members of the guanacastepene family of natural products and epimer **2**.

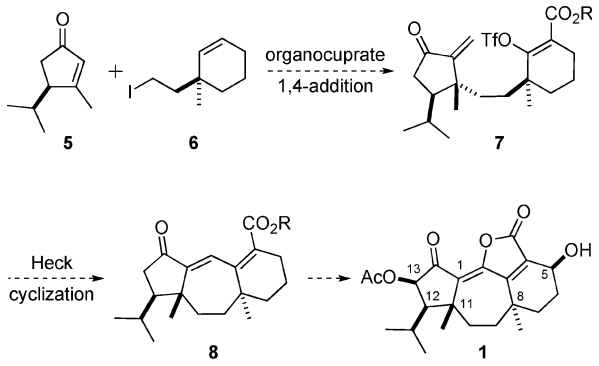
resistant *Enterococcus faecium*, stimulated much interest in their total synthesis. Although the ability of guanacastepene A to lyse human blood cells dampened interest in their therapeutic potential,[9] the guanacastepenes inspired the development of much new synthetic organic chemistry.[10] The initial total synthesis accomplishment in the area was registered by the Danishefsky group, who reported in 2002 the total synthesis of (±)-guanacastepene A.[11] Subsequently, a total synthesis of (±)-guanacastepene C was reported by Mehta,[12] and most recently total syntheses of (+)- and (−)-guanacastepene E were described by Shipe and Sorensen.[13] Three formal total syntheses of (±)-guanacastepene A have been reported also.[13−15]

We report herein a convergent total synthesis of the tetracyclic guanacastepene lactone, (+)-guanacastepene N. A high-yielding 7-endo Heck cyclization forms the cornerstone of our route to the guanacastepenes.

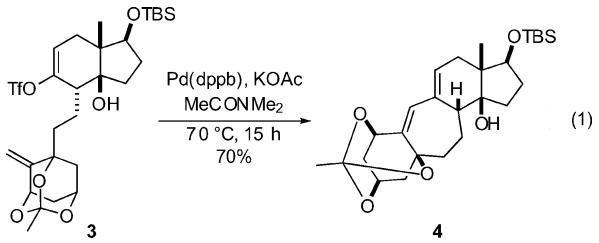
Results and Discussion

Preliminary Results and Initial Planning. The novel guanacastepene architecture poses at least three challenges for total synthesis: the quaternary carbon stereocenters C8 and C11, the all-cis relationship of the three adjacent substituents on the five-membered ring, and the central seven-membered ring. From the first publications in this area, the challenge in assembling the seven-membered ring of the guanacastepenes has been highlighted as several ring-forming reactions that reliably construct six-membered rings have proven unsuccessful in this context.[10,14,16]

Scheme 1. Synthetic Strategy for Preparing (+)-Guanacastepene N



As a result of discoveries made during a total synthesis investigation in a different area, we were drawn to a strategy in which a 7-endo Heck cyclization would construct the central cycloheptene ring of the guanacastepenes. During these earlier studies directed at complex cardenolides such as ouabain,[17] we examined the Heck cyclization of dienyl triflate **3**. Although we had projected a 6-exo/3-exo cascade cyclization sequence,[3a] this reaction occurred selectively in a 7-endo sense to form tetracarbocyclic product **4** (eq 1).[18] The fused A−B−C ring system of this product bears notable resemblance to the guanacastepene diterpene skeleton.



The strategy we adopted at the outset of our synthetic studies in the guanacastepene area is outlined in Scheme 1. This plan envisioned two pivotal steps. In the first, all of the carbon atoms of the guanacastepene skeleton would be joined by conjugate addition of a cuprate reagent derived from (*S*)-cyclohexenyl iodide **6** to (*R*)-cyclopentenone **5**. This step was certain to be challenging, as the β carbon of enone **5** was fully substituted and adjacent to a bulky isopropyl substituent. However, if this addition could be accomplished, the isopropyl group was expected to guide stereoselection.[19]

The second pivotal step would be Heck cyclization of dienyl triflate **7**. Our expectation that this reaction would take place in a 7-endo fashion was bolstered by the analysis depicted in Figure 2. Although an eclipsed insertion topography could be readily accessed in a 7-endo process, coiling the palladacyclohexene ring under the methylene cyclopentanone ring to align the C−Pd σ and alkene π bonds in a 6-exo sense would be sterically impossible as it thrusts the C8 methyl substituent into the five-membered ring.[20]

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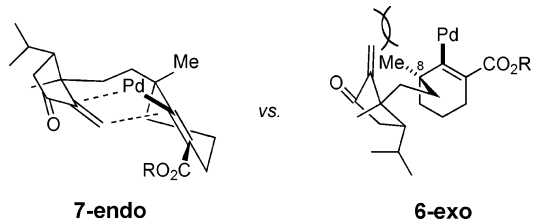
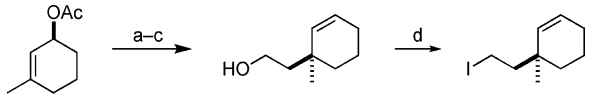


Figure 2. Eclipsed insertion topographies for cyclizations of the alkenylpalladium intermediate derived from triflate **7**.

Scheme 2. Synthesis of Enantioenriched Cyclohexene **6**[a]

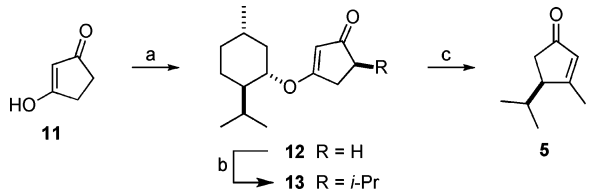


[a] (a) LDA, THF, −78 °C, 30 min, then DMPU, TBSCl, −78 °C → rt, 30 min; (b) toluene, 80 °C, 10 h; (c) DIBAL-H, toluene, −78 °C → rt, 1 h; (d) I_2, Ph_3P, imidazole, CH_2Cl_2, 0 °C → rt, 5 h, 69% (overall), 80% ee. LDA = lithium diisopropylamide; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; TBSCl = *tert*-butyldimethylsilyl chloride; DIBAL-H = diisobutylaluminum hydride; rt = room temperature.

Assembling the Heck Cyclization Precursor. The (*S*)-cyclohexenyl iodide **6** was prepared by the straightforward sequence summarized in Scheme 2. This synthesis began with (*R*)-3-methylcyclohex-2-yl acetate (**9**), which was prepared in 95% ee and 36% overall yield by lipase-catalyzed kinetic resolution of racemic 3-methyl-2-cyclohexen-1-ol, followed by acetylation.[21] We found it convenient to use Lipozyme, a lipase immobilized on porous silica granules, in this kinetic resolution employing vinyl acetate.[22] Ireland−Claisen rearrangement of the ketene silyl acetal derived from acetate **9**,[23] followed by reduction of the resulting silyl ester with diisobutylaluminum hydride (DIBAL-H), provided 3,3-disubstituted cyclohexene **10**, which was directly converted to iodide **6**.[24]

The short synthesis we developed to prepare enantiopure (*R*)-4-isopropyl-3-methylcyclopent-2-en-1-one (**5**) is described in Scheme 3. Our approach employed a Stork−Danheiser construction of a 3-substituted cycloalk-2-ene-1-one,[25] modified by the presence of a chiral auxiliary, in conjunction with ispropylation of a zincate enolate.[26] Thus, condensation of (+)-menthol with 1,3-cyclopentadione (**11**) furnished β-alkoxycyclopentenone **12** in 76% yield. Formation of the kinetic zincate enolate of vinylogous ester **12** by sequential reaction with LDA and Et_2Zn in THF at −78 °C, followed by addition of 2-iodopropane, furnished diastereomer **13** and its epimer in 71% yield and a 1.5:1 ratio.[27,28] These isomers were readily separated on a multigram scale by preparative HPLC. Attempted isopropylation of the corresponding lithium enolate failed to provide the desired alkylation products. Finally, reaction of vinylogous ester **13** with MeLi followed by acidic workup provided (*R*)-cyclopentenone **5** in 79% yield.

Scheme 3. Preparation of Enantioenriched Cyclopentenone **5**[a]



[a] (a) Menthol, *p*-TsOH, benzene, 80 °C, 9 h, 76%; (b) LDA, THF, −78 °C, 20 min, then Et_2Zn, 2-iodopropane, DMPU, −78 °C → rt, 20 h, 71%, 1.5:1 mixture of diastereomers, separated by HPLC; (c) MeLi, THF, −78 → 0 °C, 3 h; aqueous $NaHSO_4$, 79%, 88% ee. THF = tetrahydrofuran; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

Following the three-step sequence outlined in Scheme 3, cyclopentenone **5** was accessed in 26% overall yield and 88% ee. Although stereoselection in the alkylation was only moderate and a HPLC separation was required, multigram quantities of (*R*)-**5** could be prepared in a few days. As no attempt to optimize the alcohol auxiliary was made, it is likely that considerable improvement to this sequence would be possible. During our studies, the Trauner group[19] published a stereocontrolled, albeit longer, synthesis of the *S* enantiomer of cyclopentenone **5** from (1*R*,4*S*)-4-hydroxy-2-cyclopentyl acetate.[29]

With building blocks **5** and **6** in hand, we turned to explore their linkage by means of a diastereoselective conjugate addition. As we wished to combine the 1,4-addition with functionalization of the α-carbon of enone **5**, we hoped to carry out the conjugate addition in the presence of a silylating agent to generate enoxysilane **15**, which we envisaged converting in standard fashion to α-methylene ketone **17**.[30] We quickly confirmed our expectations, and the experience of the Trauner group in a related reaction,[19] that steric hindrance renders enone **5** a very poor substrate for 1,4-addition. After an initial brief survey, success was first achieved by converting alkyl iodide **6** to a rarely utilized, higher order cuprate reagent of stoichiometry $R_5Cu_3Li_2$,[31] and carrying out the conjugate addition in diethyl ether in the presence of Me_3SiCl (eq 2). Trapping of the enoxysilane intermediate **15** in situ with Eschenmoser's reagent (**16**),[32] and subsequent *N*-methylation and β-elimination, delivered dienone **17** in moderate yield (eq 2). However, the sacrificial use of an excess of alkyl iodide **6** coupled with some irreproducibility of this sequence precluded the implementation of these reaction conditions in the context of the total synthesis.

To find better conditions for the conjugate addition step, we examined a number of potential coupling conditions using

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(21) (a) Wang, Y.-F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C.-H. *J. Am. Chem. Soc.* **1988**, *110*, 7200−7205. (b) Carea, G.; Danieli, B.; Palmisano, G.; Riva, S.; Santagostina, M. *Tetrahedron: Asymmetry* **1992**, *3*, 775−784.
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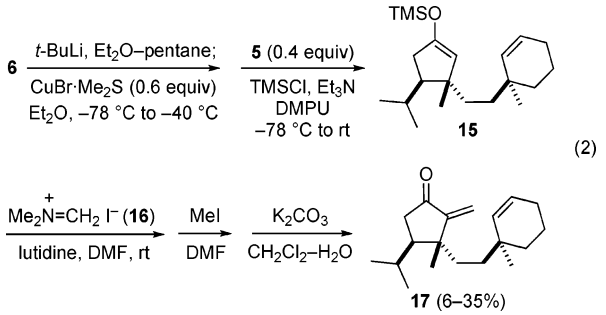
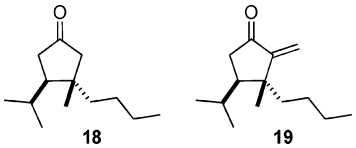


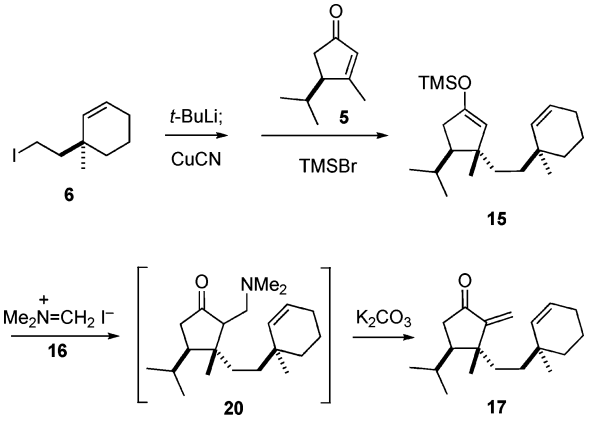
n-BuLi as a surrogate for the lithium reagent derived from **6**. These studies identified cyanocuprates[33] as the optimum nucleophile, silyl halides as effective activators, and hydrocarbon−ether mixtures as preferred solvents. As has been observed previously, we found Me_3SiBr to be more effective than Me_3SiCl;[34] for example, cyclopentanone **18** was formed in 56% yield when 1 equiv of Me_3SiBr was employed and in 44% yield using an equivalent amount of Me_3SiCl. These studies also examined the best method for generating a primary alkyllithium reagent, in this case *n*-BuLi, from the corresponding iodide. In our hands, yields of cyclopentanones **18** or **19** were optimum when *n*-BuLi was generated in 1:1 ether−pentane by adding 1.0 equiv, rather than 1.5 or 2 equiv, of *t*-BuLi to 1-iodobutane at −78 °C.[35]



Application of the conditions optimized in the butyl model series to the union of (*S*)-iodide **6** and (*R*)-cyclopentenone **5** is summarized in Scheme 4. The cyanocuprate reagent was generated from iodide **6** in 1:1 pentane−ether by sequential addition at −78 °C of 1 equiv of *t*-BuLi and 1 equiv of CuCN. After the reaction was allowed to warm to −30 °C, it was recooled to −78 °C, and 1 equiv of Me_3SiBr and 0.7 equiv of enone **5** were added. After the crude enoxysilane intermediate was allowed to react with formaldiminium ion **16** at room temperature, the Mannich product **20** was quaternized with MeI. Base-promoted elimination of this intermediate delivered dienone **17** reproducibly in 53−58% overall yield.

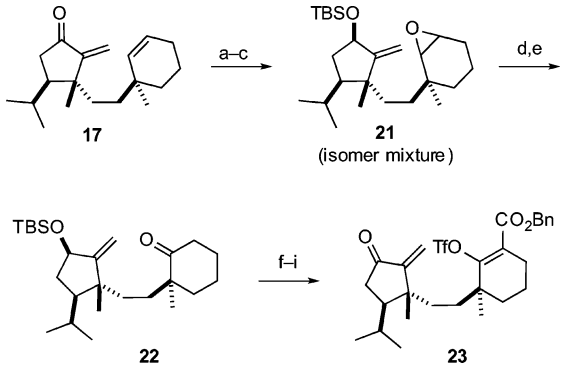
Dienone **17** was converted to Heck cyclization substrate **23** by an efficient multistep sequence of standard reactions requiring purification of only one intermediate (Scheme 5). This elaboration began with regioselective epoxidation of **18** with *m*-chloroperoxybenzoic acid (*m*-CPBA) at 0 °C. The resulting 1:1 mixture of epimeric epoxides was reduced under Luche conditions,[36] and the derived β allylic alcohol was protected with a TBS group to give **21**. Without purification, this intermediate was reduced with $LiEt_3BH$ in THF at room temperature, and the resulting mixture of secondary alcohols was oxidized[37] to provide ketone **22** in 83% overall yield for the five steps.[38]

Scheme 4. Stereoselective Conjugate Addition of Alkyl Iodide **6** to Enone **5** and Introduction of the Exomethylene Group[a]



[a] Optimized conditions: (i) **6**, *t*-BuLi (1 equiv), Et_2O−pentane, −78 °C, 30 min; (ii) CuCN (1 equiv), −78 → −30 °C; (iii) Me_3SiBr (1 equiv), THF, −78 °C, then add **5** (0.7 equiv), −78 °C, 6 h; (iv) **16**, 2,6-lutidine, DMF, 0 °C, 1 h; (v) MeI, Et_2O, rt, 12 h; (vi) K_2CO_3, CH_2Cl_2/MeOH/H_2O (4:1:3), rt, 3 h, 53−58% overall from **5**.

Scheme 5. Elaboration of Intermediate **18** to Heck Cyclization Precursor **23**[a]

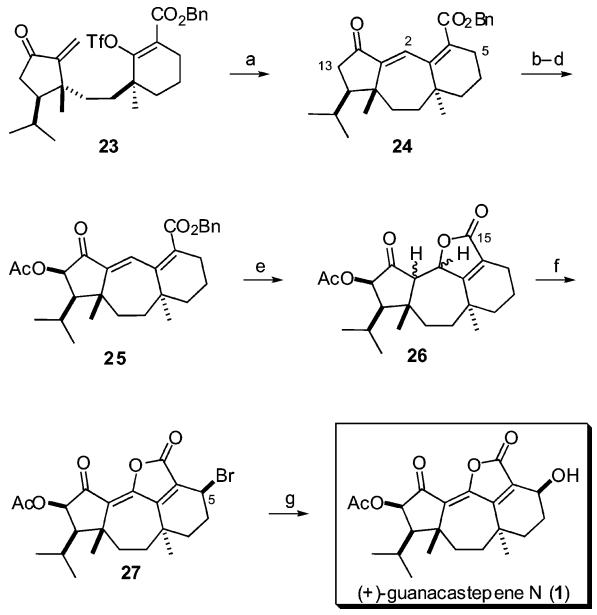


[a] (a) *m*-CPBA, CH_2Cl_2, 0 °C, 3 h; (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C, 1 h; (c) TBSCl, imidazole, CH_2Cl_2, rt, 30 min; (d) $LiEt_3BH$, THF, 0 °C, 2 h; (e) NMO, TPAP, CH_2Cl_2, rt, 1 h, 83% overall (five steps); (f) $LiN(SiMe_3)_2$, THF, −78 → −30 °C, 10 min, then DMPU, benzyl cyanoformate, −78 → −45 °C, 10 min; (g) $KN(SiMe_3)_2$, THF, −78 °C, 20 min, then Tf_2O, −78 °C, 10 min; (h) HF, CH_3CN/MeOH/H_2O (8:2:1), 0 °C, 3 h; (i) NMO, TPAP, CH_2Cl_2, rt, 4 h, 47−53% overall (four steps). DMF = *N*,*N*-dimethylformamide; TBSCl = *tert*-butyldimethylsilyl chloride; NMO = *N*-methylmorpholine-*N*-oxide; TPAP = tetra-*n*-propylammonium perruthenate; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

In four additional steps, intermediate **22** was elaborated to the Heck cyclization precursor **23**. Alkoxycarbonylation of the lithium enolate of **22** with benzyl cyanoformate[39] furnished the corresponding β-keto ester, which exists as a mixture of keto and enol tautomers. Finding conditions for the reliable and efficient conversion of this intermediate to the corresponding vinyl triflate proved surprisingly difficult. After much experimentation, we discovered that rapid addition of trifluoromethanesulfonic anhydride (Tf_2O) to the potassium enolate of this β-keto ester intermediate in THF at −78 °C was optimal. Without purification, the enol triflate product was exposed to aqueous HF to cleave the TBS protecting group. Oxidation of the resulting allylic alcohol proceeded uneventfully to furnish Heck

(33) For an example of the use of a cyanocuprate reagent in a challenging conjugate addition to a sterically encumbered cyclopentenone, see: Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11−13.
(34) (a) Bergdahl, M.; Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *Tetrahedron* **1989**, *45*, 535−543. (b) Knochel, P.; Majid, T. N.; Tucker, C. E.; Venegas, P.; Cahiez, G. *J. Chem. Soc., Chem. Commun.* **1992**, 1402−1403. (c) Piers, E.; Oballa, R. M. *Tetrahedron Lett.* **1995**, *36*, 5857−5860.
(35) Bailey, W. F.; Brubaker, J. D.; Jordan, K. P. *J. Organomet. Chem.* **2003**, *681*, 210−214.
(36) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226−2227.
(37) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625−1627.
(38) The β-configuration of the silyl ether of **22** was confirmed by 2D NMR experiments (NOE enhancements between the methine hydrogens of the five-membered ring).
(39) Mander, L. N.; Sehti, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425−5428.

Scheme 6. 7-Endo Heck Cyclization and Completion of the Total Synthesis of (+)-Guanacastepene N (**1**) and (+)-5-Epi-guanacastepene N (**2**)[a]



[a] (a) $Pd_2(dba)_3 \cdot CHCl_3$ (12 mol %), dppb (24 mol %), KOAc, DMA, 80 °C, 12 h, 75%; (b) TESOTf, Et_3N, CH_2Cl_2, −78 °C, 4 h; (c) DMDO, CH_2Cl_2/acetone, −78 °C, 10 h (dr = 9:1); (d) Ac_2O, Et_3N, DMAP, rt, 3 h, 67% (three steps); (e) Et_3SiH, $Pd(OAc)_2$, Et_3N, CH_2Cl_2, rt, 2 h, 77%; (f) NBS, benzoyl peroxide, CCl_4, reflux, 1.5 h, 64% (dr = 20:1); (g) See Table 1. dba = dibenzylideneacetone; dppb = bis(diphenylphosphino)butane; DMA = *N*,*N*-dimethylacetamide; TESOTf = triethylsilyltriflate; DMDO = dimethyldioxirane; DMAP = 4-*N*,*N*-(dimethylamino)pyridine; NBS = *N*-bromosuccinimide.

cyclization precursor **23** in an overall yield of 47−53% from intermediate **22**. It merits note that attempted removal of the TBS group with tetrabutylammonium fluoride or HF buffered with pyridine led to rapid decomposition of the vinyl triflate functionality.

Heck Cyclization and Elaboration to (+)-Guanacastepene N. With a reliable route to vinyl triflate intermediate **23** in place, the pivotal Heck cyclization to construct the central seven-membered ring could be tested. We were delighted to find that incubation of dienyl triflate **23** with a palladium catalyst generated from $Pd_2(dba)_3 \cdot CHCl_3$ and bis(diphenylphosphino)-butane (dppb) in *N*,*N*-dimethylacetamide (DMA) at 80 °C in the presence of excess KOAc provided tricyclic dienone **24** in 75% yield (Scheme 6). As we had expected, the benzyl ester was stable to these cyclization conditions. Intramolecular Heck reaction of the methyl ester analogue of **23** under identical conditions furnished the corresponding tricyclic product in 83% yield; however, the methyl ester functionality could not be cleaved efficiently at a subsequent stage, thus necessitating our use of the benzyl ester for the total synthesis.[40,41]

Elaboration of tricyclic Heck product **24** to guanacastepene N necessitated oxidation at C2, C5, and C13. The β-acetoxy substituent at C13 was introduced first by employing the procedure developed by the Danishefsky group during their synthesis of guanacastepene A.[11] Thus, oxidation[42] of the triethylsilyl enol ether derived from **24** with dimethyldioxirane (DMDO) furnished a 9:1 mixture of C13 alcohols favoring the desired β epimer.[43] After acetylation, these isomers were separated to provide β-acetoxy ketone **25** in 67% overall yield from intermediate **24**.

At this stage, several members of the guanacastepene family were potentially accessible by a few synthetic transformations. A number of conditions for the unmasking of the benzyl ester functionality of acetoxy keto ester **25** were screened.[44] However, no suitable method for the conversion of ester **25** to the corresponding carboxylic acid or an activated derivative thereof could be identified. Nevertheless, we did discover that reaction of benzyl ester **25** with $Pd(OAc)_2$ in the presence of triethylsilane[45] cleanly delivered tetracyclic lactone **26** in 77% yield as a mixture of all four possible diastereomers. The inconsequential lack of stereocontrol in the cyclization of the presumed carboxylic acid intermediate to form **26** contrasts with the high stereoselection reported in cyclizations of related dienone intermediates in which C15 is a primary alcohol.[13,14]

To advance lactones **26** to guanacastepene N, the dienone functionality would need to be reinstalled and a β hydroxyl group introduced at C5. Gratifyingly, we discovered that reaction of lactones **26** with excess *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide in refluxing CCl_4 stereoselectively introduced a β bromine at C5 and at the same time reinstalled the central unsaturation, the latter transformation presumably occurring by allylic bromination at C2 followed by elimination of HBr. Tetracyclic allylic bromide **27** was obtained from this reaction in 49−64% yield and with high diastereoselectivity (dr = 20:1).[46] As the B and C rings of the delocalized radical precursor of bromide **27** would be nearly planar, stereocontrol in this bromination must derive from the α-oriented axial-methyl substituent at C8.

Several approaches for retentive replacement of the β Br substituent with OH were examined (Table 1). Solvolysis of **27** in acetone/water in the presence of Ag(I) salts preferentially produced **2**, the unnatural C5-epimer of guanacastepene N (Table 1, entries 1−3). To our surprise, the nature of the Ag(I) counterion appears to play a role in this transformation, with a decrease in its coordinating ability leading to greater amounts of guanacastepene N being produced. Useful levels of stereocontrol in this conversion were realized by regeneration of the delocalized radical from bromide **27** by reaction with $(n\text{-Bu})_3SnH$ in the presence of air, followed by in situ reduction of the allylic peroxide intermediate with Ph_3P (Table 1, entry 4). This sequence generated (+)-guanacastepene N (**1**) and its C5 epimer **2** in a 10:1 ratio and 47% yield. Separation of this product mixture by preparative thin-layer chromatography on SiO_2 provided pure samples of (+)-guanacastepene N (**1**), $[\alpha]^{22}_D$ +148 (c = 1.0, CH_2Cl_2), and (+)-C5-epi-guanacastepene N (**2**). The ^1H and ^{13}C NMR spectra of synthetic (+)-guanacastepene

(40) The speculative possibility that the ethyl thioester congener of **23** could be employed in a Heck cyclization was examined, because a thioester could likely serve at a later stage as an excellent precursor of the C4 aldehyde.[41] However, this thioester proved unstable to a variety of Heck reaction conditions.

(41) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050−7051.

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(43) For a recent exposition of stereochemical control elements in this conversion, see: Cheong, P. H.-Y.; Yun, H.; Danishefsky, S. J.; Houk, K. N. *Org. Lett.* **2006**, *8*, 1513−1516.

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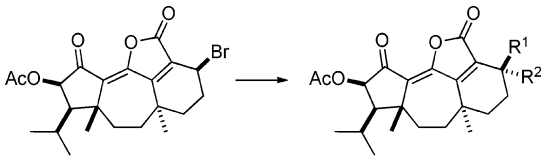
(45) Sakaitani, M.; Kurokawa, N.; Ohfune, Y. *Tetrahedron Lett.* **1986**, *27*, 3753−3754.

(46) The C5 configuration of **27** was elucidated by 2D NMR experiments (COSY, HMQC, HMBC, NOESY) and comparison of the ^1H NMR data to those of epimers (+)-**1** and (+)-**2**.

Table 1. Diastereoselection in the Conversion of Bromide **27** to (+)-Guanacastepene N (**1**) and Epimer **2**



27 **1** R^1 = OH, R^2 = H; **2** R^1 = H, R^2 = OH

entry	conditions	yield (%)	**1**:**2**
1	AgOTf, acetone/H_2O (9:1), room temperature, 15 min	50	1:5
2	$AgSbF_6$, acetone/H_2O (9:1), room temperature, 48 h	44	1:1.8
3	Ag_2O, acetone/H_2O (9:1), room temperature, 48 h	24	1:1.5
4	Bu_3SnH, air, toluene, room temperature, 16 h, then Ph_3P, $CHCl_3$, room temperature, 2 h	47	10:1

N (**1**) were identical to the corresponding spectra of the natural product published by Clardy and co-workers.[8,47]

Conclusions

The enantioselective total synthesis of (+)-guanacastepene N (**1**) was accomplished by a convergent sequence. This synthesis constitutes the first total synthesis of a guanacastepene containing a lactone fragment and the second enantioselective total synthesis in this area.[13] The central strategic step in the synthesis was a high yielding intramolecular 7-endo Heck reaction to construct the central seven-membered B ring of the guanacastepene ring system. In the course of this synthetic endeavor, chiral cyclopentenone and cyclohexene building blocks constituting the A and C rings of the guanacastepenes were accessed by short and reliable routes, and linked by a challenging conjugate addition reaction. The convergent strategy described herein provides intermediates that may serve as branching points for accessing other members of the guanacastepene family, as well as derivatives thereof for a more detailed evaluation of their pharmacological profile.

Experimental Section[48]

(3*R*,4*R*)-4-Isopropyl-3-methyl-3-[(*S*)-1-methylcyclohex-2-en-1-yl)-ethyl]-2-methylenecyclopentanone (17). A pentane solution of *t*-BuLi (1.33 M, 5.8 mL, 7.7 mmol) was added dropwise to a solution of alkyl iodide **6** (1.94 g, 7.74 mmol) and dry Et_2O (5.82 mL) at −78 °C.[35] This solution was maintained at −78 °C for 30 min, and then CuCN (693 mg, 7.74 mmol) was added in one portion with stirring. After 5 min at −78 °C, the solution was allowed to warm to −30 °C and maintained at this temperature until a color change to yellow or tan was clearly visible (typically after ∼5−10 min). The reaction was recooled to −78 °C, and dry THF (5.8 mL) and TMSBr (1.2 g, 7.7 mmol) were added sequentially. Stirring was continued another 5 min, and then a solution of enone **5** (713 mg, 5.16 mmol) in dry THF (5.8 mL) was slowly added by cannula. After an additional 6 h at −78 °C, the solution was diluted with hexanes (100 mL), allowed to warm to room temperature, and washed with a mixture of saturated aqueous NH_4Cl and aqueous NH_4OH (9:1), H_2O, and brine. After drying over anhydrous Na_2SO_4, this solution was concentrated at ambient temperature, and dry DMF (26 mL) and 2,6-lutidine (1.8 mL, 16 mmol) were added. This solution was then added dropwise to a solution of Eschenmoser's salt (**16**) (2.92 g, 15.8 mmol) and DMF (26 mL) at 0 °C.[32] The resulting mixture was stirred at 0 °C for 1 h and then diluted with EtOAc (100 mL). This solution was washed with saturated aqueous $NaHCO_3$ solution (310 mL), and then brine, dried over anhydrous Na_2SO_4, and concentrated. The resulting residue was taken up in Et_2O (40 mL), and MeI (4.0 mL, 64 mmol) was added. After 12 h at room temperature, the solution was concentrated and the residue was dissolved in CH_2Cl_2 (40 mL). Methanol (10 mL) and aqueous K_2CO_3 solution (15%, 30 mL) were added, and the mixture was stirred vigorously for 3 h. The reaction mixture was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2, Biotage 40M+, 150 × 40 mm, hexanes/EtOAc 9:1, flow rate 20 mL/min) to afford 811 mg (57% overall) of dienone **17** as a colorless oil: $[\alpha]^{25}_D$ −3.8° (c = 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (s, 1H), 5.58 (ddd, J = 4.0, 4.0, 10.0 Hz, 1H), 5.31 (d, J = 10.0 Hz, 1H), 5.07 (s, 1H), 2.43 (dd, J = 8.5, 19.0 Hz, 1H), 2.16 (dd, J = 7.0, 18.5 Hz, 1H), 1.93−1.84 (m, 4H), 1.62−1.42 (m, 5H), 1.33 (ddd, J = 5.5, 5.5, 13.0 Hz, 1H), 1.26−1.20 (m, 2H), 1.12 (s, 3H), 1.11 (m, 1H), 0.98 (d, J = 6.5 Hz, 3H), 0.91 (s, 3H), 0.77 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7, 154.3, 136.7, 125.9, 115.9, 46.2, 45.5, 39.2, 36.9, 35.0, 34.8, 34.6, 34.2, 28.9, 27.7, 25.3, 22.9, 19.9, 19.4; IR (film) 2958, 2931, 2871, 1727 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{30}O_6Na$ (M + Na), 297.2194; found, 297.2196.

Heck Cyclization of Triflate 23. Preparation of (5a*S*,7a*R*,8*R*)-8-Isopropyl-5a,7a-dimethyl-4,5,5a,6,7,7a,8,9-octahydro-3*H*-1-oxa-benzo[*cd*]cyclopenta[*h*]azulene-2,10-dione (24). A suspension of $Pd_2(dba)_3$·$CHCl_3$ (80 mg, 0.078 mmol) and dppb (66 mg, 0.16 mmol) in dry, deoxygenated *N*,*N*-dimethylacetamide (DMA, 1 mL) was stirred for 30 min at room temperature under N_2. A solution of triflate **23** (360 mg, 0.65 mmol) in dry, deoxygenated DMA (5.5 mL) and KOAc (190 mg, 1.94 mmol) was added to the resulting dark orange solution, and the mixture was stirred under N_2 at 80 °C for 12 h. The resulting tan solution was poured into a biphasic mixture of EtOAc and brine (100 mL, 1:1), and the aqueous phase was extracted with EtOAc (50 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Biotage 40 M, 40 × 150 mm, toluene/acetone 10:0 → 20:1, flow rate 15 mL/min) to yield pure **24** (197 mg, 75%) as a colorless oil: $[\alpha]^{26}_D$ −162 (c = 2.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.29 (m, 5H), 7.20 (bs, 1H), 5.15 (d, J = 12.2 Hz, 1H), 5.12 (d, J = 12.2 Hz, 1H), 2.53−2.44 (m, 2H), 2.34−2.27 (m, 1H), 2.07 (dd, J = 13.2, 18.0 Hz, 1H), 1.87 (t, J = 12.5 Hz, 1H), 1.77−1.42 (m, 8H), 1.03 (s, 3H), 1.02 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, toluene-d_8, 363 K)[49] δ 202.5, 168.5, 168.0, 145.7, 137.2, 132.2, 131.6, 129.2, 128.9, 128.4, 66.9, 51.1, 46.8, 39.9, 38.5, 38.3, 34.7, 28.8, 28.1, 26.9, 24.5, 22.2, 19.9, 19.1;[50] IR (film) 2954, 2925, 2856, 1717, 1636, 1457, 1378, 1277, 1225, 1025, 752 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{35}O_3$ (M + H), 407.2586; found, 407.2580.

(3*S*,5a*R*,7a*R*,8*R*,9*R*)-9-Acetoxy-3-bromo-8-isopropyl-5a,7a-dimethyl-4,5,5a,6,7,7a,8,9-octahydro-3*H*-1-oxabenzo[*cd*]cyclopenta[*h*]azulene-2,10-dione (27). Triethylsilane (122 mg, 1.05 mmol) and Et_3N (28 mg, 0.28 mmol) were added to an orange solution of $Pd(OAc)_2$ (31 mg, 0.14 mmol) in dry CH_2Cl_2 (1.5 mL).[45] The resulting dark solution was stirred at room temperature for 30 min, and then added to a solution of ester **25** (32.4 mg, 0.070 mmol) in dry CH_2Cl_2 (1.5 mL). The reaction was maintained at room temperature for 2 h, diluted with EtOAc (15 mL), and filtered through Celite. The filtrate was washed with saturated aqueous NH_4Cl, dried over Na_2SO_4, and concentrated. The residue was

(47) The assignment of the configuration at C5 of (+)-**1** and (+)-**2** was further corroborated by 2D NMR spectroscopy (COSY, HMQC, HMBC, NOESY).
(48) General experimental details are provided in the Supporting Information.
(49) Interpretation of ^{13}C NMR spectra recorded in $CDCl_3$ at room temperature was complicated by the occurrence of slowly interconverting conformational isomers of the central seven-membered B ring. Spectra of some intermediates were therefore recorded at 363 K in toluene-d_8.
(50) One peak is missing, which we attribute to overlap with the solvent signal.

purified by column chromatography (SiO_2, hexanes/EtOAc 2:1) to yield 20.1 mg (77%) of tetracyclic lactone **26**, a mixture of four stereoisomers, as a colorless oil.

This sample of lactone **26** was dissolved in CCl_4 (3 mL), *N*-bromosuccinimide (37 mg, 0.21 mmol) and benzoyl peroxide (6.5 mg, 0.027 mmol) were added, and the reaction flask was immediately lowered into a preheated silicon oil bath (90 °C). The suspension was heated at reflux for 1.5 h (a yellow homogeneous solution was obtained after ca. 10 min), and then allowed to cool to room temperature, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by HPLC (Alltech, Alltima SiO_2 5 μ, 250 × 10 mm, hexanes/EtOAc linear gradient 80:20 → 45:55 in 10 min, flow rate 7.0 mL/min, t_R = 7.2 min) to yield 15.5 mg (64%) of bromide **27** as a yellow semisolid: $[\alpha]^{22}_D$ +160 (c = 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 (d, J = 7.7 Hz, 1H), 5.07 (d, J = 4.2 Hz, 1H), 2.52 (dddd, J = 3.4, 4.9, 13.8, 16.0 Hz, 1H), 2.40−2.32 (m, 2H), 2.19−1.99 (m, 7H), 1.91 (dd, J = 7.7, 9.9 Hz, 2H), 1.63−1.60 (m, 2H), 1.38 (s, 3H), 1.21 (s, 3H), 1.16 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 169.7, 165.8, 160.0, 147.6, 133.0, 129.1, 73.6, 55.2, 48.0, 37.1, 35.5, 34.3, 34.1, 32.3, 29.0, 27.3, 25.4, 24.4, 23.5, 23.3, 21.1; IR (film) 2966, 2925, 2877, 1775, 1748, 1611, 1453, 1372, 1214, 1017, 953 cm^{-1}; UV (CH_2Cl_2) λ_{max} = 326 nm (15 800 M^{-1} cm^{-1}); HRMS (ESI) m/z calcd for $C_{22}H_{27}O_5BrNa$ (M + Na), 473.0940; found, 473.0936.

(+)-Guanacastepene N (1). Tri-*n*-butyltin hydride (39 mg, 130 μmol) was added to a 0 °C solution of bromide **27** (6 mg, 13 μmol) in toluene (2 mL). Air was bubbled through the solution, which was stirred at 0 °C for 5 min, and then at room temperature. After 12 h, the solution was concentrated, and the residue was redissolved in $CHCl_3$ (0.5 mL). Triphenylphosphine (10 mg, 38 μmol) was added, and the solution was kept at room temperature for 2 h. This solution was concentrated, and the residue was purified by HPLC (Alltima SiO_2 5 μ, 250 × 10 mm, hexanes/EtOAc linear gradient 4:1 → 1:9 in 20 min, flow rate 7.0 mL/min, t_R = 12.5 min) to yield 2.4 mg (47%) of a mixture of epimers **1** and **2** (9:1, determined by ^{1}H NMR analysis), which was separated using preparative TLC (SiO_2, hexanes/EtOAc 1:1). (+)-Guanacastepene N (**1**): a pale yellow solid; $[\alpha]^{22}_D$ +148 (c = 1.0, CH_2Cl_2);[51] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60 (d, J = 7.7 Hz, 1H), 4.64 (d, J = 5.1 Hz, 1H), 2.37 (dd, J = 7.1, 14.4 Hz, 1H), 2.20−2.12 (m, 3H), 2.08−2.02 (m, 3H), 1.92−1.86 (m, 2H), 1.61−1.52 (m, 2H), 1.36 (s, 3H), 1.18 (s, 3H), 1.15 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 169.7, 168.0, 161.8, 147.6, 133.1, 129.1, 73.5, 58.6, 55.3, 47.9, 35.7, 34.3, 33.9, 32.7, 26.9, 25.9, 25.4, 24.1, 23.5, 23.3, 21.1; IR (film) 3491, 2923, 1781, 1746, 1619, 1372, 1219, 1019, 955 cm^{-1}; UV (CH_2Cl_2) λ_{max} = 318 nm (14 170 M^{-1} cm^{-1}); HRMS (ESI) m/z calcd for $C_{22}H_{28}O_6Na$ (M + Na), 411.1783; found, 411.1777.

(51) The optical rotation of natural guanacastepene N was not reported.[8a]

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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