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Natural Products

Epoxide-Opening Cascades Triggered by a Nicholas Reaction: Total Synthesis of Teurilene**

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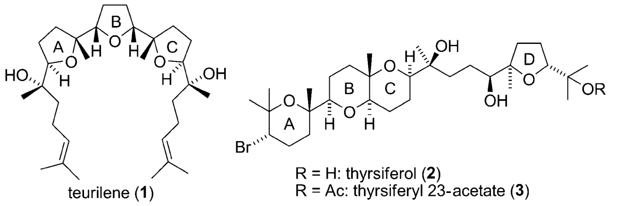
The way in which nature approaches the synthesis of complex molecules is a great source of inspiration to organic chemists for planning a synthetic route to a natural product. In this context, cascade cyclizations are considered a valuable tool for obtaining molecular complexity in a straightforward manner.[1] Focusing on polycyclic ethers, it is well accepted by the scientific community that these types of compounds originate from a cascade cyclization of a polyepoxide backbone,[2,3] thus leading to structures such as the ones depicted in Figure 1. Therefore, epoxide-opening cascades have been used as a valuable methodology to synthesize polycyclic ether natural products such as polyether ionophores as well as squalene-derived and ladder-type polyethers.[4] Additionally, another valuable synthetic strategy is the bidirectional approach. Several groups have achieved the synthesis of many natural products using this concept.[5]



teurilene (**1**)

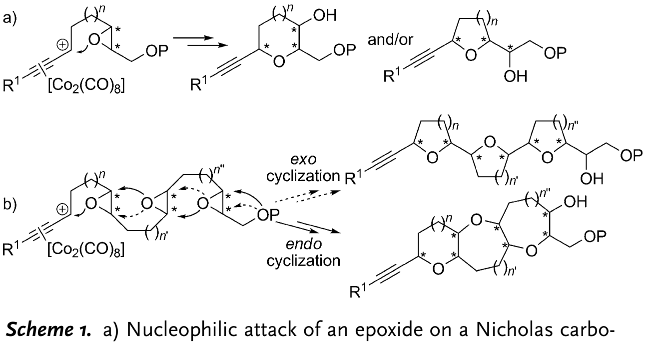
R = H: thyrsiferol (**2**)
R = Ac: thyrsiferyl 23-acetate (**3**)

Figure 1. Natural products isolated from *Laurencia obtusa*.

The combination of bidirectional synthesis and the epoxide cascade cyclization have rendered beautiful and efficient synthetic routes such as the total synthesis of (+)-α-onocerin and glabrescol developed by Corey et al.[6,7] However, these examples are not the general rule. The main drawback of using the polyepoxide-opening strategy is the lack of control in the activation of the correct epoxide. As a consequence, the yield of the cascade process is affected when more than two epoxides are involved.[8–10] Thus, the development of mild reaction conditions to allow selective activation of a polyepoxide chain (three or more epoxides) is imperative to guiding the cascade event in the correct direction. To address this problem, Jamison et al. used a bromonium-initiated epoxide-opening cascade in the synthesis of *ent*-dioxepandehydrothyrsiferol.[11]

Within our program directed to the synthesis of biologically active molecules and the development of new synthetic methodologies,[12] we became interested in the synthesis of teurilene (**1**), thyrsiferol (**2**), and their congeners. Teurilene (**1**) is a squalene-derived triterpene polyether isolated by Kurosawa et al. from the red algae *Laurencia obtusa* along with thyrsiferol (**2**) and its acetyl derivative thyrsiferyl 23-acetate (**3**; Figure 1).[13] In spite of having eight stereogenic centers and three tetrahydrofuran (THF) rings in its structure, **1** has a *meso* symmetry (C_s), thus making it an achiral compound. This unique structural feature combined with the cytotoxic activity[14] have driven several scientific groups to synthesize and develop synthetic methodologies to access this natural product.[15a,16] Up to now there are only two total syntheses reported of teurilene (**1**), and although elegant, both of them present problems in the synthesis of the three THF rings in good yields.[16]

Inspired by the biogenesis of polyether natural products,[2,3] we have developed a reliable and efficient methodology to synthesize cyclic ethers of different sizes.[17] This method relies on the nucleophilic attack of an epoxide on a dicobalt hexacarbonyl stabilized propargylic cation (Scheme 1a).[18] Considering the mildness of our procedure, we envisioned its use as a suitable trigger to guide the cyclization process in a polyepoxide chain, thus yielding polycyclic ethers in one step (Scheme 1b).



Scheme 1. a) Nucleophilic attack of an epoxide on a Nicholas carbocation leading to cyclic ethers of different size. b) Epoxide-opening cascade triggered by a Nicholas reaction.

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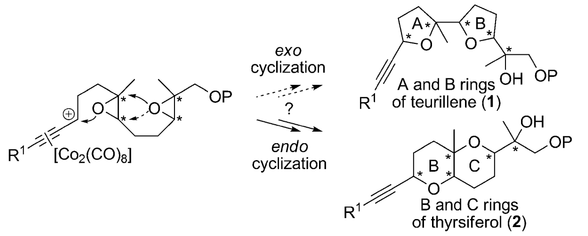
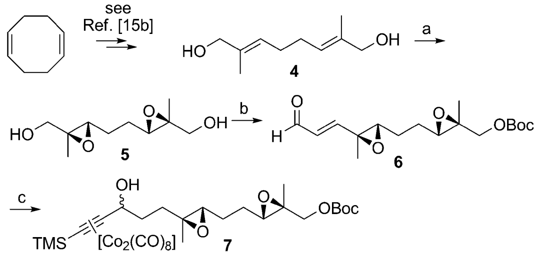
Herein we report the first epoxide-ring-opening cascade triggered by a Nicholas reaction, which provides predictable carbocation formation under mild reaction conditions and ensures the stereoselectivity control in the cyclization process. Additionally, by using this strategy and the bidirectional synthetic approach, we disclose the total synthesis of the squalene-derived triterpene polyether teurilene (**1**).

To verify our hypothesis of the predictability in the cascade cyclization event, we first decided to test it in a system having two epoxides on the carbon chain. If the process evolved as expected, that is, *exo* cyclization, it would generate two of the three THF rings of **1** in one step (Scheme 2). However, if the cyclization is *endo* then rings B and C of the **2** would result.



Scheme 2. Cascade cyclization triggered by a Nicholas reaction in a bis(epoxide) model.

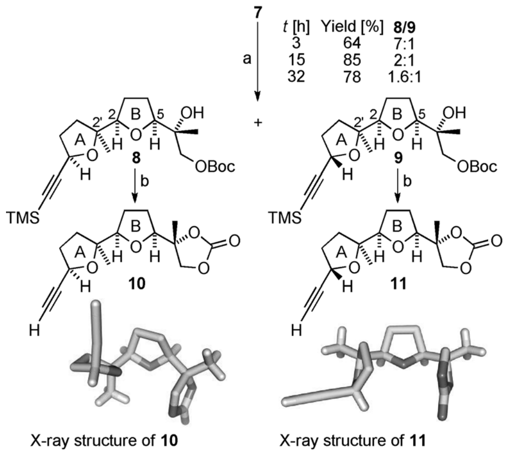
With the concept of bidirectional synthesis in mind, and based on valuable literature precedent,[15] the bis(epoxide) **5** was easily obtained from the commercially available 1,5-cyclooctadiene (Scheme 3). The introduction of the Boc protecting group broke the C_2 symmetry of **5**, and also generated a well-documented terminating nucleophile for acid-promoted cascades.[9,17,19] The primary alcohol was oxidized and homologated through a Wittig reaction leading to the α,β unsaturated aldehyde **6**. Hydrogenation over 5% Rh/Al_2O_3 generated the saturated aldehyde, which was immediately used in the coupling with the TMS acetylene anion. The resulting compound was treated with $[Co_2(CO)_8]$, thus providing the model molecule **7** for the cascade cyclization.



Scheme 3. Synthesis of **7**. Reagents and conditions: a) (+)-DIPT, Ti(O*i*Pr)$_4$, *t*BuOOH, 4 Å M.S., CH_2Cl_2, −20°C, 65%; b) 1. Boc_2O, DMAP, toluene, RT, 67%; 2. SO_3·Py, DMSO, NEt_3, CH_2Cl_2, RT; 3. Ph_3P=CH-CHO, toluene, 60°C, 85% after 2 steps; c) 1. H_2, 5% Rh/Al_2O_3, EtOAc, RT; 2. TMS acetylene, *n*BuLi, −78°C, THF, 40% after 2 steps; 3. $[Co_2(CO)_8]$, CH_2Cl_2, RT, 95%. Boc = *tert*-butoxycarbonyl, (+)-DIPT = (+)-diisopropyl L-tartrate, DMAP = 4-dimethylaminopyridine, DMSO = dimethyl sulfoxide, M.S. = molecular sieves, TMS = trimethylsilyl.

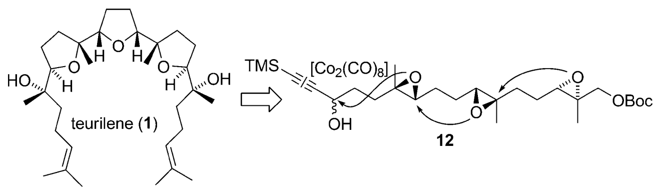
Unfortunately, when we applied the cyclization protocol,[17] there was no formation of the expected bicyclic compounds; a complex mixture resulted instead. In contrast to the system with one epoxide on the carbon chain, **7** proved to be very sensitive to activation with $BF_3\cdot Et_2O$ even at low temperatures. This result made us reconsider the strength of the Lewis acid and for this case milder acidic conditions were perhaps required. As an alternative, we developed a mild and convenient protocol to perform the Nicholas reaction using the acidic clay montmorillonite K-10.[20] To our surprise these reaction conditions also proved to be inefficient and lead to an undesired mixture of products.

We had noted that during the purification of **7** by column chromatography on silica gel, a less polar product was additionally isolated. After cobalt decomplexation this side product was indeed the cyclized product **8** (Scheme 4). This finding prompted us to use these new reaction conditions to promote the cyclization process, and it led to a mixture of compounds, **8** and **9**, in very good yield after two steps. The ratio of compounds **8** and **9** depended upon the reaction times. We should emphasize that, to the best of our knowledge, this is the first time that silica gel has been used as an acidic support to promote the Nicholas reaction for cyclic ether formation.



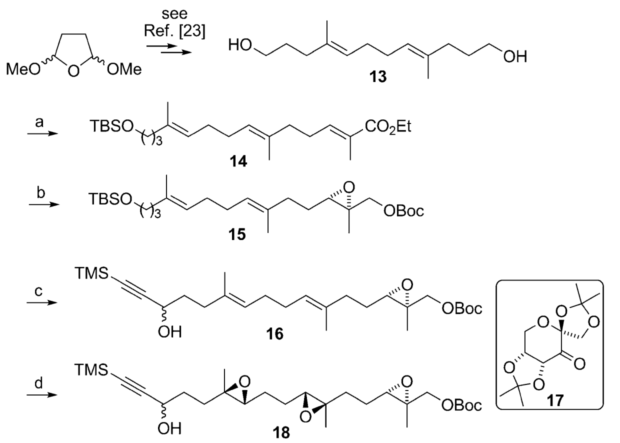
Scheme 4. Reagents and conditions: a) 1. SiO_2, CH_2Cl_2, RT;[21] 2. CAN, acetone, 0°C; c) K_2CO_3, MeOH, RT. CAN = ceric ammonium nitrate.[32]

However, **8** presented an inverted stereocenter at the propargylic position, which needed to be epimerized for the synthesis of **1**. Precedents in the literature[22] and from our own laboratory[12f,h,i,20] have shown that acidic treatment of propargyl hexacarbonyl dicobalt complexes is a suitable methodology to promote isomerization at the propargylic position. Unfortunately, we were unable to isomerize the hexacarbonyl dicobalt complex of **8** into the complex **9**. Basic treatment of **8** and **9** led to the compounds **10** and **11**, respectively, which conveniently crystallized for X-ray analysis (Scheme 4). It is noteworthy, that during the cascade process, the stereocenters at C2 and the tertiary alcohol undergo an inversion of configuration. Conversely, the configuration of the stereocenters at C2′ and C5 were retained.



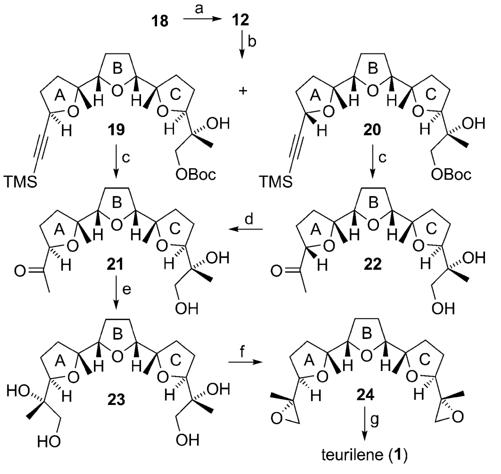
Scheme 5. Retrosynthetic analysis of teurilene (**1**) by an epoxide-opening cascade triggered by a Nicholas reaction.

Having established the expediency of our approach for the cascade cyclization, we decided to move forward and synthesize **1** by using our developed methodology. As depicted in the retrosynthetic analysis (Scheme 5), we envisaged that **1** might be secured through a sequence of reactions starting from the cobalt hexacarbonyl complex **12**. It must be emphasized that as a result of the C_s symmetry of **1**, the election of the chiral auxiliary in the asymmetric epoxidation reactions was to establish the suitable relative configuration in the polyepoxide **12**. For the synthesis of this key intermediate we have used a slightly different route (Scheme 6). By employing the bidirectional strategy, the known diol **13** was synthesized in 55 % overall yield after four steps.[23] The diol **13** was monoprotected as a silyl ether, thus leaving the bis(homoallylic) alcohol ready for homologation. By using the protocol developed by our group we obtained the α,β-unsaturated ester **14** in one step and excellent yield.[24] Reduction of the ester group was performed with aluminium hydride to provide the allylic alcohol. The first chiral epoxide was generated through the Katsuki–Sharpless asymmetric epoxidation[25] with subsequent protection with Boc to afford the compound **15**. The silyl group was removed under standard reaction conditions and the resulting alcohol was oxidized to the corresponding aldehyde, which was coupled with lithium TMS acetylide to give the propargylic alcohol **16**. Finally the remaining epoxides were installed in one step using the Shi asymmetric epoxidation,[26] thus providing the polyepoxide **18**.



Scheme 6. Reagents and conditions: a) 1. TBSCl, imidazole, CH_2Cl_2, RT, 96 % (3 iterations); 2. SO_3·Py, Et_3N, DMSO, CH_2Cl_2, $Ph_3P{=}C(CH_3)$-CO_2Et, RT, 88 %; b) 1. $AlCl_3$, $LiAlH_4$, Et_2O, 0 °C, 94 %; 2. Ti(O*i*Pr)$_4$, (+)-DET, *t*BuOOH, 4 Å M.S., CH_2Cl_2, −20 °C; 3. DMAP, Boc_2O, toluene, RT, 98 % after 2 steps; c) 1. TBAF, THF, RT, 86 %; 2. SO_3·Py, Et_3N, DMSO, CH_2Cl_2, RT; 3. TMS acetylene, *n*BuLi, THF/toluene (1:2), −78 °C, 70 % after 2 steps; d) oxone, K_2CO_3, DMM/CH_3CN/buffer pH 10.5 (2:1:1), **17**, 0 °C, 81 %. TBS = *tert*-butyldimethylsilyl, (+)-DET = (+)-diethyl L-tartrate, TBAF = tetrabutylammoniumfluoride, DMM = dimethoxymethane.

The formation of the hexacarbonyl dicobalt complex from **18** proceeded smoothly to give the intermediate **12**, which was submitted to the same reaction conditions used for the shorter homologue **7** (Scheme 7). As expected, the cyclization process provided the three THF rings in excellent yield (75 % after two steps). The cascade is high yielding, averaging 91 % yield per epoxide. Recently an interesting methodology based on an S_N2 strategy was disclosed, thus leading to three THF rings in one step in a slightly lower overall yield.[27] Intriguingly, compared to **7**, the complex **12** proved to be less reactive to the silica gel, thus needing a longer reaction time to consume the starting material. Although the cascade proceeded efficiently and followed the same stereochemical course as **7**, the reaction gave a 1:1 epimeric mixture of **19** and **20** at the propargylic position.[28] Interestingly, neither extending the reaction time nor changing the acid strength improved the isomeric ratio or the overall yield. From a synthetic standpoint, the epimeric mixture does not represent a problem for the synthesis of **1** because the isomerization of the propargylic ether can be done at a later stage of the synthetic route (see below).



Scheme 7. Reagents and conditions: a) [$Co_2(CO)_8$], CH_2Cl_2, RT, quant.; b) 1. SiO_2, CH_2Cl_2, RT, 76 h;[21] 2. CAN, acetone, 0 °C, 75 % after 2 steps; c) 1. K_2CO_3, MeOH, RT, 24 h; 2. $HgSO_4$, H_2SO_4 3 M, RT, 2 h, 87 % after 2 steps; d) K_2CO_3, MeOH, RT, 24 h, 75 % (2 iterations); e) 1. $CH_3PPh_3^+Br^-$, *n*BuLi, THF, 0 °C to RT; 2. AD-mix β, $CH_3SO_2NH_2$, *t*BuOH/H_2O (1:1), 0 °C, 75 % after 2 steps; f) 1. MsCl, Py, CH_2Cl_2, 0 °C; 2. K_2CO_3, MeOH, 0 °C to RT, 90 % yields after 2 steps; g) Allylmagnesium chloride, CuI, THF, 0 °C to RT, 93 % yields. Ms = methanesulfonyl.

The isomers **19** and **20** were treated under basic conditions to remove the trimethylsilyl group on the alkyne and the Boc group present at the primary alcohol.[29,30] The next step was the hydration of the terminal alkyne to afford the methyl ketones **21** and **22**, respectively, in excellent yield after two steps. At this stage of the synthesis, we decided to execute the isomerization of **22** into the correct isomer **21**. For this purpose **22** was exposed to basic reaction conditions and provided a 1:1 mixture of the diastereomers **21** and **22**, which were separated. The recovered **22** was submitted to another epimerization, thus generating additional quantities of the methyl ketone **21**. The transformation of the carbonyl group into the corresponding alkene was achieved through a Wittig reaction. The C_s symmetry of the target molecule was installed by a Sharpless asymmetric dihydroxylation with the AD-mix β, thus providing exclusively the *meso*-tetraol **23** in 72% yield after two steps.[31] The *meso*-tetraol **23** was bidirectionally converted into the bis(epoxide) **24** in good yield by a two-step protocol. Finally, **24** was then opened by a Grignard reagent, in the presence of CuI, thus furnishing the natural product teurilene (**1**) in excellent yield. The spectroscopic and physical data were in perfect agreement with those reported by Kurosawa and co-workers.[13]

In conclusion, we have developed a valuable cascade cyclization inspired by the postulated biogenesis of polyether compounds. Our approach relies on the predictable carbocation formation of the Nicholas reaction using very mild acidic conditions (silica gel as promoter). We should emphasize that the mildness of this process ensures excellent yields in the very often inefficient epoxide opening cascade. Additionally the synthetic route employed, which is based on standard reagents, allows the possibility of scaling up the process and approaching the synthesis of other members of polyether ionophores and the squalene-derived family. Structural modification of **1** and the synthesis of other derivatives, as well as their biological evaluation are currently being performed in our laboratory and will be published in due course.

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[28] The hexacarbonyl dicobalt complexes of both isomers could be easily isolated by column chromatography on silica gel.

[29] Longer reaction times were needed to remove the five-membered carbonates intermediates.

[30] At that point of the synthesis we tried the transformation of the terminal alkyne into the required 2-propenyl function, which required a chemo- and regioselective carbometalation of the alkyne function. Unfortunately, this transformation always provided the internal alkene. See: a) K. M. Laemmerhold, B. Breit, *Angew. Chem.* **2010**, *122*, 2417 – 2420; *Angew. Chem. Int. Ed.* **2010**, *49*, 2367 – 2370; b) E. Negishi, D. E. Van Horn, T. Yoshida, *J. Am. Chem. Soc.* **1985**, *107*, 6639 – 6647.

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[32] CCDC 910167 (**10**) and CCDC 910166 (**11**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.