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Synthetic Approaches to Guanacastepenes. Enantiospecific Syntheses of BC and AB Ring Systems of Guanacastepenes and Rameswaralide†

A. Srikrishna* and Dattatraya H. Dethe

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India
ask@orgchem.iisc.ernet.in

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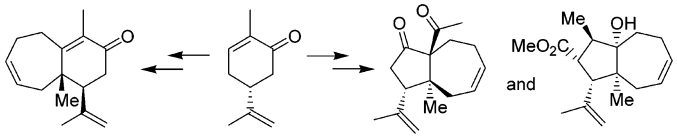
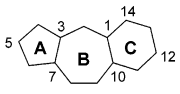
ABSTRACT



A simple and efficient approach for the BC and AB ring systems of the novel diterpenes guanacastepenes and rameswaralide starting from the readily and abundantly available monoterpene (*R*)-carvone employing RCM reaction as the key step is described.

Guanacastepene A (**1**) is the first member of a small group of novel diterpenes recently isolated from an unidentified endophytic fungus (CR 115) growing on the *Daphnopsis americana* tree harvested from the Guanacaste Conservation Area of Costa Rica.[1] Guanacastepenes engendered tremendous interest among synthetic chemists due to their potent antibiotic activity[2] against the methicillin-resistant strain of *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VREF) in addition to the presence of novel molecular architecture comprising of a 5−7−6 (A−B−C) tricyclic ring system (tricyclo[8.4.0.0^{3,7}]tetradecane).[3]



tricyclo[8.4.0.0^{3,7}]tetradecane

The tricyclo[8.4.0.0^{3,7}]tetradecane system is also present in the marine diterpene rameswaralide (**2**) isolated[4] from the soft coral *Sinularia dissecta*. Rameswaralide (**2**) and its derivatives were found to function as effective anti-inflammatory agents.[5]

Representative examples of guanacastepenes along with rameswaralide are depicted in Figure 1. Even though further biological studies indicated that guanacastepene A (**1**) has a hemolytic activity against human red blood cells and can never be developed into a useful therapeutic agent, **1** was

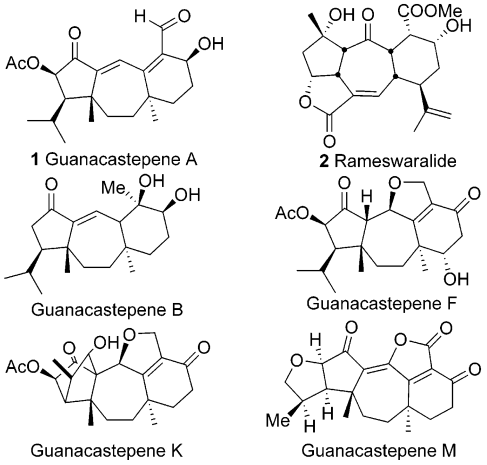


Figure 1.

† Chiral synthons from carvone. 62. For part 61, see: Srikrishna, A.; Kumar, P. R.; Rama Sastry, S. S. V. *Tetrahedron Lett.* **2004**, *45*, 383.

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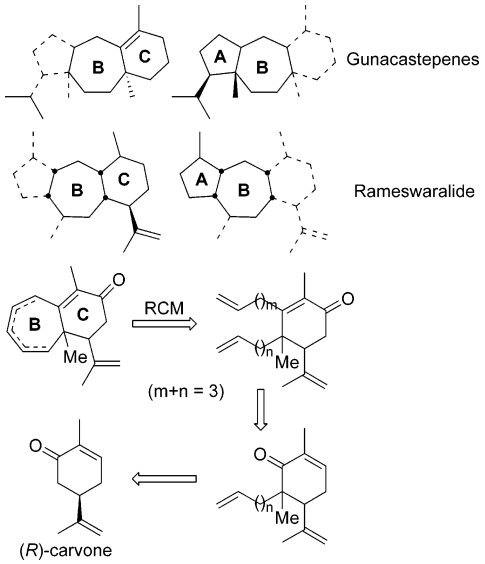
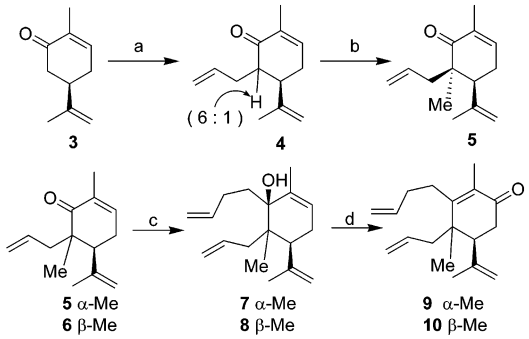
considered as a potential lead compound in the development of new antibacterial agents. Because of this, in combination with the novel carbon skeleton, guanacastepenes have stimulated significant synthetic activity in a number of research groups.[6−10] In 2002, Danishefsky and co-workers reported[6] the first total synthesis of racemic guanacastepene (±)-**1**, which was followed by a formal total synthesis by the research group of Snider.[7] In addition, in the last three years several leading research groups have reported novel approaches (mostly racemic) to AB, BC, and ABC ring systems of guanacastepenes.[8] In the context of enantioselective synthesis of guanacastepenes, Lee and co-workers described the enantiospecific construction of the tricyclic ring system of guanacastepenes starting from (*S*)-verbenone and (*S*)-citronellyl bromide.[9] Very recently, Trauner and co-workers disclosed[10] their asymmetric approach to BC ring system of guanacastepene employing a intramolecular rhodium carbenoid insertion methodology, which prompted us to report our efforts toward the enantiospecific construction of guanacastepenes. Herein, we wish to describe enantiospecific approaches to the construction of BC and AB ring systems of guanacastepenes from a common intermediate and extension of the strategy for the enantiospecific construction of BC and AB ring systems of the marine diterpene rameswaralide (**2**), another therapeutically important lead molecule.

To begin, we have developed a short and efficient enantiospecific approach to the BC ring system of guanacastepenes. Our strategy is based on the identification of the isopropenyl group of the readily available monoterpene (*R*)-carvone (**3**) as a masked hydroxy group.[11] A ring closing metathesis (RCM)[12] reaction has been contemplated as the key step for the construction of seven membered B-ring of guanacastepenes as depicted in Scheme 1 (side chains with $m = 2$ and $n = 1$ were opted for convenience).[13] It is worth noting that the strategy is suitable for the generation of either enantiomeric form of the BC ring system of guanacastepenes by controlling the stereochemistry at the C-6 position of 6,6-dialkylcarvone. The synthetic sequence is depicted in Scheme 2. Thus, kinetic alkylation[14] of (*R*)-carvone **3** using LDA and allyl bromide generated a 6:1 epimeric mixture of 6-allylcarvones **4**, which on a second alkylation with LDA and methyl iodide generated, exclusively, the *cis*-6-allyl-6-

Scheme 1



Scheme 2[a]



[a] Reagents, conditions, and yields: (a) LDA, THF, −70 °C → rt, CH_2═$CHCH_2Br$, 12 h, 85%; (b) LDA, THF, −70 °C → rt, CH_3I, 12 h, 84%; (c) Li, CH_2═$CH(CH_2)_2Br$, THF,))), rt, 1 h; (d) PCC, silica gel, CH_2Cl_2, rt, 4 h; 70% (for two steps).

(1) (a) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116. (b) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900.

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

(3) According to systematic nomenclature (von Baeyer system), the tricyclic 5−7−6 ring system present in guanacastepenes is tricyclo[8.4.0.0^{3,7}]-tetradecane. However, it is not clear to us why a different numbering (based on tricyclo[9.3.0.0^{3,8}]tetradecane) was given for guanacastepenes. In this paper, we follow the systematic numbering with the two quaternary ring junction carbons numbered as 7 and 10 (instead of 11 and 8).

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(5) Faulkner, D. J.; Venkateswarlu, Y. PCT Int. Appl., WO0027839, 2000. CAN 132:352768.

(6) (a) Lin, S.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2188. (b) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2185.

(7) Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030.

(8) (a) Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399. (b) Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6789. (c) Dudley, G. B.; Danishefsky, S. J.; Sukenick, G. *Tetrahedron Lett.* **2002**, *43*, 5605. (d) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569. (e) Snider, B. B.; Shi, B. *Tetrahedron Lett.* **2001**, *42*, 9123. (f) Magnus, P.; Waring, M. J.; Ollivier, C.; Lynch, V. *Tetrahedron Lett.* **2001**, *42*, 4947. (g) Magnus, P.; Ollivier, C. *Tetrahedron Lett.* **2002**, *43*, 9605. (h) Mehta, G.; Umarye, J. D. *Org. Lett.* **2002**, *4*, 1063. (i) Mehta, G.; Umarye, J. D.; Gagliardini, V. *Tetrahedron Lett.* **2002**, *43*, 6975. (j) Mehta, G.; Umarye, J. D.; Srinivas, K. *Tetrahedron Lett.* **2003**, *44*, 4233. (k) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063. (l) Nakazaki, A.; Sharma, U.; Tius, M. A. *Org. Lett.* **2002**, *4*, 3363. (m) Boyer, F.-D.; Hanna, I. *Tetrahedron Lett.* **2002**, *43*, 7469. (n) Du, X.; Chu, H. V.; Kwon, O. *Org. Lett.* **2003**, *5*, 1923. (o) Brummond, K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491.

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(10) Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett.* **2003**, *5*, 0000.

(11) Srikrishna, A.; Anebouselvy, K. *Tetrahedron Lett.* **2002**, *43*, 2769.

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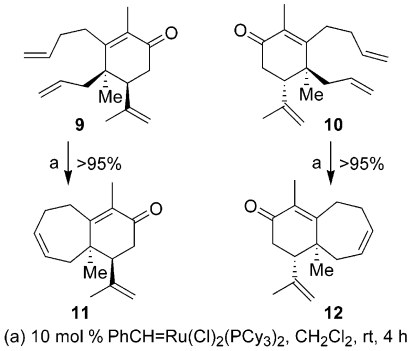
methylcarvone **5**. Reversing the sequence of alkylations transformed **3** into the *trans*-6-allyl-6-methylcarvone **6**. A butenyl side chain is to be introduced vicinal to the allyl group for the generation of the appropriate RCM precursor for the BC ring system of guanacasterpenes, and an efficient 1,3-alkylative enone transposition strategy[15] was exploited. Accordingly, sonochemically accelerated Barbier reaction of enones **5** and **6** with lithium and 4-bromo-1-butene furnished the allylic tertiary alcohols **7** and **8**, which on oxidation with pyridinium chlorochromate (PCC) and silica gel in methylene chloride generated the RCM precursors, the enones **9** and **10**. Treatment of the compound **9** with 10 mol % of Grubbs first-generation catalyst [PhCH═Ru(Cl)$_2$(PCy$_3$)$_2$] in methylene chloride at room temperature furnished the cyclized product **11** in nearly quantitative yield. In a similar manner,

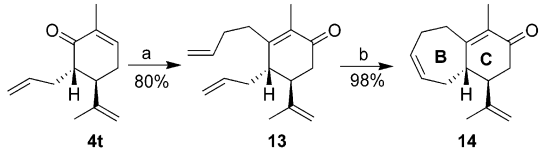


RCM reaction of compound **10** furnished the cyclized product **12** in near quantitative yield. Since the isopropenyl group can be considered as a masked hydroxy group at C-11 (ca. guanacastepene F), compounds **11** and **12** represent the BC ring system of guanacastepenes. Degradation of the isopropenyl group and further elaboration of **11** and **12** would obviously generate opposite enantiomers of guanacastepenes as the stereochemistry at the ring junction is opposite in **11** and **12**. It is worth mentioning that the present strategy, in addition to the generation of optically active BC ring system of guanacastepenes, is also very simple and efficient when compared to various strategies reported so far. It was readily identified that the enantiospecific methodology developed for the efficient construction of BC ring system of guanacastepene, can be further extended to the BC ring system of rameswaralide (**2**). Thus, silica gel column chromatography of the epimeric mixture of 6-allylcarvone furnished the pure *trans*-isomer **4t**. Sonochemically accelerated Barbier reaction of **4t** with lithium and butenyl bromide followed by oxidation of the resultant tertiary alcohol with PCC and silica gel furnished the transposed enone **13** in 80% yield. RCM reaction of the compound **13** with Grubbs catalyst furnished the cyclized product **14**, containing the BC ring system of rameswaralide **2** including the *trans*-stereochemistry of the isopropenyl group and ring junction hydrogen and the ketone group at C-13 position.

(13) Few other research groups have also employed RCM reaction for the generation of the seven-membered ring.[8d,h−j,l,m]

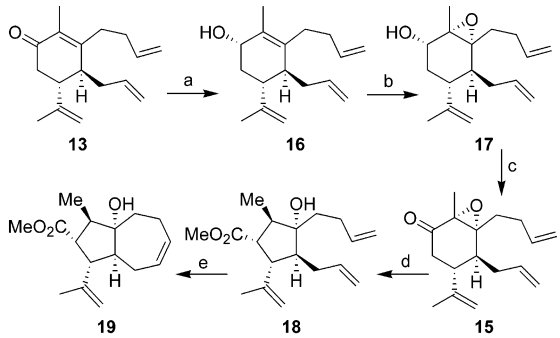
(14) Gesson, J.-P.; Jacquesy, J.-C.; Renoux, B. *Tetrahedron* **1989**, *45*, 5853−5866.

(15) Buchi, G.; Egger, B. *J. Org. Chem.* **1971**, *36*, 2021.



After successfully accomplishing the BC ring systems of guanacastepenes and rameswaralide, attention was turned to the construction of AB ring systems of these tricyclic diterpenes. It was conceived that the same intermediates can be employed for the construction of AB ring systems of guanacastepenes and rameswarlide by contracting the cyclohexane to cyclopentane ring in the compounds **11**, **12**, and **14**. For convenience, the ring contraction was investigated on the compounds **9**, **10**, and **13**, i.e., prior to the construction of B ring by RCM reaction. Rearrangement of an α,*β*-epoxy ketone was explored for the ring contraction. First, attention was focused on the construction of the AB ring system of rameswaralide from the enone **13** via the epoxide **15** (Scheme 3). Since the direct nucleophilic epoxidation of the enone **13** was unsuccessful, and also keeping in mind that the AB ring junction is *cis* in rameswaralide, an hydroxy directed epoxidation was employed.

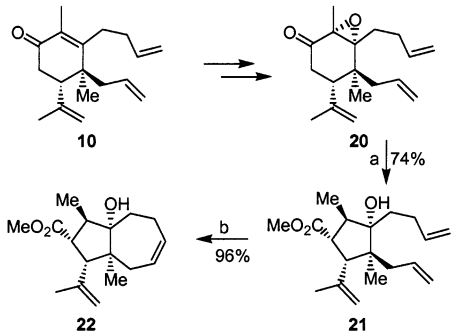
Scheme 3[a]



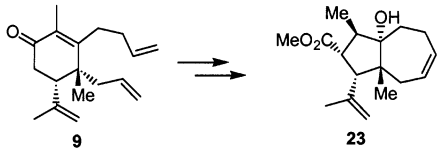
[a] Reagents, conditions, and yields: (a) LAH, Et$_2$O, −70 °C, 2 h, 95%; (b) *m*-CPBA (1 equiv), CH$_2$Cl$_2$, NaHCO$_3$, 0 °C, 1 h, 65%; (c) PCC, silica gel, CH$_2$Cl$_2$, rt, 6 h, 90%; (d) (i) NaOMe, MeOH, reflux, 1 h, (ii) CH$_2$N$_2$, Et$_2$O, 0 °C, 2 h, 75%; (e) 10 mol %, PhCH═Ru(Cl)$_2$(PCy$_3$)$_2$, CH$_2$Cl$_2$, rt, 2 h, 95%.

Thus, reduction of the enone **13** with lithium aluminum hydride (LAH) in ether at low temperature produced the syn allylic alcohol **16** in a highly diastereoselective manner. Reaction of the allyl alcohol **16** with 1 equiv of *m*-chloroperbenzoic acid (*m*-CPBA) in methylene chloride at ice temperature furnished the epoxide **17** in a highly regio- and stereoselective manner, which on oxidation with PCC and silica gel in methylene chloride furnished the epoxyketone **15**. A Favorskii-type ring contraction was explored. Thus, treatment of the epoxyketone **15** with sodium methoxide in refluxing methanol followed by esterification of the product with diazomethane furnished the cyclopentanecarboxylate **18** in 75% yield. Quite expectedly, RCM reaction of the ester **18** with 10 mol % of Grubbs first-generation catalyst furnished the cyclized product **19** in nearly quantita-

tive yield. Since the isopropenyl group is a masked hydroxy group at C-6 position, the ester **19** represents the AB ring system of rameswaralide including the *cis*-ring junction and the presence of a methyl group at C-4 position. Subsequently, enantiospecific construction of the AB ring system (hydroazulene part) of guanacastepenes was investigated following a similar strategy via the ketoepoxide **20**. Analogous to the preparation of **15**, a three-step sequence viz. reduction, epoxidation, and oxidation transformed the enone **10** into the ketoepoxide **20** in a highly regio- and stereoselective manner. Treatment of the ketoepoxide **20** with sodium methoxide in refluxing methanol followed by diazomethane esterification furnished the ester **21** in 75% yield. RCM reaction of the ester **21** with 10 mol % of Grubbs first-generation catalyst furnished the cyclized product **22**. Same sequence of reactions transformed the enone **9** into the bicyclic ester **23**.



Reagents, Conditions and Yields: (a) i. NaOMe, MeOH, reflux, 1 h; ii. CH_2N_2, Et_2O, 0 °C, 2 h; (b) CH_2Cl_2, rt, 10 mol % $PhCH{=}Ru(Cl)_2(PCy_3)_2$, 2 h.



The stereostructures of the bicyclic esters **22** and **23** were established from their spectral data and were finally confirmed by the single-crystal X-ray diffraction analysis[16] of the ester **22**, which is depicted in Figure 2. Compound **22** is an analogue of the AB ring system of guanacastepene including the correct stereochemistry at the C-6 and C-7 positions and also *cis* ring junction. Accordingly, ester **23** is an analogue of the AB ring system of 6-epiguanacastepene. However, compounds **22** and **23** have extra secondary methyl and ester groups at C-4- and C-5 carbons when compared

(16) Crystal data for **22**: X-ray data were collected at 293K on a SMART CCD-BRUKER diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.7107$ Å). Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F2 using SHELXL-97. The non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were refined isotropically. Compound **22**: $C_{17}H_{26}O_3$; MW = 278.38; colorless crystal; crystal system, orthorhombic; space group P2-(1)2(1)2(1); cell parameters, $a = 8.603(6)$ Å, $b = 9.260$ (7) Å, $c = 19.568$-(14) Å; $V = 1559.04$ Å^3, $Z = 4$, $D_c = 1.186$ g cm^{-3}, $F(000) = 608.0$, $\mu =$ 0.08 mm^{-1}. Total number of l.s. parameters = 186, R1 = 0.0427 for 2625 $F_o > 4\sigma(F_o)$ and 0.0468 for all 2860 data. wR2 = 0.1060, GOF = 1.085, restrained GOF = 1.085 for all data. An ORTEP diagram of compound **22** with 50% ellipsoidal probability has been shown in Figure 2. Crystallographic data is being deposited with Cambridge Crystallographic Data Center (CCDC 222214).

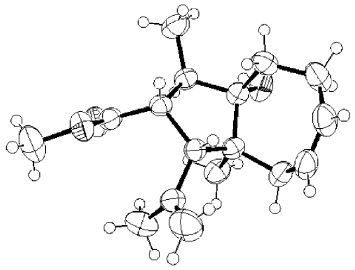
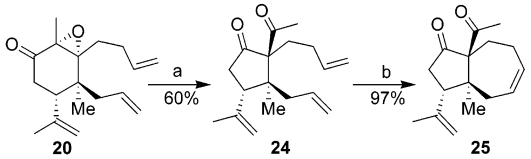


Figure 2. X-ray structure of **22**.

to guanacastepenes. To generate functionalized AB ring system of guanacastepenes, an alternative Lewis acid mediated ring contraction of the ketoepoxide **20** was tried. Thus, treatment of the ketoepoxide **20** with boron trifluoride etherate in methylene chloride at room temperature furnished the ring contracted β-diketone **24**. RCM reaction of the β-diketone **24** with 10 mol % of Grubbs first generation catalyst in methylene chloride at room temperature furnished the cyclized product **25** in nearly quantitative yield.[17] Compound **25** represents a typical AB ring system of guanacastepenes containing the correct stereochemistry at the C-6 and C-7 positions. The additional acetyl group at the ring junction (at C-3) can easily be removed since it is part of a β-diketone.



In conclusion, we have developed a very simple and efficient approach for the BC ring systems of the novel diterpenes guanacastepenes and rameswaralide starting from the readily and abundantly available monoterpene (*R*)-carvone employing RCM reaction as the key step. The methodology also provides either enantiomer of the BC ring system of guanacastepenes. Key intermediates used in this strategy have been further exploited and were conveniently converted into the AB ring systems of guanacastepenes and rameswaralide. Currently, we are investigating further elaboration of these ring systems first into ABC ring systems of these diterpenes and then to the natural guanacastepenes and rameswaralide.

Acknowledgment. We thank the CCD facility of I.I.Sc. for providing the X-ray diffraction data.

Supporting Information Available: Characterization data for all the compounds and copies of the ^{13}C NMR spectra of **5**, **6**, **9**−**15**, and **18**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The structure of **25** was established from its spectral data and further confirmed by single-crystal X-ray diffraction analysis.