Synthesis of the guanacastepene A–B hydrazulene ring system through photochemical ring transposition†

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The A–B hydrazulene ring system of the guanacastepenes has been synthesised using a photochemical ring transposition of a 6–6 bicycle.

In 2000 Clardy and co-workers reported the isolation of guanacastepene A, **1**, from an endophytic fungal strain growing in a branch of a *Daphnopsis americana* tree in the Guanacaste rainforest of Costa Rica (Fig. 1).[1] The natural product was isolated as part of a screening program which assayed fungal extracts for activity against drug-resistant strains of *Staphylococcus aureus* and *Enterococcus faecium*. Following the initial report on guanacastepene A, Clardy reported the isolation and characterisation of an additional fourteen structurally and chemically diverse guanacastepenes from the same fungus.[2]

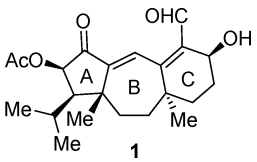
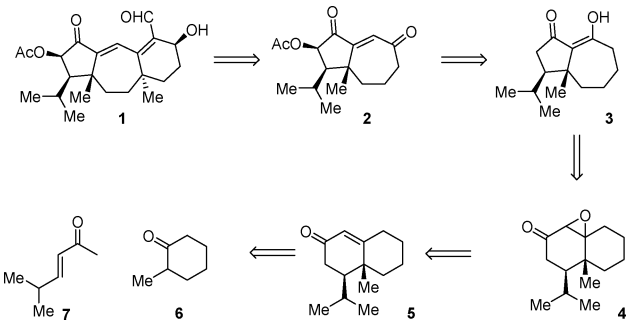


Fig. 1 Guanacastepene A.

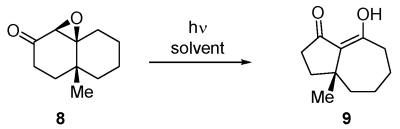
The novel carbon skeleton coupled with the highly promising antibiotic activity of guanacastepene A made the guanacastepenes excellent targets for chemical synthesis, and an intense level of synthetic activity ensued. Completed total syntheses of members of the guanacastepene family have been reported by Danishefsky (A),[3] Mehta (C),[4] Sorensen (E),[5] Overman (N)[6] and Trauner (E)[7] in addition to three formal syntheses and a variety of synthetic approaches.[8]

Our strategy for the synthesis of guanacastepene A is based upon the transposition of a 6–6 bicycle to the relevant 5–7 hydrazulene system found in the guanacastepenes. Accordingly, the tricyclic natural product is first disconnected back to the hydrazulene **2**. This AB → ABC strategy has proven to be popular, with the stereocontrolled installation of the third C ring from ketones such as **2** having being demonstrated by the Danishefsky and Snider research groups.[3,9] The 5–7 bicycle arises from the simpler hydrazulene **3**, which is the product of the key ring transposition: a photochemical rearrangement of keto-epoxide **4**. The decalin structure can be synthesised through a Robinson condensation of 2-methyl-cyclohexanone and 5-methyl-hex-3-en-2-one, or their synthetic equivalents (Scheme 1).



Scheme 1 Synthetic plan for guanacastepene A.

Initial work focussed on simple epoxy-ketone models of the key photochemical transposition—a reaction developed extensively by Jeger in the steroid field.[10] Paquette was the first to explore the reaction in the synthesis of non-steroidal natural products, using the transposition to synthesise the isoingenane and dolastane natural product skeletons.[11,12] Outside of these reports, this potentially powerful reaction has seen little application in complex molecule synthesis. We began by preparing the known epoxy-ketone **8** and were encouraged to find that irradiation in ethanol through a pyrex filter produced smooth transposition to the hydrazulene **9** in 50% isolated yield (Scheme 2). The chromophore-containing 1,3-diketone product **9** appears to undergo slow photodegradation under the reaction conditions, necessitating a compromise between conversion and isolated yield, an observation inline with previous studies on this reaction.[11] A brief screen of solvents established ethanol as being the medium of choice for the reaction.



Solvent	Yield of **9** (%)	Recov'd SM (%)
EtOH	50	25
MeCN	28	7
hexane	22	6
dioxane	49	16
MeCN/acetone (9:1)	0	0

Scheme 2 Photochemical transposition of simple epoxy-ketone **8**.

We next prepared the ketal-containing epoxy-ketone **11** *via* a five-step procedure starting from the diosphenol **10**, verifying the *cis*-arrangement of the epoxide and C11 methyl group in **11** with

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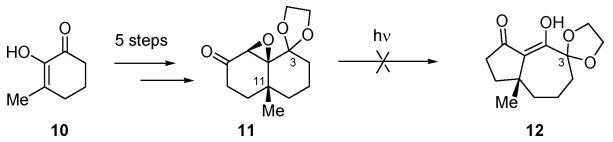
an X-ray structure (Scheme 3).‡ The aim here was to incorporate protected carbonyl functionality into C3 of the nascent B-ring that could be used as a starting point for future C-ring synthesis. Disappointingly, all efforts to transpose **11** into the corresponding hydrazulene met with failure. Extensive degradation of the keto-enol starting material was observed and no clean products could be isolated from the photoreactor. On the basis of this negative result, we turned our attention to synthesising a more highly-functionalised A-ring precursor, with the intention of oxidising the C3 position at a later point in the synthesis.

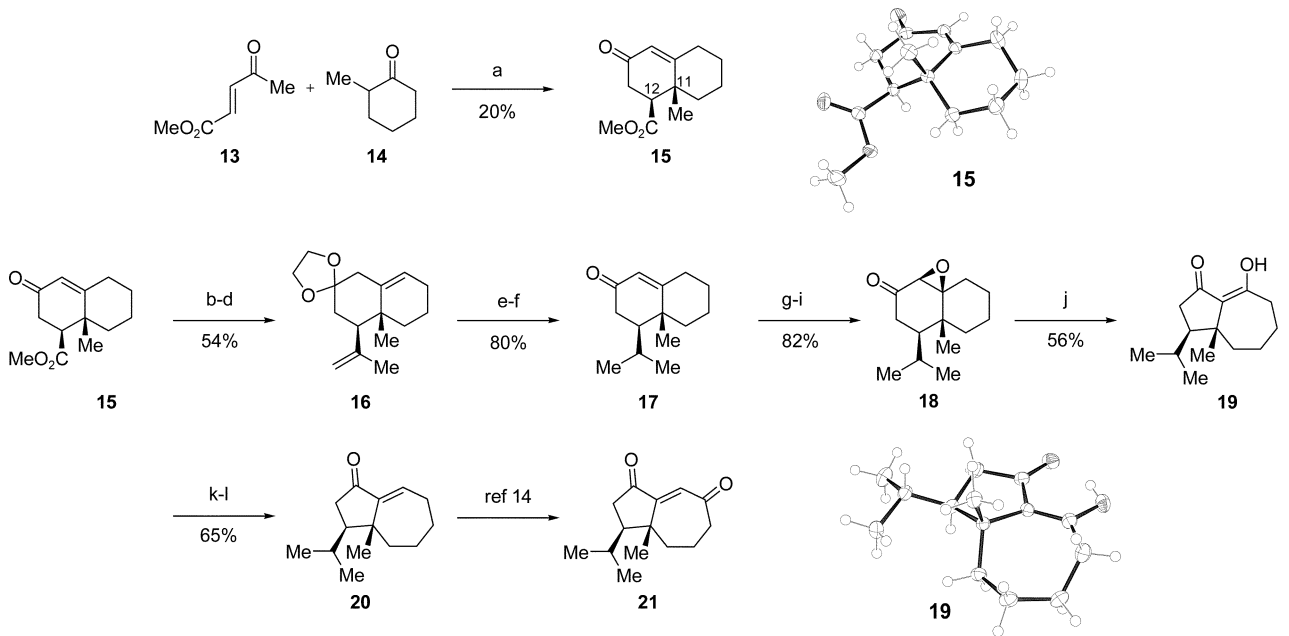


Scheme 3 Attempted transposition of ketal-containing epoxy-ketone **11**.

Construction of the guanacastepene A AB bicycle *via* the transposition route calls for the preparation of a 6–6 system having the *cis* isopropyl and methyl groups at C11 and C12 in place. This arrangement of a tertiary branched group adjacent to a quaternary centre is beyond the scope of Robinson annulation chemistry, as the initial Michael addition is very slow due to severe steric hindrance. As expected, all attempts to implement the reaction using the unactivated precursors **6** and **7** were unsuccessful. Activation at one, or both, of the isopropyl and methyl group appendages is required. After numerous trials, the literature condensation of enone-oate **13** with 2-methyl-cyclohexanone proved to be the most effective synthetic method (Scheme 4).[13] Whilst the yield of this procedure is a modest 20%, the operational simplicity and scalability of the reaction, being the first step in the route, made it the preferred method. In addition, the Robinson annulation product **15** is formed as a 10 : 1 mixture of diastereoisomers, in favour of the desired *cis* C11–C12 stereochemistry. Acid-catalysed epimerisation places the ester group in the more stable pseudo-equatorial position, confirmed by X-ray diffraction.‡

Functionalisation of **15** to the requisite ring transposition substrate **18** began with protection of the ketone as a ketal, accompanied by concomitant double bond migration. The ester moiety was then transformed into an isopropenyl group by treatment with two equivalents of MeLi followed by elimination of the resulting alcohol with $POCl_3$. Deketalisation gave an enone, which could be selectively hydrogenated (15 bar) at the isopropenyl group using Wilkinson's catalyst to afford enone **17**. The required epoxy-ketone photosubstrate **18** could be accessed through treatment of **17** with basic peroxide, but only in mediocre yield. It proved more efficient to first reduce the ketone, epoxidise the allylic alcohol with mCPBA, then reoxidise, producing keto-epoxide **18** as essentially a single diastereoisomer. The epoxide stereochemistry is assigned as β in line with the stereoselectivity observed in the analogous sequence during the synthesis of keto-epoxide **11**.

We were pleased to observe that irradiation of an ethanolic solution of **18** through a pyrex filter produced a clean transformation to the desired hydrazulene **19**, in similar yield to the simple model **8** (56% yield with 23% recovered SM). The expected retention of stereochemistry at the migrating C11 centre was confirmed by the X-ray crystal structure shown in Scheme 4. The enol oxidation level at C2 is found in the majority of the guanacastepenes, and may provide a useful functional handle for future elaboration of **19**. For the present time, however, we thought it prudent to reduce to the enone oxidation level *via* hydrogenolysis of the derived enol triflate. Enone **20** has been prepared previously by Chiu and



Scheme 4 Synthesis of **12**. *Reagents and Conditions*: (a) TsOH (cat), benzene, Dean–Stark, 48 h, (b) $HO(CH_2)_2OH$, TsOH (cat), benzene, Dean–Stark, (c) MeLi (2.5 equiv), THF, 0 °C, 18 h, (d) $POCl_3$ (3 equiv), pyridine, rt, 18 h, (e) TsOH (cat), acetone, reflux, 2.5 h, (f) $(PPh_3)_3RhCl$ (10 mol%), MeOH, H_2, 15 bar, rt, 12 h, (g) $NaBH_4$ (1.1 equiv), $CeCl_3{\cdot}7H_2O$ (2.2 equiv), MeOH, 0 °C, 1 h, (h) mCPBA (1.5 equiv), $NaHCO_3$ (2 equiv), DCM, 0 °C, 1.5 h, (i) PDC (2 equiv), DCM, 0 °C, 18 h, (j) hν (Hanovia 400 W medium pressure Hg lamp), EtOH, 0 °C, 9 h, (k) Tf_2O (2 equiv), iPr_2EtN (2 equiv), DCM, 0 °C, 1 h, (l) $Pd(OAc)_2$ (cat), PPh_3 (cat), Et_3N (3 equiv), HCO_2H (2 equiv), DMF, 60 °C, 4 h.

co-workers in their approach to guanacastepene A, and demonstrated to be a good substrate for allylic oxidation—providing a handle for eventual introduction of the C-ring.[14]

In conclusion, we have developed a novel approach to the guanacastepene AB hydrazulene using a photochemical transposition of a 6–6 system as the key step. Future work will examine functionalisation of the product hydrazulenones for the synthesis of the guanacastepene family of diterpenes.

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Notes and references

‡ CCDC reference numbers 638397–638399. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b704865c

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