

Total Synthesis of (–)-Heptemerone B and (–)-Guanacastepene E

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Abstract: A concise, stereoselective, and convergent total synthesis of the unnatural enantiomer of the neodolastane diterpenoid heptemerone B has been completed. Saponification of (–)-heptemerone afforded (–)-guanacastepene E. The absolute stereochemistry of (–)-heptemerone B was thus established as 5-(S), the same as (–)-guanacastepene E. The longest linear sequence of the synthesis comprises 17 (18) steps from simple known starting materials. Our general synthetic approach integrates a diverse set of reactions, including an intramolecular Heck reaction to create one quaternary stereocenter and a cuprate conjugate addition for the establishment of the other. The central seven-membered ring was closed with an uncommon electrochemical oxidation, whereas the five-membered ring was formed through ring-closing metathesis. The absolute configuration of the two key building blocks was established through an asymmetric reduction and an asymmetric ene reaction.

Introduction

The guanacastepenes and heptemerones comprise a unique family of diterpene natural products isolated by the groups of Clardy and Sterner, respectively (Chart 1). Guanacastepene A (**1**), the founding member of the family, stems from an unidentified endophytic fungus colonizing the *Daphnopsis americana* tree in the Guanacaste conservation area of Costa Rica. It showed interesting activities against drug-resistant strains of *Staphylococcus aureus* and *Enterococcus faecalis*.¹ Subsequent systematic investigations of the fungal extracts revealed the presence of 14 other members of the family, termed guanacastepenes B–O.^{1b} Interestingly, the unidentified fungus failed to produce guanacastepenes independent from its tree host, a common phenomenon when complex ecological interactions between different species are disrupted.

More recently, Sterner et al. reported the isolation of the heptemerones from an “inkcap” mushroom, *Coprinus heptemerus*.² The heptemerones strongly inhibit fungal germination of the plant pathogen *Magnaporthe grisea*, the cause of rice blast disease and a major menace to rice cultivating nations. Their cytotoxic and antibiotic activities, however, were found to be low.

Structurally, the guanacastepenes and heptemerones share a tricyclic neodolastane carbon skeleton typified by two angular

methyl groups in a 1,4 relationship at C8 and C11 and an additional isopropyl substituent at C12. Although most of the guanacastepenes and heptemerones share a nonpolar, unfunctionalized “upper rim”, they are distinguished from each other by their different patterns of oxygenation and unsaturation found on the “lower rim” of the molecules.

In light of their attractive structures and interesting biological activities, it is not surprising that the guanacastepenes have proven to be a fertile ground for total synthesis.³ Although the initial excitement about the biological activity of guanacastepene A (**1**) has been somewhat spoiled by its reported hemolytic activity,⁴ the guanacastepenes and heptemerones remain potential drug leads and continue to inspire synthetic chemists. Accordingly, numerous approaches toward their total synthesis have surfaced in the literature in recent years. By contrast, the total synthesis of a heptemerone has not been reported, reflecting the relatively recent appearance of these compounds on the scene.

To date, four total syntheses, a number of formal syntheses, and myriad approaches toward the guanacastepenes have surfaced in the literature, representing a remarkably diverse range of synthetic strategies described in more than 40 publications.⁵ Danishefsky and co-workers reported the first total synthesis of racemic guanacastepene A (**1**) in 2002,^{5d,e} followed by an asymmetric version in 2005.^{5j} Snider et al.⁵ⁿ and Hanna et al.^{5p} published formal total syntheses of racemic guanacastepene A in 2003 and 2004, respectively, and Mehta et al.^{5v}

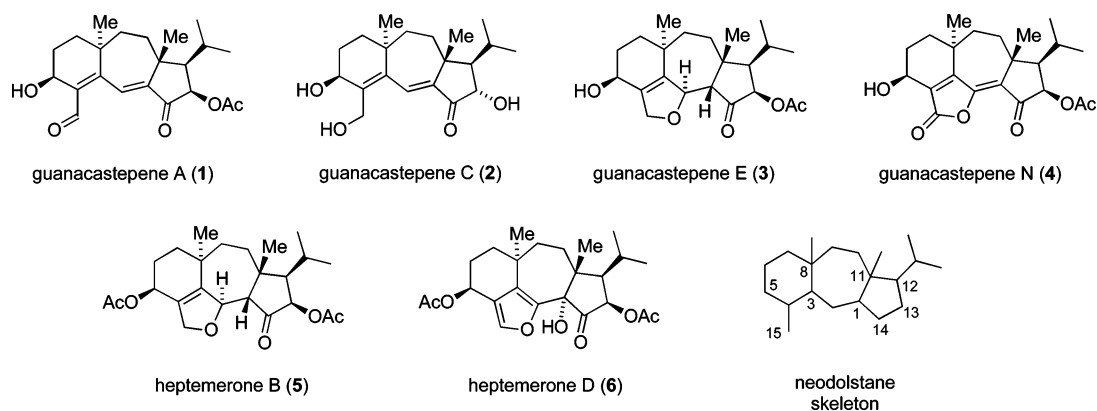
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- (4) Singh, M. P.; Janso, J. E.; Luckman, S. W.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256–261.

Chart 1. Selected Guanacastepenes, Heptemerones, and the Neodolastane Skeleton^a

^a Conventional guanacastepene numbering is used on the neodolastane skeleton.

reported the total synthesis of racemic guanacastepene C (2) in 2005. In 2006, the asymmetric syntheses of guanacastepene E (3) and guanacastepene N (4) were completed by Shipe and Sorensen^{5x} and Overman et al.,^{5y} respectively. In addition to these completed total syntheses, the groups of Magnus,^{5z,aa} Lee,^{4c,5ab,ac} Tius,^{5ad} Kwon,^{5ae,af} Srikrishna,^{5ag} Chiu,^{5ah} Brummond,^{5ai} Stoltz,^{5aj} and Yang^{5ak,al} have published approaches to the guanacastepenes. Our group has also published approaches toward a number of guanacastepene architectures.^{5am–ao} We now report synthetic studies that have culminated in the first total synthesis of heptemerone B (5) and its conversion into guanacastepene E (3). For historic and economic reasons, these studies were conducted in the unnatural enantiomeric series.^{5ao}

Results and Discussion

Retrosynthetic Analysis. Our retrosynthetic analysis of (–)-guanacastepene E (3) begins by disconnecting the central seven-membered ring to arrive at furyl ketone 7 (Scheme 1). In the forward direction, oxidative coupling of the furan and ketone functionalities in 7 would close this ring. Further disconnection of 7 yields the left-hand building block 8 and the right-hand building block 9. These components would be joined by (formal) hydrometallation of 8, followed by a diastereoselective conjugate addition to cyclopentenone 9. Compounds 8 and 9 could be traced back to iodofuran 10 and dienone 11 through an intramolecular Heck reaction and ring-closing metathesis (RCM), respectively. Finally, these components could be fully disconnected to known molecules: aldehyde 12, diiodofuran 13, vinylmagnesium bromide, chiral glyoxylate 14, and heptene 15.

Synthesis of the Left- and Right-Hand Building Blocks.

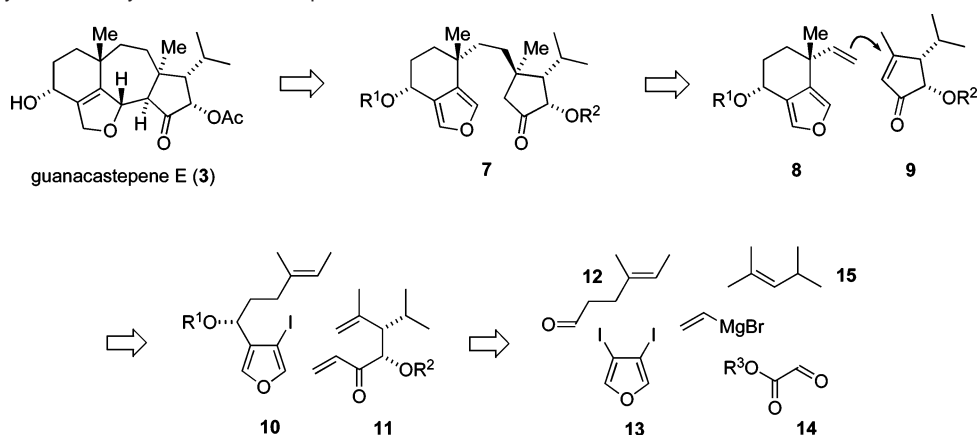
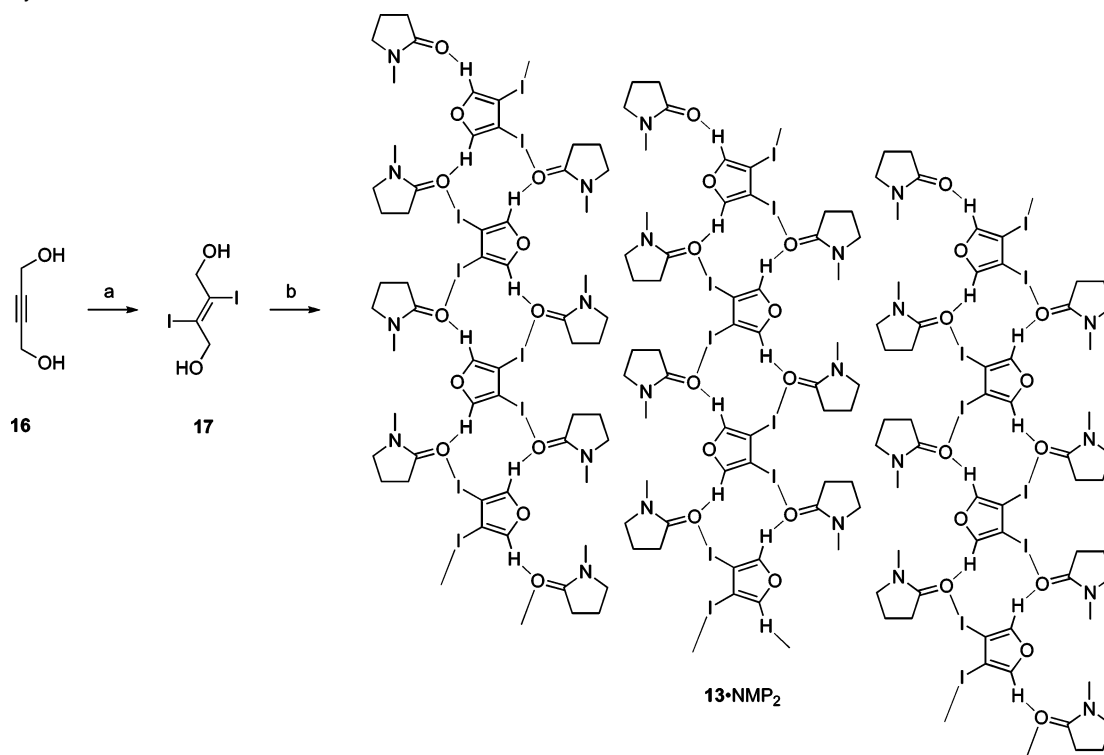
To reduce this plan to practice, we began to accumulate a stockpile of known 3,4-diodofuran (13) (Scheme 2). Although the preparation of this compound from 2-butyne-1,3-diol (16) according to a published procedure⁶ proved difficult, our systematic efforts to improve this transformation were rewarded with a notable result. When the oxidative cyclization of diiododiol 17 was run with 1-methyl-2-pyrrolidinone (NMP) as a cosolvent, we repeatedly observed the formation of large amounts of a white precipitate lining the reaction vessel. Initially assuming the precipitate to be an inorganic or polymeric byproduct, we eventually decided to take a closer look at this material in order to get a better idea about the mass balance of the reaction. To our surprise, the white material proved to be highly soluble in chloroform-*d*, and the ¹H NMR spectrum revealed an exact 2:1 mixture of NMP and the desired product 13. Thus, the precipitate turned out to be the coordination polymer 13·NMP₂.

The X-ray structure of 13·NMP₂ reveals the source of its unusual stability (Figure 1). The carbonyl groups of the amide moiety in NMP form bonding interactions not only with the hydrogens in the furan, which are known to act as hydrogen-bond donors, but also with the iodine atoms. Similar interactions in iodoalkynes have been studied by Goroff et al.⁷ Overall, these bonding interactions lead to the formation of ribbons of

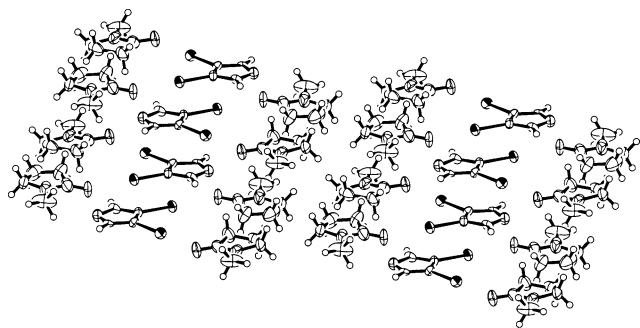
- (5) (a) Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399–2402. (b) Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6789–6791. (c) Dudley, G. B.; Danishefsky, S. J.; Sukenick, G. *Tetrahedron Lett.* **2002**, *43*, 5605–5606. (d) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2185–2188. (e) Lin, S. N.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2188–2191. (f) Mandal, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2004**, *45*, 3827–3829. (g) Mandal, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2004**, *45*, 3831–3833. (h) Yun, H. D.; Meng, Z. Y.; Danishefsky, S. J. *Heterocycles* **2005**, *66*, 711–725. (i) Yun, H. D.; Danishefsky, S. J. *Tetrahedron Lett.* **2005**, *46*, 3879–3882. (j) Mandal, M.; Yun, H. D.; Dudley, G. B.; Lin, S. N.; Tan, D. S.; Danishefsky, S. J. *J. Org. Chem.* **2005**, *70*, 10619–10637. (k) Cheong, P. H. Y.; Yun, H.; Danishefsky, S. J.; Houk, K. N. *Org. Lett.* **2006**, *8*, 1513–1516. (l) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569–572. (m) Snider, B. B.; Shi, B. *Tetrahedron Lett.* **2001**, *42*, 9123–9126. (n) Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030–1042. (o) Boyer, F. D.; Hanna, I. *Tetrahedron Lett.* **2002**, *43*, 7469–7472. (p) Boyer, F. D.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, *6*, 1817–1820. (q) Boyer, F. D.; Hanna, I. *J. Org. Chem.* **2005**, *70*, 1077–1080. (r) Mehta, G.; Umarye, J. D. *Org. Lett.* **2002**, *4*, 1063–1066. (s) Mehta, G.; Umarye, J. D.; Gagliardini, V. *Tetrahedron Lett.* **2002**, *43*, 6975–6978. (t) Mehta, G.; Umarye, J. D.; Srinivas, K. *Tetrahedron Lett.* **2003**, *44*, 4233–4237. (u) Mehta, G.; Umarye, J. D. *Tetrahedron Lett.* **2003**, *44*, 7285–7289. (v) Mehta, G.; Pallavi, K.; Umarye, J. D. *Chem. Commun.* **2005**, 4456–4458. (w) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063–2066. (x) Shipe, W. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 7025–7035. (y) Iimura, S.; Overman, L. E.; Paulini, R.; Zakarian, A. *J. Am. Chem. Soc.* **2006**, *128*, 13095–13101. (z) Magnus, P.; Waring, M. J.; Ollivier, C.; Lynch, V. *Tetrahedron Lett.* **2001**, *42*, 4947–4950. (aa) Magnus, P.; Ollivier, C. *Tetrahedron Lett.* **2002**, *43*, 9605–9609. (ab) Nguyen, T. M.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 4033–4036. (ac) Nguyen, T. M.; Seifert, R. J.; Mowrey, D. R.; Lee, D. S. *Org. Lett.* **2002**, *4*, 3959–3962. (ad) Nakazaki, A.; Sharma, U.; Tius, M. A. *Org. Lett.* **2002**, *4*, 3363–3366. (ae) Du, X. H.; Chu, H. F. V.; Kwon, O. *Org. Lett.* **2003**, *5*, 1923–1926. (af) Du, X. H.; Chu, H. F. V.; Kwon, O. Y. *Tetrahedron Lett.* **2004**, *45*, 8843–8846. (ag) Srikrishna, A.; Dethle, D. H. *Org. Lett.* **2004**, *6*, 165–168. (ah) Chiu, P.; Li, S. L. *Org. Lett.* **2004**, *6*, 613–616. (ai) Brummond, K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491–3494. (aj) Sarpong, R.; Su, J. T.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 13624–13625. (ak) Li, C. C.; Liang, S.; Zhang, X. H.; Xie, Z. X.; Chen, J. H.; Wu, Y. D.; Yang, Z. *Org. Lett.* **2005**, *7*, 3709–3712. (al) Li, C. C.; Wang, C. H.; Liang, B.; Zhang, X. H.; Deng, L. J.; Liang, S.; Chen, J. H.; Wu, Y. D.; Yang, Z. *J. Org. Chem.* **2006**, *71*, 6892–6897. (am) Gradl, S. N.; Kennedy-Smith, J. J.; Kim, J.; Trauner, D. *Synlett* **2002**, 411–414. (an) Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett.* **2003**, *5*, 4113–4115. (ao) Hughes, C. C.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 3425–3428.

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(7) (a) Rege, P. D.; Malkina, O. L.; Goroff, N. S. *J. Am. Chem. Soc.* **2002**, *124*, 370–371. (b) Webb, J. A.; Klijin, J. E.; Hill, P. A.; Bennett, J. L.; Goroff, N. S. *J. Org. Chem.* **2004**, *69*, 660–664.

Scheme 1. Retrosynthetic Analysis of Guanacastepene E**Scheme 2.** Synthesis of $13 \cdot \text{NMP}_2$ ^a

^a (a) ref 6; (b) $\text{K}_2\text{Cr}_2\text{O}_7$, H_2SO_4 , hexanes, NMP, 85 °C. NMP = 1-methyl-2-pyrrolidinone.

**Figure 1.** ORTEP representation of $13 \cdot \text{NMP}_2$.

diiodofurans in alternating orientations lined on both sides by NMP molecules.

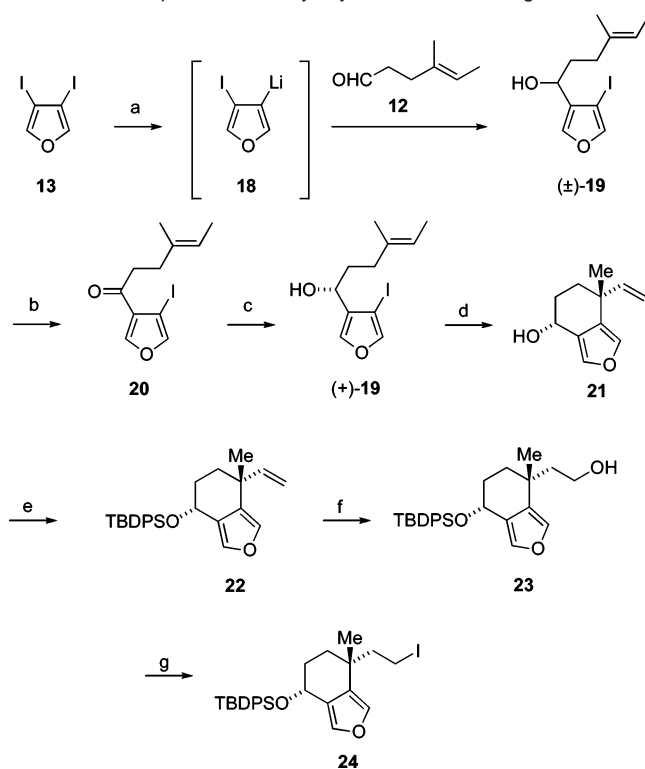
The coordination polymer $13 \cdot \text{NMP}_2$ could easily be broken apart by partitioning its components between brine and meth-

ylene chloride. With sufficient quantities of **13** thus available, we proceeded to study the asymmetric synthesis of a left-hand building block corresponding to **8** (Scheme 3). Mono-lithiation of **13** at low temperature, followed by addition of the resultant organolithium species **18** to (*E*)-4-methylhex-4-enal (**12**), gave racemic alcohol (\pm)-**19**, whose oxidation furnished furyl ketone **20**.

Initially, we explored asymmetric Heck cyclizations of **20** to achieve the formation of the six-membered ring.⁸ Although this cyclization could be effectively carried out racemically under Jeffery conditions,⁹ all attempts to perform this reaction with chiral catalysts proved disappointing. We therefore turned our attention to diastereoselective Heck cyclizations of enantio-merically enriched iodofuryl carbinol (+)-**19**. To this end, **20**

(8) For a review of asymmetric intramolecular Heck reactions, see: (a) Donde, Y.; Overman, L. E. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000; pp 675–697.

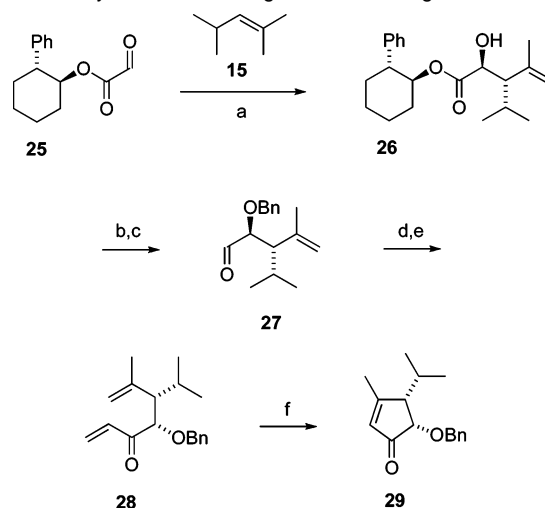
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Scheme 3. Preparation of Furyl Cyclohexanol Building Block **24**^a

^a (a) *n*-BuLi, Et₂O, -78 °C, then **12**, 62%; (b) Dess–Martin periodinane, CH₂Cl₂, room temperature, 88%; (c) (+)-DIP–Cl, THF, -20 °C, 75%, 94% ee; (d) Pd(OAc)₂, Et₃N, (*n*-Bu)₄NBr, MeCN, H₂O, 75 °C, 75%; (e) TBDPSCI, imid, DMAP, CH₂Cl₂, 0 °C, 98%; (f) (1) 9-BBN, THF, reflux, (2) EtOH, NaOH, H₂O₂, room temperature, 81%; (g) I₂, PPh₃, imid, THF, 0 °C → room temperature, 90%. DIP–Cl = *B*-chlorodiisopinocampheylborane, TBDPSCI = *tert*-butyldiphenylsilyl chloride, imid = imidazole, DMAP = 4-*N,N*-(dimethylamino)pyridine, 9-BBN = 9-borabicyclo[3.3.1]nonane.

was reduced using (+)-*B*-chlorodiisopinocampheylborane [(+)-DIP–Cl],¹⁰ affording (+)-**19** in 94% enantiomeric excess. After considerable experimentation, it was found that reaction of (+)-**19** with palladium(II) acetate [Pd(OAc)₂], triethylamine (Et₃N), and tetra-*n*-butylammonium bromide (TBAB) in an acetonitrile (MeCN) and water mixture gave a 5.1:1 mixture of the desired diastereomer **21** and its epimer (not shown). The free secondary hydroxyl group proved to be necessary to achieve high diastereoselectivity, as cyclizations of the corresponding methyl or silyl ethers resulted in low diastereomeric ratios. Protection of the secondary alcohol as the *tert*-butyldiphenylsilyl (TBDPS) ether **22**, followed by hydroboration/oxidation, gave primary alcohol **23**. Functional group interconversion under Appel conditions¹¹ then afforded primary iodide **24**, our standard left-hand building block.

Our next goal was to implement a synthetic route toward an appropriately functionalized right-hand building block corresponding to **9** (cf. Scheme 1). To establish what would ultimately become the *cis* relationship between the C12 isopropyl and C13 alkoxy substituents in the target cyclopentenone, we utilized a chiral auxiliary-mediated carbonyl–ene reaction developed by Whitesell and co-workers (Scheme 4).^{12,13} Reaction of the known chiral glyoxylate **25** with 2,4-dimethyl-2-pentene (**15**), in the presence of tin(IV) chloride (SnCl₄), yielded

Scheme 4. Synthesis of the Right-Hand Building Block **29**^a

^a (a) 1.1 equiv of SnCl₄, CH₂Cl₂, -78 °C, 64%, 10:1 dr; (b) NaH, benzyl bromide, (*n*-Bu)₄Ni, THF, 100%; (c) DIBAL, CH₂Cl₂, -78 °C, 85%; (d) vinylmagnesium bromide, CeCl₃, THF, -78 °C, 82%; (e) Dess–Martin periodinane, CH₂Cl₂, 86%; (f) Grubbs second-generation catalyst, PhMe, reflux, 86%. DIBAL = diisobutylaluminum hydride.

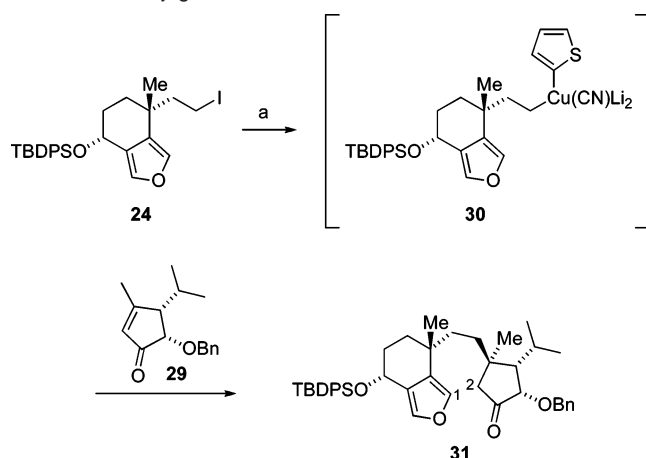
the desired *anti* adduct **26** as the major product, together with a small amount of its *syn* isomer (not shown) (10:1 dr).¹⁴ Protection of **26** as a benzyl ether, followed by diisobutylaluminum hydride (DIBAL) reduction to remove the chiral auxiliary, gave aldehyde **27**. Addition of vinylmagnesium bromide in the presence of CeCl₃¹⁵ followed by oxidation then afforded dienone **28**. Cyclization of **28** via RCM proceeded without incident to afford enantiomerically pure cyclopentenone **29** in excellent yield.¹⁶

Conjugate Coupling and Anodic Oxidative Cyclization. With enantiomerically enriched building blocks **24** and **29** in hand, we began to study the challenging conjugate addition to link the two halves of the molecule (Scheme 5). We were pleased to find that this linkage could be achieved reliably using a combination of Lipshutz and Yamamoto protocols for cuprate conjugate additions.^{17,18} Iodine–lithium exchange involving **24**

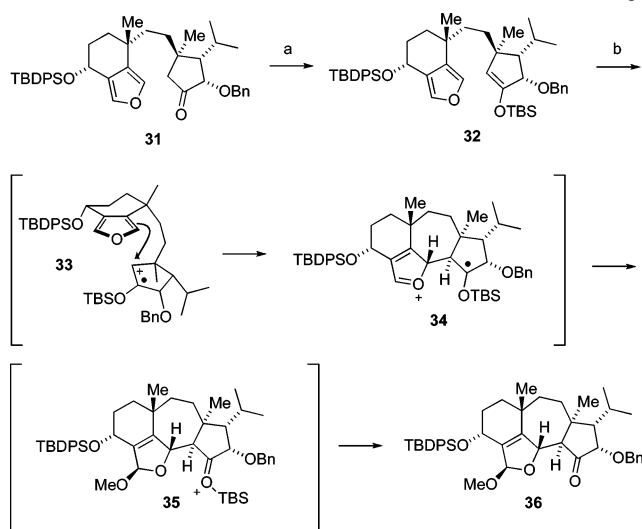
- (12) (a) Whitesell, J. K.; Chen, H.-H.; Lawrence, R. M. *J. Org. Chem.* **1985**, *50*, 4663–4664. (b) Whitesell, J. K.; Lawrence, R. M.; Chen, H.-H. *J. Org. Chem.* **1985**, *50*, 4779–4784. For a review on cyclohexyl-based chiral auxiliaries, see: (c) Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953–964. Racemic *trans*-2-phenylcyclohexanol was made according to: (d) Schwartz, A.; Madan, P.; Whitesell, J. K.; Lawrence, R. M. *Org. Synth. Coll. Vol. 8* **1993**, 516.
- (13) A recently reported enzymatic resolution of racemic *trans*-2-phenylcyclohexanol was found to be extremely efficient and easy to run on large scale: She, Y.-H.; Wu, C.-F.; Shia, K.-S.; Wu, J.-D.; Peddinti, R. K.; Liu, H.-J. *Synthesis* **2005**, 749–752.
- (14) In the racemic series, the two diastereomers could be separated by fractional crystallization, and the relative stereochemistry of the major product was secured with the X-ray structure of (±)-**26** (see Supporting Information). Enantiomerically pure **26**, by contrast, was not a solid, and the two diastereomers proved to be inseparable by chromatographic methods. Therefore, we proceeded with the 10:1 mixture of diastereomers until formation of **29**, wherein the two diastereomers could be easily separated by silica gel chromatography.
- (15) Takeda, N.; Imamoto, T. *Org. Synth. Coll. Vol. 10* **2004**, p 200.
- (16) For a related RCM reaction on a model system, see ref 5am. The ring-closing metathesis reaction of enone **28** to cyclopentenone **29** has also been reported in a thesis from the MacMillan group: Jen, W. S. Development of New Asymmetric Organocatalytic Methods and Progress Towards the Total Synthesis of Guanacastepene A. California Institute of Technology, Pasadena, CA, 2003 (available at <http://etd.caltech.edu/etd/available/etd-10282003-13585.7/>, accessed November, 2006).
- (17) (a) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945–948. (b) Lipshutz, B. H. *Synthesis* **1987**, 325–341. (c) Ibusaka, T.; Yamamoto, Y. In *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; Oxford: Oxford, U.K., 1994; Chapter 7, p 143.
- (18) See ref 5ao for a model study of this conjugate addition. A similar linkage was explored in Overman et al.'s synthesis of guanacastepene N (ref 5y).

(10) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539–1546.

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Scheme 5. Conjugate Addition^a

^a (a) *t*-BuLi, Et₂O, -78 °C, then (2-thienyl)Cu(CN)Li, THF, -40 °C, then BF₃·OEt₂, **29**, 54%.

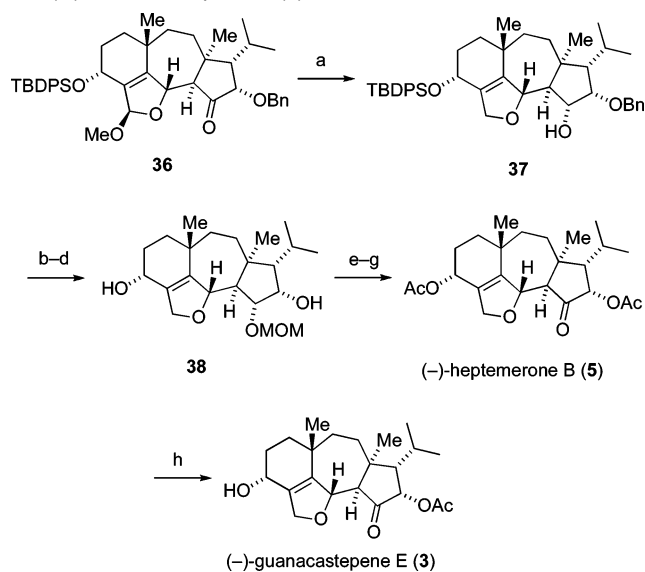
Scheme 6. Anodic Oxidation to Close the Seven-Membered Ring^a

^a (a) KHMDS, 18-crown-6, TBSOTf, THF, -78 °C, 94%; (b) RVC anode (0.9 mA), 2,6-lutidine, 0.1 M LiClO₄, 20% MeOH in CH₂Cl₂, room temperature, 16.5 h, 2.61 F/mol, 81%. KHMDS = potassium bis-trimethylsilylamide, TBSOTf = *tert*-butyldimethylsilyl triflate, RVC = reticulated vitreous carbon.

and *tert*-butyl lithium (*t*-BuLi), followed by addition of lithium 2-thienylcyanocuprate (“cuprate in a bottle”), gave a mixed higher-order cyanocuprate (**30**), which underwent 1,4 addition to cyclopentenone **29** in the presence of boron trifluoride etherate (BF₃·OEt₂). Under these conditions, furyl ketone **31** was formed in acceptable yield and as a single stereoisomer.¹⁹ Although these conditions did not allow for trapping of the intermediary enolate with electrophiles, such as trimethylsilyl chloride, this did not thwart our synthesis because the requisite enolate could be cleanly regenerated by regioselective deprotonation (see below).

Looking at furyl ketone **31**, we reasoned that the formation of the desired C1–C2 bond would require some form of umpolung, as both the furan and an enolate formed from the carbonyl functionality in **31** are nucleophiles. Such an umpolung could most easily be achieved by oxidizing either reaction partner to the corresponding radical cation. Although chemical

(19) Cyclopentanone **31** was isolated along with significant amounts of the corresponding 1,2 adduct (see Supporting Information).

Scheme 7. Conversion of Acetal **36** to (–)-Heptemerone B (**5**) and (–)-Guanacastepene E (**3**)^a

^a (a) DIBAL, PhMe, -78 °C → room temperature, 61%; (b) MOMCl, *i*-Pr₂NEt, NaI, THF, reflux, 95%; (c) TBAF, THF, 100%; (d) Na, NH₃(l), THF, -78 °C, 94%; (e) Ac₂O, DMAP, *p*-xylene, reflux, 93%; (f) BF₃·OEt₂, DMS, CH₂Cl₂, -20 °C; (g) Dess–Martin periodinane, CH₂Cl₂, 69% (2 steps); (h) K₂CO₃, MeOH, 28% (39% BORSM). MOMCl = chloromethylmethyl ether, TBAF = tetra-*n*-butylammonium fluoride, DMS = dimethylsulfide, BORSM = based on recovered starting material.

methods for one-electron oxidations could be imagined,²⁰ we found an electrochemical variant more attractive (Scheme 6). Moeller and Wright have shown that silyl enol ethers can be coupled with furans through anodic oxidation in an alcoholic solvent.²¹ To adapt this methodology to our system, ketone **31** was converted to silyl enol ether **32** by regioselective deprotonation followed by silylation. With **32** in hand, we were in a unique position to explore the usefulness of electrochemistry on a relatively complex substrate.

In the event, anodic oxidation of **32**, under the conditions described by Moeller, gave tetracycle **36** in good yield and as a single isomer. According to Wright et al.’s mechanistic studies,^{21e} this cyclization probably proceeds through oxidation of the silyl enol ether to the corresponding radical cation **33**, followed by stereoselective intramolecular attack of the furan. Interception of the resulting carboxonium radical cation **34** by methanol, further oxidation, and finally desilylation of intermediary cation **35** furnishes acetal **36**.

Total Synthesis of Heptemerone B and Guanacastepene E. At this stage, all that remained to complete the synthesis of guanacastepene E or its close congener heptemerone B was reductive removal of the methoxy group, deprotection, and

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(21) (a) Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 9106–9111. (b) Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2003**, *125*, 36–37. (c) Wright, D. L.; Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Frey, D. A. *Org. Lett.* **1999**, *1*, 1535–1538. (d) Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Wright, D. L. *Org. Lett.* **2002**, *4*, 3763–3765. (e) Sperry, J. B.; Whitehead, C. R.; Ghiviriga, I.; Walczak, R. M.; Wright, D. L. *J. Org. Chem.* **2004**, *69*, 3726–3734. (f) Sperry, J. B.; Wright, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 8034–8035. (g) Sperry, J. B.; Wright, D. L. *Tetrahedron* **2006**, *62*, 6551–6557. (h) Sperry, J. B.; Ghiviriga, I.; Wright, D. L. *Chem. Commun.* **2006**, *2*, 194–196. For reviews of anodic electrochemistry, see (i) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527–9554. and (j) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605–621.

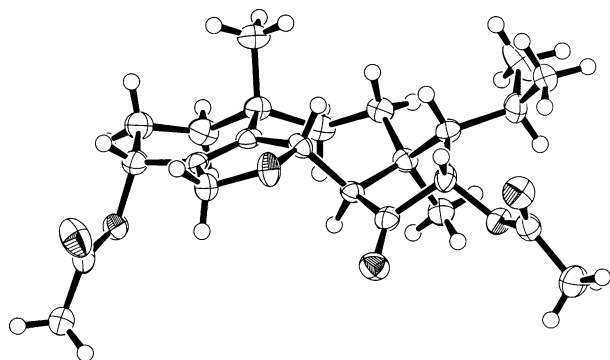


Figure 2. X-ray structure of (–)-heptemerone B (**5**).

acetylation. This seemingly straightforward endgame, however, proved to be quite challenging, requiring careful differentiation of functional groups with similar reactivities. Nevertheless, a satisfactory solution was ultimately found (Scheme 7). First, the acetal functionality in **36** was reduced by treatment with a large excess of DIBAL.^{21a,b} Under these conditions, the cyclopentenone was also reduced to afford secondary alcohol **37** as a single diastereomer, whose relative stereochemistry was assigned by NOE measurements (see Supporting Information). All other conditions that were tried in hopes of avoiding this second reduction (e.g., $\text{Et}_3\text{SiH}/\text{BF}_3\cdot\text{OEt}_2$) led to elimination of methanol and aromatization of the dihydrofuran ring.

Although **37** could be cleanly oxidized to the corresponding α -benzyloxy ketone, all efforts to subsequently remove the benzyl group were low-yielding and were ultimately abandoned. After extensive experimentation, we found that this benzyl group could be removed under dissolving metal conditions, but only after protection of the secondary hydroxyl group at C13 as a MOM ether and cleavage of the C5 silyl ether. The resulting MOM ether **38** was acetylated and subsequently deprotected and oxidized, which afforded heptemerone B (**5**) in very good overall yield. The synthetic material was obtained as a crystalline solid and was identical in all respects to natural **5**, with the exception of its optical rotation, which had the opposite sign ($[\alpha]_{\text{D}} -116^\circ$, $c = 0.36$, CHCl_3 ; lit. $[\alpha]_{\text{D}} +73^\circ$, $c = 0.5$, CHCl_3).^{3a} Therefore, natural heptemerone B, and presumably all of the heptemerones, have the absolute configuration shown in Chart 1. The X-ray structure of synthetic (–)-heptemerone B (**5**) is shown in Figure 2.

Finally, selective saponification of (–)-heptemerone B (**5**) gave (–)-guanacastepene E (**3**) (yield not optimized). Synthetic guanacastepene E was identical to the natural material in all

respects (NMR, MS, IR) save the optical rotation, reflecting its unnatural absolute configuration ($[\alpha]_{\text{D}} -135^\circ$, $c = 0.23$, CHCl_3 ; lit. $[\alpha]_{\text{D}} +25.9^\circ$, $c = 0.17$, CHCl_3).²²

Conclusion

In summary, concise syntheses of (–)-heptemerone B and (–)-guanacastepene E have been developed. Our syntheses are highly convergent and require 17 (18) steps in their longest linear sequence. The absolute configuration of the heptemerones has been established as corresponding to the guanacastepene series. Our work highlights the usefulness of electrochemistry in the synthesis of complex target molecules and confirms the superiority of modern transition-metal-catalyzed methods in challenging bond formations. The quaternary stereocenters of the neodolastane skeleton were installed using organopalladium and organocuprate chemistry, whereas the five-membered ring was closed through ring-closing metathesis. The convergent nature of our approach provides access to intermediates that are potential precursors to additional members of the guanacastepene and heptemerone family.

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Supporting Information Available: Complete experimental procedures and spectral data for previously unreported compounds; ¹H and ¹³C NMR spectra for selected compounds; X-ray crystal structure coordinates for **3** (CCDC620339), **13**·NMP₂ (CCDC618409), and (±)-**26** (CCDC618410). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(22) The optical rotation of natural guanacastepene E was not reported in the original isolation study (ref 1b). The literature value reported here is from synthetic guanacastepene E (ref 6x).