Diastereoselective synthesis of an advanced intermediate of thapsigargin and other 6,12-guaianolides using a RCEYM strategy

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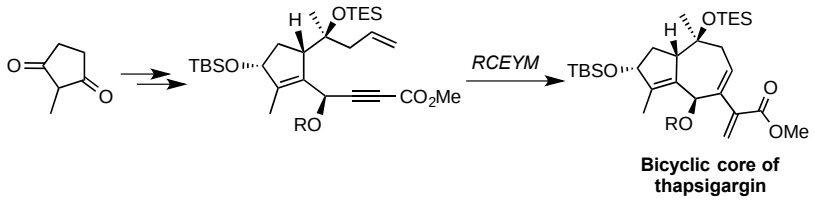
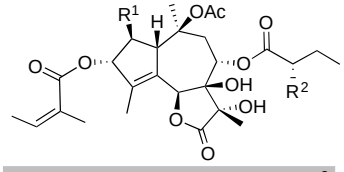
Supporting Information Placeholder



ABSTRACT: A new and flexible approach toward the synthesis of 6,12-guaianolide anticancer drugs such as trilobolides or thapsigargin is developed, which could be applied to the preparation of analogues with a modified ring system. The synthesis starts from commercial 2-methyl-cyclopentane-1,3-dione, only relying on diastereoselective reactions for the construction of the stereogenic centers at C1, C3, C6 and C10 and features a high-yielding ring-closing enyne metathesis (RCEYM) step for the formation of the [5,7] bicyclic core.

Cancer is still a major health issue and solutions for all facets of this problem include the continuous search for new active molecules. Among them, thapsigargin **1a** (Tg, Figure 1),[1] emerged during the last decade as a highly promising anticancer lead compound, and prodrug derivatives of **1a** are currently in phase II clinical trials directed toward a variety of cancers such as prostate cancer or hepatocellular carcinoma, as well as neovascular tissues in a broad range of other cancer cells.[2] This plant secondary metabolite, as well as its structurally closely related 2-deoxy natural congeners trilobolides **1b**, **1c**[3] or thapsivillosin F **1d**,[4] belong to the class of the 6,12-guaianolide sesquiterpenes[5] known for their prominent endo/sarcoplasmic calcium ATPase (SERCA) inhibitor activities.[6]

To date, three total syntheses of this class of guaianolides were reported with more than a 13-year gap between the first synthesis and the two most recent ones. The pioneering work of Ley's group in 2003 was based on a Favorskii rearrangement of a carvone-derived cyclohexanone precursor for the elaboration of the polyhydroazulene scaffold of the molecule, followed by extensive functional transformations.[7]



		R^1	R^2
thapsigargin (Tg)	**1a**	octanoyloxy	H
trilobolide	**1b**	H	Me
nor-trilobolide	**1c**	H	H

Figure 1. Thapsigargin and trilobolides

Two additional total syntheses appeared very recently.[8] Baran's group published a concise route featuring a classical photochemical rearrangement of a santonin-type intermediate obtained from dihydrocarvone. Subsequent adequate functionalizations led to **1a**.[8a] Evans and coworkers assembled the bicylic core of thapsigargin in a very efficient fashion using an intramolecular pinacol coupling.[8b] Other partial approaches of the polyhydroazulene skeleton of these molecules have been also published.[9]

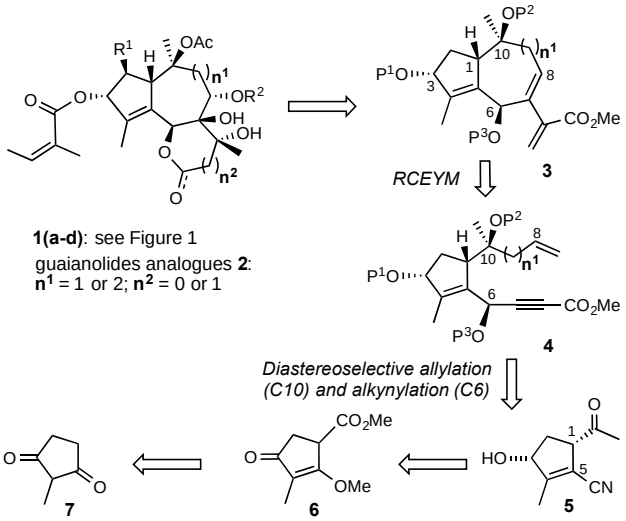
In our laboratories, due to the high pharmacological potential of thapsigargin and the continuing scientific impetus to understand more fully and/or modulate the

interaction of this family of molecules with therapeutically significant SERCA targets, it was decided that we would develop synthetic strategies able to deliver "upon request" the natural molecules, as well as unnatural skeleton-modified analogues. To be practical, the developed routes have to require only incremental modifications from the initially developed synthetic route.

In an integrated program devoted to the synthesis of thapsigargin family **1** itself as well as targeted analogues possessing a modified framework, an allene-yne Pauson-Khand double annulation reaction was employed for an asymmetric synthesis of a complex system related to thapsigargin.[10] More recently, application of this approach for the synthesis of functionalized guaiane-type skeletons, as well as several heterobicyclo[5.3.0] frameworks has been reported.[11]

A second synthetic approach is also currently being developed in our laboratories, where the functionalized octahydroazulene precursor of thapsigargin is designed to be built from a conveniently-ramified cyclopentenol precursor of type **4** (**n**^{1} = 1) using a ring-closing enyne metathesis (RCEYM) as the key step[12] to form bicycle **3**, according to the strategy depicted in Scheme 1.[13] Besides synthesizing Tg-type guaianolides with the natural 5-7-5 core, the embraced project will also involve access to homologated analogues **2** characterized by 5-8-5, 5-7-6, or even 5-8-6 modified frameworks. It is interesting to note that, for access to these analogues, the RCEYM synthetic route described in the present paper and the previously described allene-yne Pauson-Khand are quite complementary. For example, in the RCEYM case, 5-8-5 tricyclic analogues could be directly accessible using the homologated enyne **4** (**n**^{1} = 2) as a precursor.

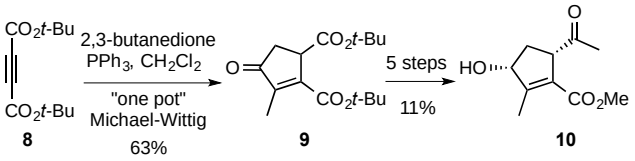
Scheme 1. Retrosynthesis for Tg family of guaianolides and analogues



As a key strategic sequence for the viability of the approach in the case of thapsigargin and other guaianolides, two successive diastereoselective additions, an allylation at C10,[14] then an alkynylation reaction at C6, are envisioned to prepare **4** (**n**^{1} = 1) from the cyanocyclopentenyl methyl ketone **5**. For the construction of the latter, we planned a sequence similar to that used by Ciufolini *et al.* for the synthesis of sordarin,[15] i.e., sequential condensation of Mander's cyanoformate[16] for the carboxylation of 2-methyl-1,3-cyclopentanedione **7**, and cyanation with Nagata's diethylaluminum cyanide[17] to obtain **5**. We report here the results of our efforts for this project.

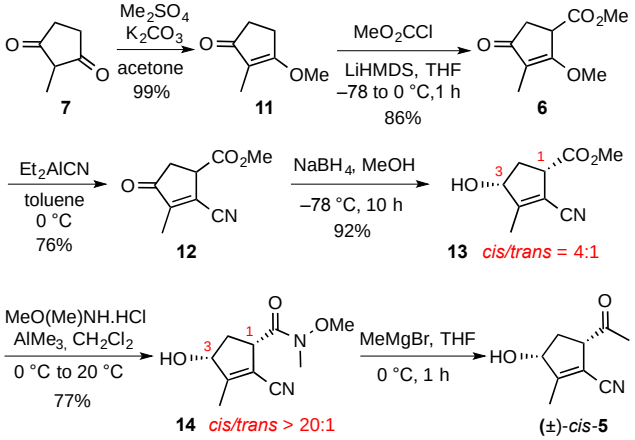
It is worth noting that the choice of the above route to **4** was dictated by the low overall yield of the preceding route based on a Michael/Wittig one-pot sequence for the construction of the required di-substituted cyclopentene precursor **10**, as summarized in Scheme 2.[18] Although large scale one-pot condensation of di-*tert*-butyl acetylenedicarboxylate **8** and 2,3-butanedione (large excess) led to di-*tert*-butyl ester **9** in 63% after optimization, we were nevertheless unable to obtain the di-substituted cyclopentenol ketoester **10** required for continuation of the synthesis in an acceptable yield.

Scheme 2. Previous Michael-Wittig approach[18]



Our first objective was the synthesis of the (±)-*cis* hydroxy methyl ketone **5** from commercial diketone **7** (Scheme 3). Condensation of Mander's reagent on the extended enolate derived from enol ether **11** using LiHMDS yielded **6** in 71% yield; this yield could be improved to 86% by using methyl chloroformate. No O-acylation was observed with the latter reagent, presumably due to the hard nature of the enolate. Compound **6** was subsequently submitted to the conjugate addition of cyanide using the Nagata reagent.

Scheme 3. Synthesis of methyl ketone **5**

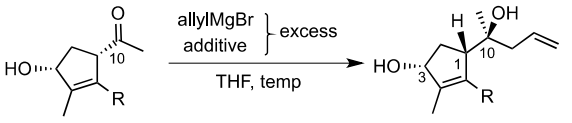


The resulting ketone **12** was reduced with sodium borohydride at –78 °C, giving a 4:1 inseparable mixture of

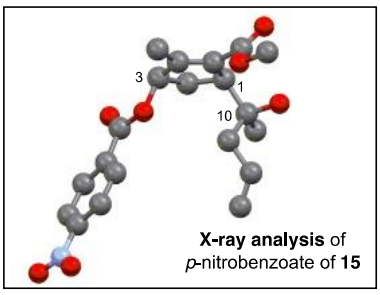
1,3-*cis*/1,3-*trans* alcohols **13**.[14] Further transformation into Weinreb amide **14**[18] gave, after chromatography, the required pure 1,3-*cis* isomer, which was converted into 1,3-*cis* methyl ketone **5** upon addition of MeMgBr. This ketone was prone to epimerization in contact with silica gel, so it was carried on to the next step without purification.

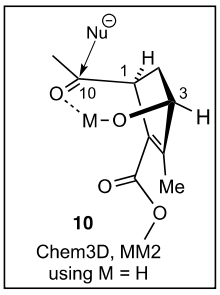
With this ketone in hand, we next addressed the two important stereoselective addition reactions to set up the stereogenic centers at C6 and C10. For the allylation of methyl ketone **5**,[19] we hypothesised that a bridge chelate between the secondary hydroxyl and the methyl ketone would promote a stereoselective addition at C10 (Scheme 4).[20] A preliminary study for this step was carried out using the methyl ester **10** synthesized in the previous approach. First attempts with 2 equiv of allylmagnesium bromide led to a complex mixture of compounds, so we turned to milder nucleophiles. After some efforts, the best result was obtained by adding a large excess of allylzinc chloride formed *in situ* by adding a stoichiometric amount of dry $ZnCl_2$ to a solution of allylmagnesium bromide. Under these conditions, a single adduct was formed in good yield, and X-ray analysis of the derived *p*-nitrobenzoate[21] showed that it was the desired diastereomer **15** (Scheme 4). This result is in agreement with a remote chelate TS, as depicted. Unfortunately, when these conditions were applied to the corresponding cyanomethyl ketone **5**, an almost 1:1 ratio of isomers was obtained. When performing the allylation reaction at room temperature, the ratio increased to 80:20. This trend could reflect temperature-dependent aggregation forms of the mixed magnesium-zinc metal reacting species that can interact with the cyano-containing substrate,[22a] or could be due

Scheme 4. Stereoselective allylation reactions



	R	additive	temp (°C)		yield (%)	dr
10	CO_2Me	$ZnCl_2$	20	**15**	88	> 95:5
5	CN	$ZnCl_2$	–78 to 0	**16**	54	45:55
		$ZnCl_2$	20		60	80:20
		$CeCl_3$	–78		87	85:15

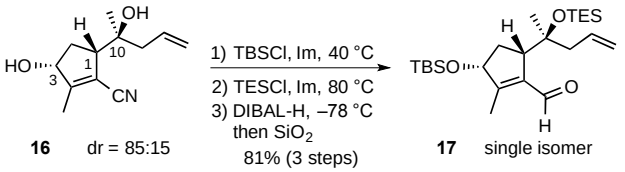


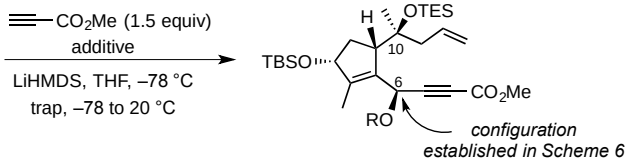


to the reversibility of the addition of allylzinc reagent to ketones.[22b] However, the best result was obtained with the corresponding allylcerium derivative, and alcohol **16** was obtained in 85:15 dr and 87% yield (over two steps) from Weinreb amide **14**.

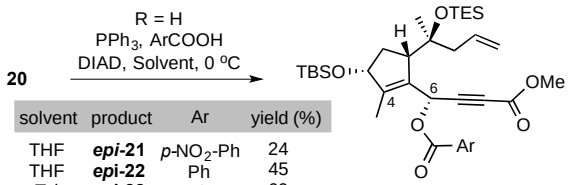
The diastereomers were successfully separated by careful chromatography after protection of the secondary hydroxyl at C3 by a TBS group (Scheme 5). Further protection of the tertiary OH at C10 as a TES ether, followed by reduction of the cyano function by DIBAL-H at –78 °C afforded aldehyde **17**, which was then submitted to the alkynylation reaction with methyl propiolate.[23] This reaction proved to be somewhat capricious and was first carried out using an external trap of the generated alkoxide with an electrophile to get a good yield. Quench with TMSCl gave the persilylated ether **18** in quantitative yield, while the acetylated analogue **19** was obtained in 74% yield. Direct hydrolysis of the condensation reaction mixture failed to give the corresponding alcohol **20** in reproducible yields. However, when this reaction was carried out in the presence of dry $CeCl_3$,[24] the free alcohol **20** was isolated in 81% yield. One explanation for the improvement in the presence of $CeCl_3$ could be the formation of a more stable cerium alkoxide species, allowing a milder hydrolysis process (complexation of this alkoxide with the oxygen of the C10 TES ether is possible).[25] Under all conditions tested, a single diastereomer was obtained at C6.

Scheme 5. Synthesis of the precursors of RCEYM





additive	trapping agent	product	R	yield (%)
none	TMSCl	**18**	TMS	quant
none	AcCl	**19**	Ac	74
none	H_2O	**20**	H	non reproducible
$CeCl_3$	H_2O	**20**	H	81



solvent	product	Ar	yield (%)
THF	***epi*-21**	*p*-NO_2-Ph	24
THF	***epi*-22**	Ph	45
Tol	***epi*-22**	Ph	60

Unfortunately, all attempts to obtain a crystalline derivative failed, either at this level, or after performing the RCEYM annelation. Since NMR experiments were also inconclusive, even on the bicyclic adducts, we decided to prepare the epimer of **20** at C-6 to compare the data in both series. It is worth noting that from a synthetic point

of view, the use of an epimer of natural Tg at C-6 as an intermediate could prove useful if the formation of the γ-lactone ring was performed by a Mitsunobu reaction.[26] Therefore, transformation of **20** into ***epi*-21** was carried out (Scheme 5), at first with *p*-NO_2-benzoic acid, but the yield was very low, due to the formation of secondary products resulting from, *inter alia*, S_N2' reactions at C4. Conducting the reaction in the presence of benzoic acid in toluene resulted in a clean reaction, giving ***epi*-22** as a single adduct.

The excellent diastereoselectivity observed for the alkynylation reaction is likely to result from: 1) an approach of the nucleophile from the less hindered convex face of **17**, and 2) a reacting conformation of the aldehyde being s-*cis*, as depicted on Figure 2. This conformation, and not the more stable s-*trans* one, is thought to be the reactive one due to a more favorable TS for the carbonyl addition reaction, in a manner similar to that calculated from FMO calculations by Houk et *al.* in the case of the addition of cyanide to acrolein.[27] The alkynylation reaction of **17** would therefore probably proceed in accordance to the Curtin-Hammett principle. However, a more in-depth study of the two possible transitions states is required to clarify this question.

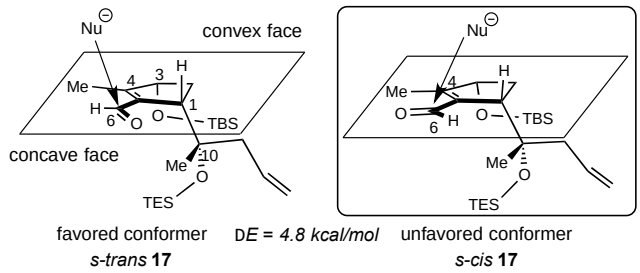
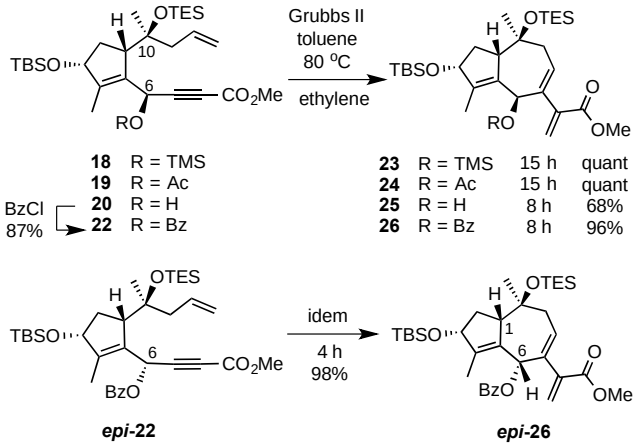


Figure 2. Chem3D minimizations (MM2) for the *s-cis* and *s-trans* aldehyde **17**

We next turned to the ring-closing enyne metathesis reaction.[28] A first set of assays established that the best precatalyst for the annelation reaction was Grubbs II, while maintaining the reaction under an ethylene atmosphere.[29] Under these conditions at 80 °C in toluene, the protected enynes **18** and **19** cyclized cleanly to give the desired octahydroazulene adducts **23** and **24** in quantitative yield (Scheme 6). These adducts correspond to the exo adducts expected for a seven-membered ring formation by RCEYM. The unprotected precursor **20** also cyclized under the same conditions, although the reaction was not as clean, giving variable non-identified minor compounds in addition to the expected adduct **25** (68% yield).

Scheme 6. RCEYM annelation



The C6 Mitsunobu-epimerized enyne ***epi*-22** was also submitted to RCEYM conditions. In this case, total conversion occurred at 80 °C in shorter reaction times than previously. At this level, unequivocal assignment of the configuration at C6 was made by comparing ^{1}H NMR data of ***epi*-26** with those of compound **26**, obtained by a RCEYM reaction of benzoate **22**, readily prepared from **20**. A strong nOe interaction between H-1 and H-6 allowed unambiguous assignment of the configuration at C-6 of ***epi*-26** as the "unnatural" epimer, as depicted (see Supporting Information for NOESY experiments).

In conclusion, an advanced intermediate (**23**) of thapsigargin and other guaianolides has been synthesized in 12 steps and 31% overall yield. The key step is an efficient RCEYM reaction that forms the 5,7 ring system in quantitative yield. Further work for the enantioselective synthesis of this intermediate is in progress, as well as the construction of analogues with a novel 5,8 core. Functionalization of both **23** and ***epi*-26** toward guaianolides will be explored.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org."
Experimental procedures, characterization data and NMR spectra (PDF).
X-ray data for *p*-nitrobenzoate of **15** (CIF).

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Notes

The authors declare no competing financial interests.

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