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Stereoselective Total Syntheses of Guanacastepenes N and O

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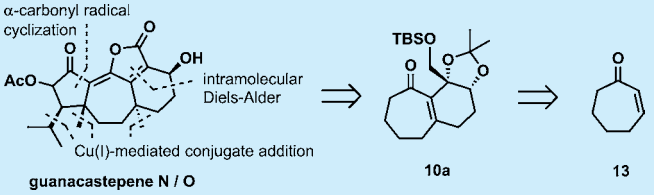
Supporting Information

ABSTRACT: Total syntheses of (±)-guanacastepenes N and O were accomplished with 2-cycloheptenone as starting material. The six- and five-membered rings of the core [5, 7, 6] ring skeleton were constructed with an intramolecular Diels–Alder reaction and α-carbonyl radical cyclization. The quaternary centers and their stereochemistry were established with sequential Cu(I)-mediated conjugate additions. A sequence with dihydroxylation, conjugate addition, and β-elimination was devised to incorporate all oxygen functionalities at positions. The total synthesis is adaptable for the synthesis of enantiopure guanacastepenes N and O using chiral intermediate (*R*)-3-vinyl-2-cycloheptenol obtained from lipase-catalyzed kinetic resolution.



Guanacastepenes constitute a family of 15 novel diterpenes with linearly fused five-, seven-, and six-membered rings as the core structure. They were isolated from an unidentified endophytic fungus collected in Guanacaste Conservation Area in Costa Rica by Clardy's group.[1] Among them, guanacastepene A was found to exhibit excellent antibiotic activity against both methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*.[2] The moderate activity of guanacastepenes against Gram-positive bacteria and an average activity against Gram-negative bacteria demonstrated their great potential to be a new lead for antibiotics.[3] However, the hemolytic activity to human red blood cell was a drawback, which could be decoupled from antibiotic activity by structure modification.[4]

Due to their novel complicated structures and intriguing antibiotic activity, guanacastepenes have attracted much attention from synthetic chemists in the past decade. Total syntheses of guanacastepenes A, C, E, N, and O (Figure 1) have been achieved via diverse synthetic strategies.[4]

Our plan for the total syntheses of guanacastepenes N and O is shown in Scheme 1. In the key step, we planned annulation of five-membered ring via α-carbonyl radical cyclization of iodoketone **8**,[5] which would afford linearly fused core structure **7**. Compound **7** could be transformed into furan **6**. Lactone **4**

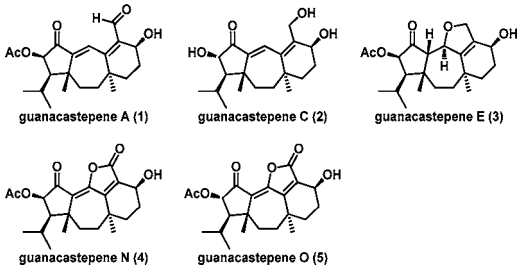
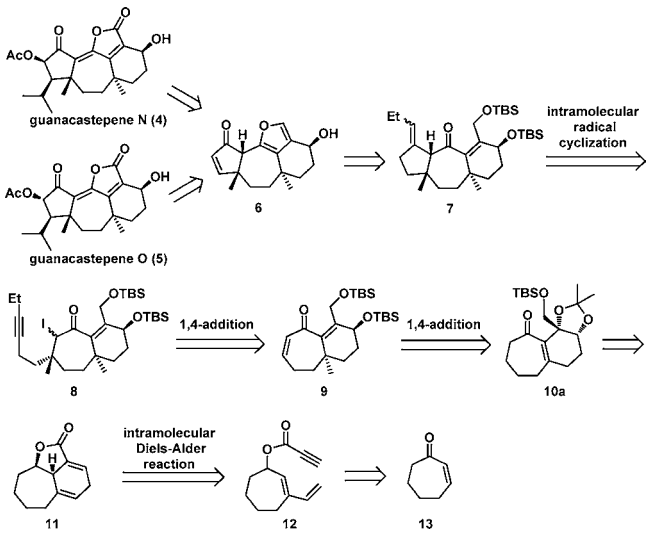


Figure 1. Guanacastepenes A, C, E, N, and O.

Scheme 1. Retrosynthesis of Guanacastepenes N and O



or **5** could be obtained on oxidation of furan **6**. Compound **8** would be prepared from dienone **9** according to the method developed in our group.[6] Key intermediate **9** with all hydroxyl substituents at desired positions would be prepared from **10a** by a conjugate addition–elimination protocol that was incidentally discovered during our work. Enone **10a** should be readily obtained from **11**. Compound **11** was obtained from an intramolecular Diels–Alder reaction of compound **12**, which was readily prepared from **13** using conventional methods. The isopropyl group on the five-membered ring and two methyl groups on the quaternary carbons would be all introduced by 1,4-conjugate addition to enone moieties.

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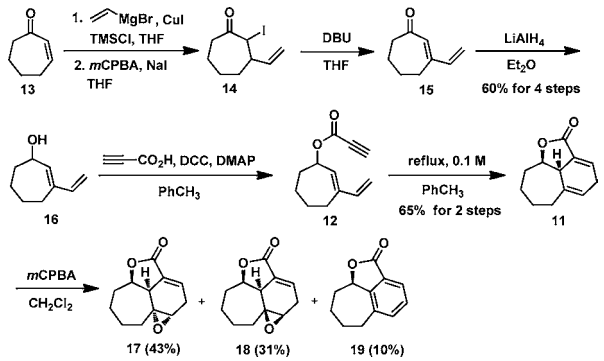
Our total synthesis commenced with 1,4-addition of vinylmagnesium bromide to 2-cycloheptenone (Scheme 2).[7]

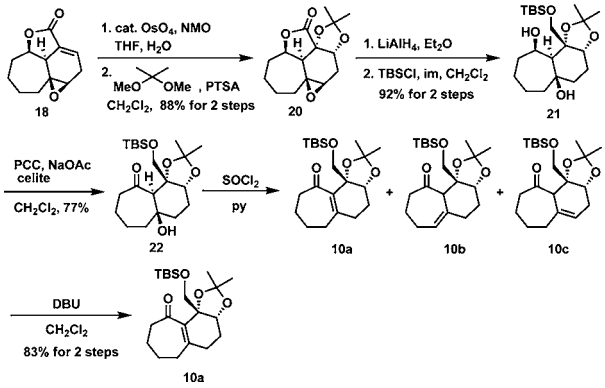
Scheme 2. Synthesis of Compounds 17 and 18



Trapping of the resulting enolate with TMSCl yielded TMS-enol ether, which without purification was iodinated with NaI and *m*CPBA in THF to give α-iodoketone **14**.[8] Elimination of HI from **14** by DBU afforded dienone **15**. Reduction of **15** with LAH furnished dienol **16** in 60% overall yield from **13**. Esterification of **16** with propiolic acid in the presence of DCC and DMAP yielded ester **12**. Intramolecular Diels–Alder reaction of **12** smoothly generated diene-lactone **11**.[9] Intermediate **11** was treated with *m*CPBA to give a mixture of α-epoxy-lactone **17**, β-epoxy-lactone **18**, and a small amount of aromatized product **19**, which were separated by silica-gel column chromatography. X-ray analysis of compound **18** confirmed its stereochemistry (see Supporting Information).

With β-epoxide **18** at hand, a highly diastereoselective dihydroxylation followed with diol protection gave β-epoxy lactone **20** in 88% yield (Scheme 3). LAH reduction of **20** led

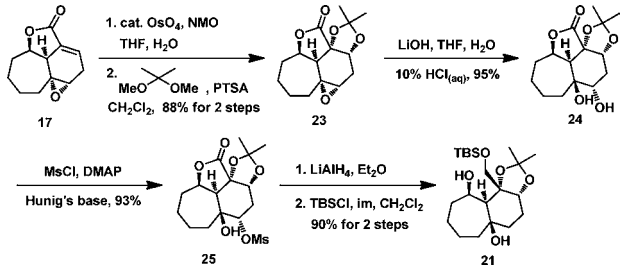
Scheme 3. Synthesis of Enone 10a



to a triol, which was treated with TBSCl to give diol **21** in 92% yield. Oxidation of the secondary alcohol in **21** gave ketone **22** in 77% yield. Dehydration of **22** with thionyl chloride in pyridine gave a mixture of conjugated enone **10a** and its deconjugated isomers **10b** and **10c**. The mixture was treated with DBU to give **10a** as a single isomer.[10] X-ray crystallographic analysis confirmed the stereochemistry of **10a** and **22** (see Supporting Information).

Alternatively, dihydroxylation of α-epoxy-lactone **17** and protection of the resulting diol portion afforded acetonide **23** (Scheme 4). The epoxide in **23** was then opened under basic conditions to give lactone **24**. The stereochemistry of **23** and

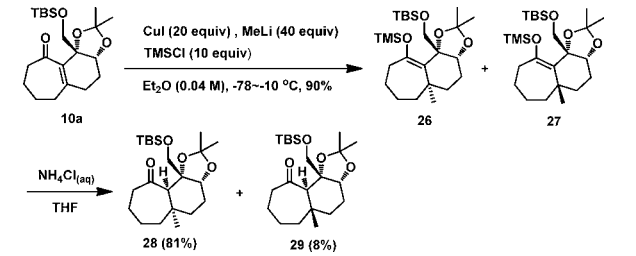
Scheme 4. Synthesis of Diol 21



24 was again confirmed with X-ray crystallographic analysis (see Supporting Information). Selective mesylation of secondary alcohol in **24** followed by LAH reduction of lactone portion yielded a triol. The primary alcohol group was then selectively protected with TBSCl/imidazole to afford diol **21**, which is identical to compound **21** prepared from β-epoxide-lactone **18**.

At this point, we tried conjugate addition of lithium dimethylcuprate in the presence of TMSCl to enone **10a**, but no desired product was detected. We found that addition of lithium dimethylcuprate in excess amount (20 equiv) was required to produce TMS-enol ethers **26** and **27** in 90% yield with a stereoselectivity 10:1 in favor of the α-face attack (Scheme 5). This mixture was then treated with ammonium

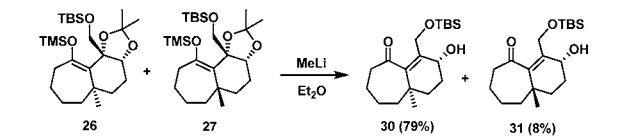
Scheme 5. Synthesis of Compounds 28 and 29



chloride to afford ketones **28** and **29**. The stereochemistry of **28**, after separation on a column chromatograph, was assigned with a NOE experiment (see Supporting Information).

The mixture of TMS-enol ethers **26** and **27** was treated with MeLi to perform β-elimination and removal of the acetonide group in one step to furnish enones **30** and **31** (Scheme 6).

Scheme 6. Synthesis of Enones 30 and 31 via β-Elimination Reaction



To invert the stereochemistry of the hydroxyl group in **30**, we performed a Mitsunobu reaction to convert the α-alcohol **30** to benzoyl ester **32** (Scheme 7). Hydrolysis of **32** followed by protection of the secondary alcohol with a TBS group gave **33**. Treatment of enone **33** with LDA and TMSCl followed by Saegusa oxidation afforded dienone **9**.[11]

After the construction of the fused [7,6] ring system, dienone **9** was reacted with 3-hexynemagnesium bromide in the presence of CuI and TMSCl and then treated with NaI/*m*-CPBA to give α-iodoketone **34** in 91% yield as a mixture of

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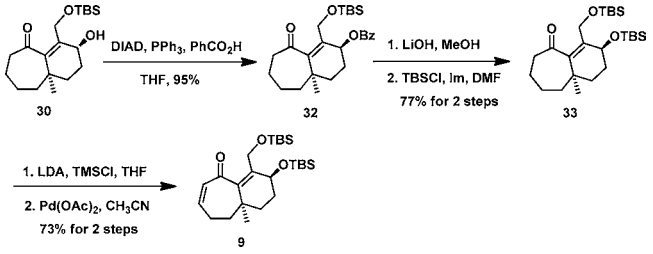
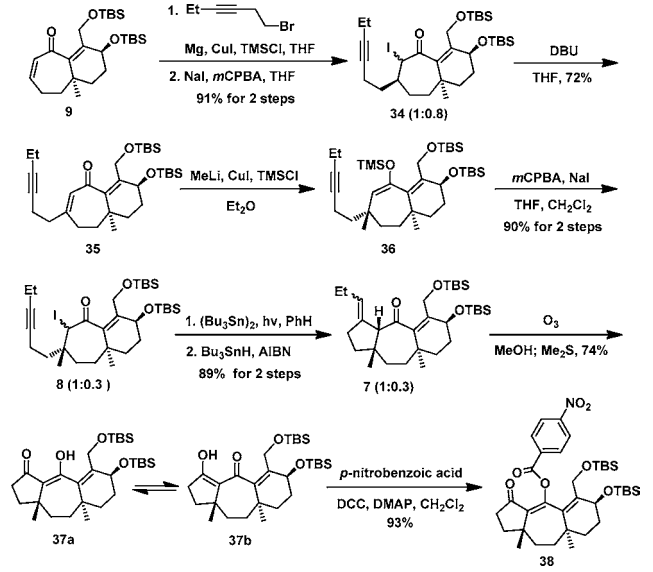
Scheme 7. Synthesis of Dienone 9



diastereomers (*dr* = 1:0.8) (Scheme 8). Elimination of HI from **34** with DBU furnished dienone **35**. Reaction of **35** with

Scheme 8. Synthesis of Compounds 37a, 37b, and 38



lithium dimethylcuprate in the presence of TMSCl furnished **36** as a single diastereomer. Crude **36** was treated with NaI/*m*-CPBA afforded α-iodoketone **8** as a mixture of two diastereomers (*dr* = 1:0.3). Iodine-atom transfer cyclization of **8** followed by reduction with tributyltin hydride/AIBN gave ketone **7** as a mixture of *E* and *Z* isomers (*E*/*Z* = 1:0.3).[12] Ozonolysis of **7** gave products **37a** and **37b** as a mixture of enol/keto tautomers.

To confirm the structure, the enol/keto mixture was treated with *p*-nitrobenzoic acid to give *p*-nitrobenzoate **38** as a single compound. The structure of **38** was determined with X-ray crystallographic analysis (Figure 2).

To continue our synthesis, tautomers **37a** and **37b** were treated with benzoic acid to afford compound **39** (Scheme 9). Formation of TMS-enol ether from **39** followed by Saegusa oxidation provided the desired enone **40** in 81% yield.[13] To install the isopropyl group, we performed Cu(I)-mediated conjugate addition, but the bridgehead methyl group in **40** directed the conjugate addition of isopropyl from the α-face, which led to undesired epimer. To tackle this problem, we first converted the planar hydroazulene ring system into a convex hydroazulene structure. Benzoate **40** was thus hydrolyzed with lithium hydroxide to afford enol **41**. Removal of both TBS groups of **41** with hydrochloric acid followed by dehydration furnished furan **6**. The stereochemistry of **6** was confirmed with a NOE experiment (see Supporting Information). Conjugate addition of isopropylmagnesium chloride from the convex face

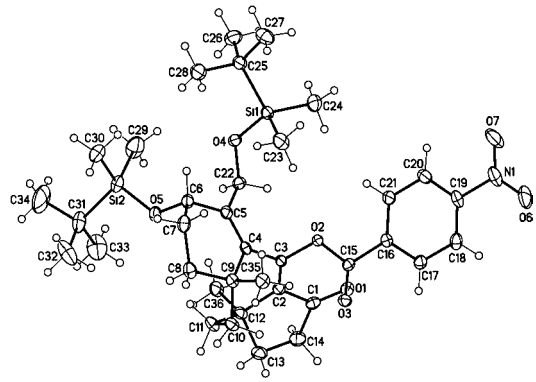
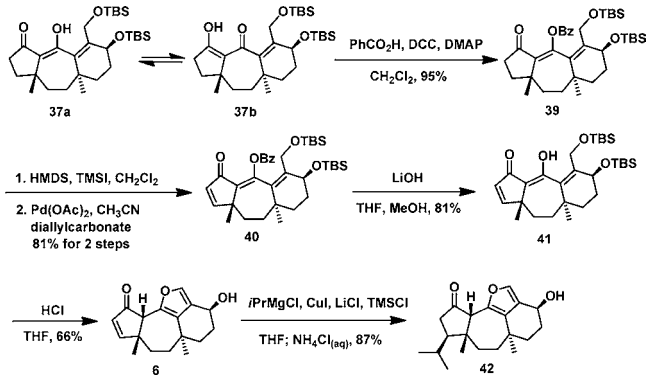


Figure 2. X-ray crystal structure of **38**.

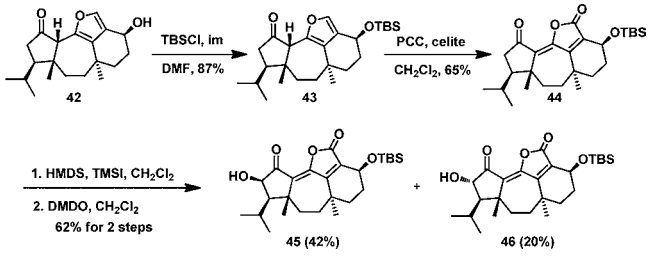
Scheme 9. Synthesis of Furan 42



of the hydroazulene system of furan **6** produced **42** as a single diastereomer in 87% yield. The stereochemistry of **42** was also determined with a NOE experiment (see Supporting Information).

The secondary alcohol in furan **42** was protected with a TBS group to give **43**. Compound **43** was oxidized with PCC to afford unsaturated lactone **44** (Scheme 10).[14] Compound **44** was then converted into the corresponding TMS-enol ether and then exposed to DMDO to give compounds **45** and **46** (2:1),[15,16] which were separated by column chromatography.

Scheme 10. Synthesis of Lactones 45 and 46



The synthesis of guanacastepene N was eventually completed on acetylation and deprotection of the TBS group from **45**. Guanacastepene O was obtained with the same procedure from **46** (Scheme 11).

Furthermore, we prepared chiral dienol **16** by CALB-catalyzed kinetic resolution (Scheme 12).[17] Treatment of racemic **16** with vinyl acetate and CALB gave (*S*)-**16** in 47% yield (99% ee) and (*R*)-**49** in 45% yield (98% ee). The absolute configuration of (*S*)-**16** was determined with X-ray analysis of *p*-nitrobenzoyl derivative (*S*)-**50** (see Supporting Information).

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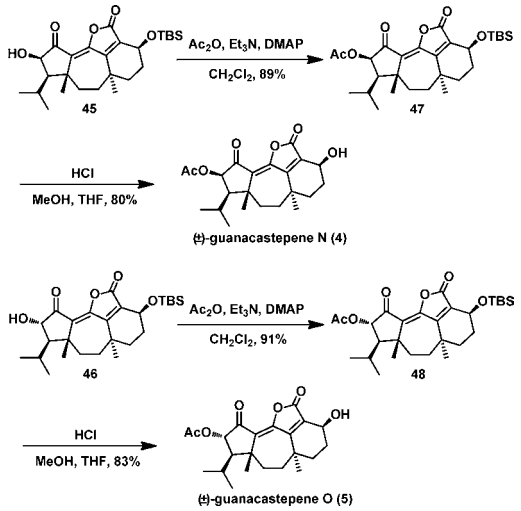
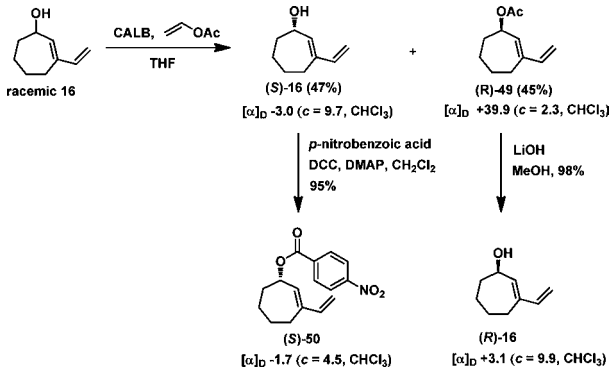
Scheme 11. Synthesis of Guanacastepenes N and O



Scheme 12. Synthesis of Chiral Dienol (*R*)-16



Hydrolysis of (*R*)-**49** afforded (*R*)-**16**, which could be used to prepare the enantiomerically pure guanacastepenes N and O.

In conclusion, we completed a stereoselective total syntheses of (±)-guanacastepenes N and O in 41 steps from 2-cycloheptenone via intramolecular Diels–Alder reaction and α-carbonyl radical cyclization. A novel and efficient conjugate addition–elimination protocol was discovered and used to incorporate all hydroxyl substituents at desired positions in key intermediate **9**. In this synthesis, five stereogenic centers were induced, each in a stereoselective manner from a single stereocenter of intermediate **16**.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectral and analytical data of all new compounds, and X-ray structural data (CIF files) of compounds **10a**, **18**, **22**, **23**, **24**, **38**, and (*S*)-**50**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01498.

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Notes

The authors declare no competing financial interest.

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