Cyclohexyne in Total Synthesis

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Total Syntheses of Guanacastepenes N and O**

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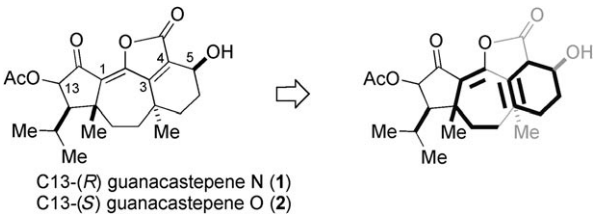
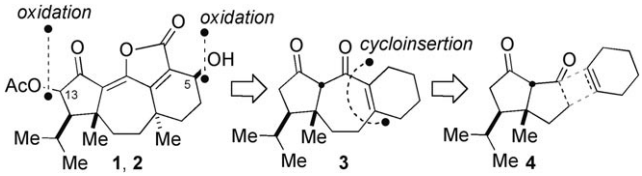
The guanacastepenes, a structurally diverse family of 15 diterpenes, were isolated in 2001.[1] The reported antibiotic activity of some of these compounds and their unprecedented tricyclic carbon scaffold piqued the interest of a number of research groups,[2] whose studies culminated in the total syntheses of a subset of this class of terpenes, namely guanacastepenes A,[3,4] C,[5] E,[4,6] and N.[7] Herein, we describe the application of a cyclohexyne cycloinsertion reaction in a bifurcated synthesis to access both C13-acetate diastereomers, guanacastepene N (**1**) and guanacastepene O (**2**) (Scheme 1).[8] In the course of the investigations, we observed that late-stage oxidation at C13 by employing Mn^{III} or Os^{VIII} results in a complementary stereochemical outcome, with the latter proceeding through an intriguing oxidative cascade involving dehydrogenation at C3 and C4 and hydroxylation at C13.



Scheme 1. Guanacastepenes N (**1**) and O (**2**) assembled by cyclohexyne cycloinsertion. Bonds/substituents introduced during these key steps or after are shown in gray.

A screening for antibiotic compounds in the extracts from a previously undescribed basidiomycete found in the eponymous Guanacaste Conservation Area in Costa Rica led to the identification of numerous polycyclic isoprenoids termed guanacastepenes.[1] The carbon framework of the guanacastepenes is unprecedented, comprising of annealed five-, seven-, and six-membered rings with two quaternary centers. In the case of guanacastepenes N and O, the underlying scaffold is decorated at the periphery with a ketone, a lactone, an alcohol, and an ester as well as double bonds between C1 and C4. Collectively, the guanacastepenes have inspired a host of innovative synthetic studies en route to the polycyclic array.[2–7] Analysis of the various approaches underscores that late-stage oxidation of the C13–C14 enol ether of the tricyclic core leads to installation of the hydroxy group with a β configuration (*R*) at C13.[3,4,7,9]

The amphiphilic structural characteristics of the guanacastepenes encode interesting biological activities, which have not been subjected to extensive scrutiny. Antibiotic activity against drug-resistant strains of *E. faecalis* and *S. aureus* along with hemolytic activity and the ability to cause K^+ efflux from *E. coli* has been reported for some members of the guanacastepene family.[1b,c] During the study of membrane-active antimicrobial natural products in our laboratory, the guanacastepenes became of interest.[10] We recently reported a novel annulation reaction involving cyclohexyne, whereby *n*-membered cyclic ketones are transformed into [(*n*+2).4.0] bicyclic scaffolds.[8] Consequently, a program aimed at the divergent syntheses of the guanacastepenes was embarked upon to investigate the implementation of the cyclohexyne ring insertion reaction in a complex setting. In particular, a versatile strategy to the guanacastepenes was envisioned, including enone **3** as the common 5-7-6 scaffold of this class of natural products (Scheme 2). Guanacastepenes N (**1**) and O (**2**) would then be accessible by stereocontrolled oxidative functionalization at C5 and C13. Enone **3** could be employed for the installation of the C8 methyl group, and in turn the 5-7-6 ring system could arise from pentalenone **4** by cycloinsertion of cyclohexyne.



Scheme 2. Retrosynthesis for guanacastepenes N (**1**) and O (**2**) involving cyclohexyne cycloinsertion.

The synthesis commenced with a two-step preparation of known cyclopentenone **7** (Scheme 3).[11] Copper-catalyzed conjugate addition of the organomagnesium reagent formed from (2-bromoallyl)trimethylsilane to commercially available enoate **5** yielded ester **6** (96%). Upon exposure of **6** to CsF, intramolecular allylation occurred followed by isomerization to give cyclopentenone **7** in 59% yield over two steps. The but-3-enyl moiety was added to **7** by using a Lipshutz higher-order cyanocuprate,[12] which led to the installation the first

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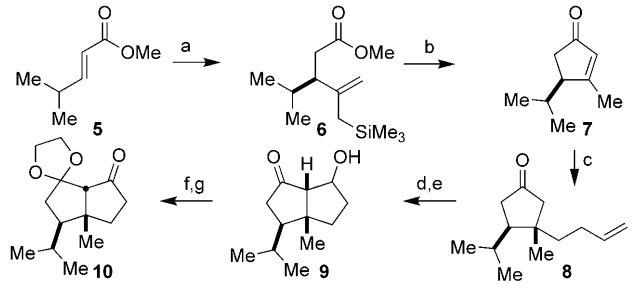
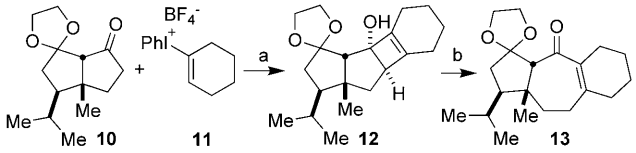


Scheme 3. Reagents and conditions: a) (3-(TMS)-prop-1-en-2-yl)MgBr, $CuBr{\cdot}SMe_2$ (4 mol%), HMPA, TMSCl, THF −40°C, 96%; b) CsF, DMSO, RT, 60%; c) but-3-enyllithium, lithium 2-thienyl-CuCN, $BF_3{\cdot}OEt_2$, THF, −78°C, **8**: 51%, **7**: 28%, 2× recycling: 70%, d.r. > 95:5; d) OsO_4 (5 mol%), NMO, aq THF; $NaIO_4/SiO_2$, CH_2Cl_2; e) KOH, MeOH, RT; f) $(CH_2OH)_2$, $(EtO)_3CH$, *p*TsOH, RT; g) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78°C to RT, 53% over 4 steps. HMPA = $(Me_2N)_3PO$, TMS = Me_3Si, DMSO = Me_2SO, NMO = *N*-methylmorpholine-*N*-oxide, Ts = toluene-4-sulfonyl.

quaternary carbon atom. Ketone **8** was isolated in 51% yield and with an excellent substrate-induced diastereoselectivity of greater than 95:5 (by ^{1}H NMR spectroscopy). Recycling of re-isolated enone **7** allowed access to **8** in 70% yield (2 cycles). Oxidative olefin cleavage and aldol addition afforded β-hydroxy ketone **9** as a mixture of alcohol epimers.[13] After condensation of **9** with ethylene glycol and oxidation of the secondary alcohol under Swern conditions,[14] ketone **10** was obtained in four steps and 53% yield from **7**.

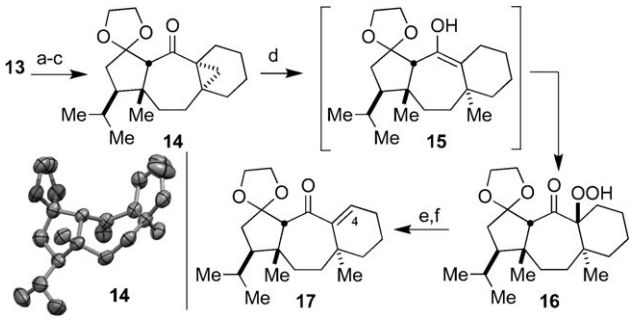
With **10** in hand, we were able to test whether the cyclohexyne ring insertion reaction would be effective in providing access to the tricyclic guanacastepene carbon scaffold. The enolate derived from **10** underwent diastereoselective addition to cyclohexyne, generated in situ from **11**, to deliver cyclobutenol **12** in 73% yield along with 13% recovered starting material (Scheme 4). In analogy to the



Scheme 4. Reagents and conditions: a) **11**, $KOCEt_3$, THF, −78°C to RT, **12**: 74%, **10**: 13%; b) $[Fe_2(CO)_9]$, benzene, 90°C then add DBU, 51%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

substrates previously reported,[8] cyclobutenol **12** underwent ring opening under basic conditions (KO*t*Bu, THF) to provide the desired 5-7-6 ring system. A mixture of conjugated and deconjugated enones was obtained along with products arising from dioxolane elimination. We, therefore, sought alternative conditions to effect the opening of the cyclobutenol intermediate. In this regard, exposure of **12** to $[Fe_2(CO)_9]$ in benzene at 90°C resulted in ring opening to give enone **13**. As a working hypothesis, we surmise that the reaction proceeds through a cycloheptanone derived dienol–$Fe(CO)_3$ complex.[15] Electrocyclic ring opening of cyclobutenes mediated by $[Fe_2(CO)_9]$ has been limited to simple hydrocarbons.[16] To the best of our knowledge, the conversion of **12** into **13** is the first application of this iron-mediated process in a complex setting. The implemented cyclohexyne insertion allowed access to the tricyclic core of the guanacastepenes in only nine steps from commerically available material.

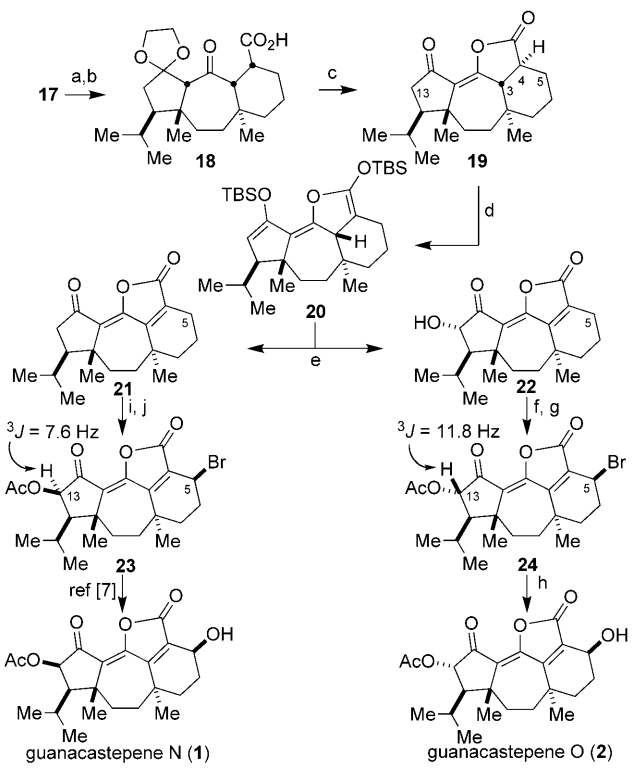
The second axial methyl group was installed diastereoselectively by execution of a modified Dauben protocol (Scheme 5).[17] Diastereoselective hydride delivery to enone



Scheme 5. Reagents and conditions: a) DIBAL-H, *n*BuLi, −78°C, 30 min, d.r. > 95:5; b) $ZnEt_2$, TFA, CH_2I_2, CH_2Cl_2, 0°C, 15 min, 61% over 2 steps; c) PDC, Ac_2O, CH_2Cl_2, RT, 99%; d) Li/NH_3, THF, then SiO_2, CH_2Cl_2, O_2; e) Me_2S, acetone, RT, 79% over 2 steps; f) $SOCl_2$, pyridine, RT, 95%. DIBAL-H = iBu_2AlH, TFA = F_3CCO_2H, PDC = pyridinium dichromate. In the crystal structure of **14** the ellipsoids are set at 50% probability.

13 from the convex face of the molecule was achieved through the use of a 1:1 mixture of DIBAL-H and *n*BuLi to obtain the corresponding allylic alcohol with > 95:5 diastereoselectivity,[18] as determined by ^{1}H NMR spectroscopic analysis. Subsequent application of Shi's modification of the Furukawa conditions ($ZnEt_2$, TFA, CH_2I_2) enabled directed cyclopropanation,[19] and after oxidation of the secondary alcohol ketone **14** was obtained in 60% yield over three steps. It is important to note that the use of Furukawa's conditions ($ZnEt_2$, CH_2I_2) generated a 1:1 mixture of diastereomeric cyclopropanes.[20] X-ray crystallographic analysis of crystalline **14** confirmed that the stereogenic centers had been installed as required.[21] Cleavage of the cyclopropyl ring under Birch conditions furnished stable enol **15**, which underwent oxidation in air when exposed to SiO_2 to yield hydroperoxide **16** in one operation.[22] Intermediate **16** was further converted into enone **17** by a reduction/elimination sequence in 75% yield from **14**.

Next in the synthesis was the introduction of the carboxy unit at C4 to access lactone **19** and the final oxidations at C3, C4, C5, and C13 (Scheme 6). To address the first task TMS-acetylene was added to enone **17** as a carboxy equivalent, by using $Me_2AlCCTMS$.[23] Alkaline workup (NaOMe) was necessary to tautomerize the intermediate enol, which otherwise underwent oxidation as previously seen for **15**. Oxidation of the alkyne with RuO_4 provided carboxylic acid **18**.[24] To avoid overoxidation of **18** it proved beneficial to stop the reaction after about 50% conversion and to resubject the

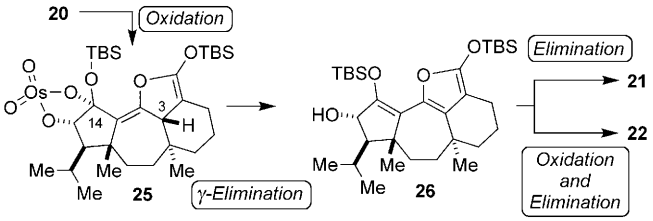


Scheme 6. Reagents and conditions: a) $Me_2AlCCTMS$, Et_2O, RT, then NaOMe, MeOH, 81%; b) $RuCl_3$, oxone, $NaHCO_3$, H_2O, MeCN, EtOAc, RT, 55% (1× recycling); c) HCl (0.1 M), THF, 57°C, then $(COCl)_2$, pyridine, CH_2Cl_2, 0°C, 15 min, 79%; d) *t*$BuMe_2SiOTf$, NEt_3, CH_2Cl_2; e) OsO_4, NMO, $MeSO_2NH_2$, acetone, HO*t*Bu H_2O, 0°C, over 2 steps: **21**: 40%; **22**: 29%, d.r. (α/β) = 9:1; f) Ac_2O, NEt_3, DMAP, CH_2Cl_2, RT, 87%; g) NBS, $(PhCOO)_2$, CCl_4, 80°C, 76%; h) Bu_3SnH, toluene, air, then PPh_3, 72%; i) $Mn(OAc)_3$, benzene, MS 3 Å, 80°C, 68%, d.r. (α/β) = 1:4; j) NBS, $(PhCOO)_2$, CCl_4, 80°C, 1 h, 58%. DMAP = 4-*N*,*N*-dimethylaminopyridine, NBS = *N*-bromosuccinimide, TBS = *tert*-butyldimethylsilyl.

isolated starting material to the same conditions. The sole protecting group of the synthesis was removed hydrolytically with aqueous HCl in THF. Rapid conversion of the carboxy ketone into lactone **19** was then effected by conversion into the corresponding acid chloride, which readily lactonized after epimerization at C4.

Exposure of **19** to TBSOTf/Et_3N furnished the corresponding bis-TBS-enol ether **20**. The reported oxidation procedures of the guanacastepene core, based on epoxidation of the C13–C14 enol ether, are known to yield predominantly the C13 β epimer (identified by a $^3J_{H13\text{-}H12}$ coupling constant of ca. 7 Hz). Consequently, we were surprised to observe that treatment of **20** with OsO_4 (cat. OsO_4, NMO, $MeSO_2NH_2$)[25] generated hydroxy ketone **22** along with C3–C4 dehydrogenated lactone **21** in 69% overall yield. Hydroxy ketone **22** was formed predominantly as the α diastereomer (d.r. = 9:1), as determined by ^1H NMR spectroscopy. Its configuration was established by analysis of the C12–C13 vicinal proton coupling constant of $^3J_{H13\text{-}H12} = 11.5$ Hz.

It is interesting that in the course of the reaction with OsO_4 the expected hydroxylation at C13 is observed along with dehydrogenation at C3–C4; the latter reaction has, to the best of our knowledge, not been documented previously. In the working hypothesis to account for the formation of **21** and **22** (Scheme 7), osmylation of the α face of enol ether **20** triggers an oxidative cascade that commences with osmate **25**, which undergoes vinylogous elimination to furnish furan **26**. This intermediate is positioned at a point of bifurcation and follows two different pathways: Elimination of the hydroxy group in **26** produces **21**, and oxidation of the furan generates **22**.



Scheme 7. Working model for the osmium-triggered oxidation cascade.

The products formed from **20** were each transformed into the targeted guanacastepenes (Scheme 6). Acylation of **22** set the stage for Wohl–Ziegler oxidation at C5, in analogy to a procedure described by Overman and co-workers,[7] which produced **24** in 76% yield. Subjecting **24** to Nakamura's conditions converted the bromide into guanacastepene O (**2**; 72%).[26] Access to guanacastepene N (**1**) from lactone **21** necessitated installation of the C13-acetate with β configuration. We found that the use of $Mn(OAc)_3$ provided the desired product (β/α = 4:1) in 68% yield,[27] which was subjected to the procedures described above to afford guanacastepene N (**1**).[7]

In summary, we have documented the rapid construction of the guanacastepene core through the implementation of a cyclohexyne cycloinsertion reaction. In this respect, an iron-carbonyl complex was used to facilitate the electrocyclic opening of the cyclobutene ring. The strategy developed includes an oxidative cascade that provides a point of divergence, thus enabling the synthesis of guanacastepene N (**1**) and the first total synthesis of guanacastepene O (**2**) from a common intermediate. The stereoselective late-stage oxidation was effected with reagents that display complementary stereoinduction (Os^{VIII} and Mn^{III}). The routes comprise a number of salient chemical transformations that allow chemo- and stereoselective access to these natural products, as evidenced by the use of only one protecting group. Access to both guanacastepenes N (**1**) and O (**2**) will enable further studies on the biological properties of these diterpene natural products.

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