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RuO_4-promoted oxidative polycyclization of isoprenoid polyenes. A further insight into the stereochemistry of the process

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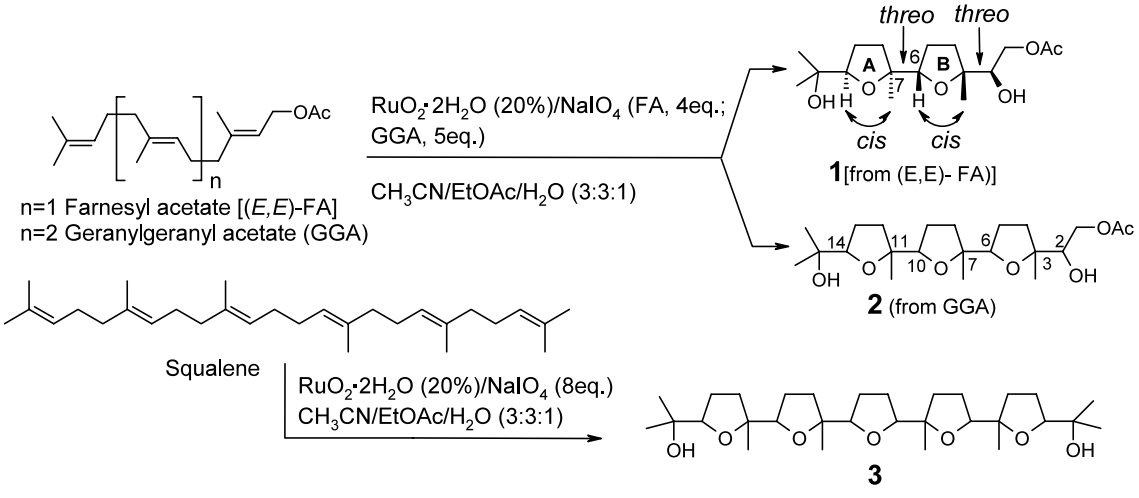
Abstract—Further studies on the RuO_4-catalyzed oxidative polycyclization of isoprenoid polyenes have been carried out. The configuration of the tris-THF product from the oxidation of geranylgeranyl acetate has been determined by a combination of spectral and chemical correlation methods. The oxidation of (*E*,*Z*)-farnesyl acetate, synthesized from nerol, has been carried out. This process stops at the first cyclization indicating that an *E* configuration of the Δ^6 double bond is needed for the second cyclization to occur. The results are discussed in comparison with previous knowledge on the related Re(VII) polycyclization of polyenic bis-homoallylic alcohols.

Adjacently linked poly-tetrahydrofurans (poly-THF) are important synthetic targets mostly in connection with their presence in the structure of biologically active substances such as *Annonaceous* acetogenins, a rapidly growing family of metabolites that show, inter alia, potent antitumoral and pesticidal activity.[1]

We have recently reported the discovery of a novel RuO_4-catalyzed oxidative process that allows the stereoselective synthesis of the bis- (**1**), tris- (**2**), and penta- (**3**), tetrahydrofuranyl diol products by one-step polycyclization of the isoprenoid polyenes (*E*,*E*)-FA, GGA and squalene, respectively (Scheme 1).[2] The configuration of the bis-THF **1** was established to be *cis–threo–cis–threo* through spectral and chemical methods. Further efforts towards the understanding of the new process are described in this paper.



Scheme 1.

Keywords: RuO_4; oxidative polycyclization; isoprenoid polyenes; tris-THF configuration; (*E*,*Z*)-farnesyl acetate.

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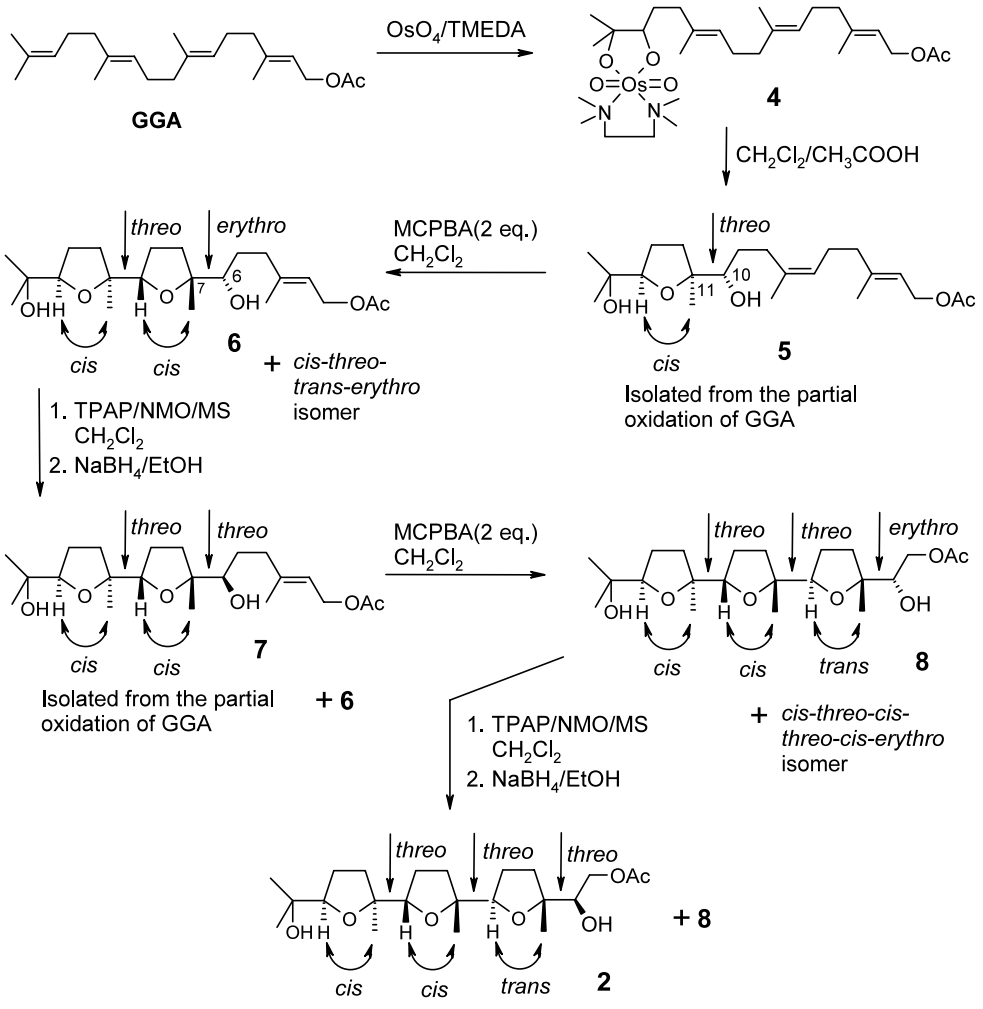
First of all the determination of the configuration of the tris-THF **2** was carried out. A *cis–threo–cis–threo–trans–threo* arrangement for this compound was established through a combination of 600 MHz 2D NMR studies (COSY, ROESY, HSQC, HMBC) and chemical correlation work. In particular, a *cis–cis–trans* sequence for the three contiguous THF rings in **2** was inferred from the observation of strong ROESY effects between H-14 and Me-11, H-10 and Me-7, and H-6 and H-2, and the absence of a ROESY correlation between H-6 and Me-3. However, NMR evidence alone did not give definitive information on the stereorelationship within the carbon pairs (C2/C3, C6/C7, C10/C11) connecting the adjacent THF rings; an all *threo* arrangement, was established as detailed in Scheme 2,[3] that also agrees with mechanistic considerations (*syn* addition of the two oxygens).[4]

By stopping the oxidation of GGA before its completion we could isolate the mono- and bis-THF diols **5** and **7** derived from partial cyclization of the polyene. 2D NMR analysis indicated that the THF ring in **5** was *cis* and the bis-THF portion in **7** was *cis–cis*, in agreement with the assumption that these compounds are put along the cascade sequence eventually leading to **2**. Next, treatment of GGA with OsO_4 (1 equiv.) in the presence of TMEDA (1 equiv.) afforded osmate ester **4** along with other osmium-containing products. *cis*-Stereoselective oxidative cyclization of **4** was achieved by using CH_3COOH in CH_2Cl_2 allowing to obtain in high yields (90%) a product indistinguishable from mono-THF diol **5**.

These conditions prevented the concomitant acetate hydrolysis that occurs when Donohoe's conditions (MeOH/HCl) were used;[5] this result secured the *threo* relationship between C-10 and C-11 and confirmed the *cis* nature of the THF in **5**.[5] Conversion of **5** into **2** was then carried out. Treatment of **5** with 2 equiv. of MCPBA caused the closure of the second THF ring, giving the *cis–threo–cis–erythro* bis-THF diols **6** along with its *cis–threo–trans–erythro* isomer, via epoxidation of the Δ^6 double bond followed by intramolecular *anti*-opening of the hydroxyepoxide intermediate. Both these compounds showed spectral properties different from those exhibited by **7**, isolated from partially oxidized GGA, suggesting a *cis–threo–cis–threo* configuration for this substance. This was confirmed by the non stereoselective transformation of **6** into **7** by oxidation



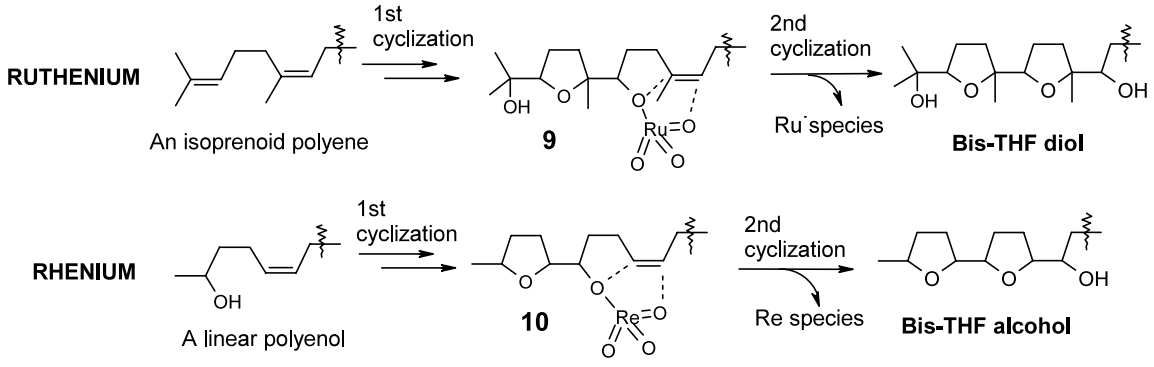
Scheme 2.

at C-6 (TPAP/NMO, 4 Å MS, CH_2Cl_2) followed by $NaBH_4$ reduction. Finally, **2** was obtained from **7** through the same sequence used for the conversion **5**→**7**.

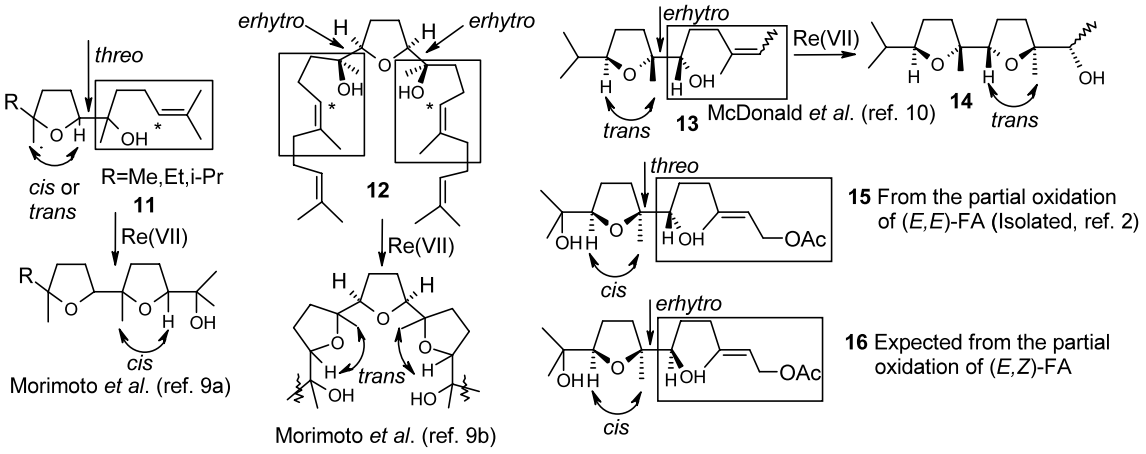
The Ru-mediated process appears to be related to the oxidative polycyclization of polyenic bis-homoallylic alcohols carried out with Re(VII) oxo species (mostly $CF_3CO_2ReO_3$ or Re_2O_7).[6] The latter process can induce both bis- or tris-cyclizations in one step or in a sequential way, and has been successfully used in the synthesis of a number of bis- and tris-THF *Annonaceous* acetogenins.[7] In the previous work,[2] the new process was rationalized through a mechanism partly similar to that proposed for the related process with rhenium. In particular, we hypothesized that both the processes could proceed trough structurally analogues perruthenate (**9**) or perrhenate (**10**) intermediates (Scheme 3) whose further evolution (cycloaddition of an O–M=O portion on the C=C two methylenes away) would give rise to the second THF ring. Reiteration of the cyclization step would occur in the process with RuO_4, with a Ru-containing portion (likely RuO_3) migrating along the growing poly-THF chain,[2] a fact that well agrees with the catalytic nature of the process.

On the above assumption, the factors governing the stereocontrol of the two related processes could be, in principle, very similar to each other. Shina et al. have proposed simple rules that allow to predict the stereochemical outcome for the second and third cyclization reactions of *linear hydroxypolyenes* (Scheme 3) with $CF_3CO_2ReO_3$.[8] These rules state that if the vicinal oxygens formed in the first cyclization (*O*-THF-C-*O*) have a *threo* relationship the next cyclization produces a *cis*-THF ring, if this relationship is *erythro* the next cyclization gives a *trans*-THF ring. Some authors found that the cyclization of ore complex polyenols follow in some cases these rules (see compounds **11**–**13**, Scheme 4).[9,10] However, care should be exercised when applying these rules to substrates other than linear polyenols because no model has been developed for these and too many factors can be invoked addressing the course of the process such as the coordinating efficiency of the first, or the first two, formed THF rings, at the metal centre, during the second or third cyclization,[8,9] as well as the conformational arrangement of the cyclizing species in turn affected by the structure itself.

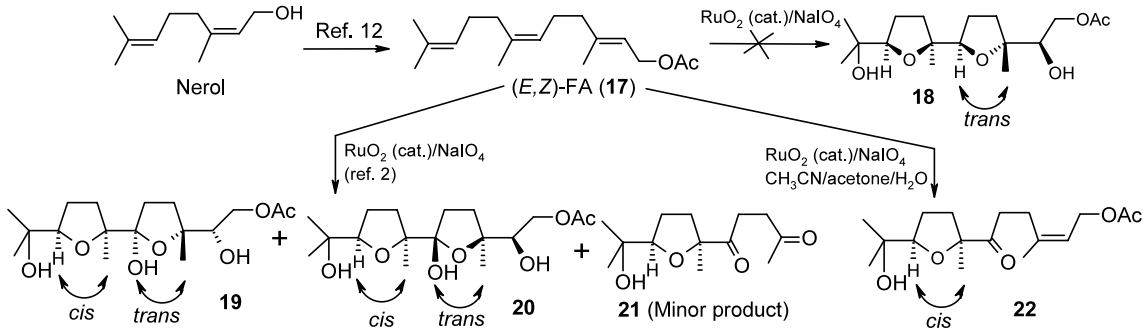
Having in mind the above limitations we note, however, that the second cyclization step for both the oxidation of (*E*,*E*)-FA and GGA proceeds (Scheme 1) with the same stereochemistry which also agrees with the Sinha's rules: to the C6/C7 (for (*E*,*E*)-FA; C10/C11 for GGA) *threo* relationship follows the formation of a *cis*-THF. However, the third cyclization of GGA pro-



Scheme 3.



Scheme 4.



Scheme 5.

ceeds with a different stereocontrol compared with the second (to the C6/C-7 *threo* relationship follows the formation of a *trans*-THF ring) albeit no substantial difference seems to exist in the cyclizing portion involved (Scheme 1) in turn also strictly similar to that involved into the second cyclization of (*E*,*E*)-FA. Hence, this result disagrees with that expected on the basis of Sinha's rules.

Further experimental evidence on the stereochemistry of cyclization of isoprenoid substrates could be gained by RuO_4 oxidation of (*E*,*Z*)-FA (**17**, Scheme 5); this should have given the *cis–erythro–trans–threo* isomer of **1** in the case the Shina's rules would apply, since an *erythro* C6/C7 relationship derives from the *Z* configuration of the Δ^6 double bond on *syn* addition of the two oxygens during the first cyclization. The synthesis of (*E*,*Z*)-FA was also stimulated by a literature precedent:[10] compound **13** (Scheme 4), is reported to cyclize (in accord with Sinha's rules) to give a *trans*-THF ring (**14**). On the basis of the close structural similarity of **13** with both **15** and **16** (Scheme 4) we hoped that the expected bis-THF **18** (Scheme 5) could be obtained on oxidation of **17**. It is to be noted that **15** has been previously obtained from the partial oxidation of (*E*,*E*)-FA and, following the hypothesis shown in Scheme 3, its perruthenate ester (**9**) should be the immediate precursor of **1**; likewise compound **16** was expected to derive from **17** by oxidative monocyclization and to give, in the form of perruthenate ester, desired **18**.

Thus, (*E*,*Z*)-FA was synthesized starting from nerol as described in the literature[11] and subjected to oxidation with RuO_4 (Scheme 5) under the usual conditions.[2] The oxidation was faster than that leading to **1** and **16** could not be isolated even stopping the process at its early stage. Frustratingly, no bis-THF product was obtained! Instead, a ca. 1:1 mixture of the two isomeric hemiacetals **19** and **20** was obtained in a 30% isolated yield, derived from the oxidative monocyclization of **17** involving the Δ^6 and Δ^{10} double bonds, to give **22** followed by dihydroxylation of the remaining olefin function and internal hemiacetal formation of the more stable *trans* isomers.[12] Minor amounts (7%) of the C-2 ketones corresponding to **19**/**20**, as well as the scission product **21**, were also obtained (Scheme 5).

We were unable to force the process towards the desired bis-THF diol product in several different experimental conditions.[13] Worth mentioning is that mono-THF ketone **22** (Scheme 5) was obtained in good yields (70%) when the oxidation was conducted in the solvent mixture CH_3CN/acetone/H_2O (3:3:1).

All the above results indicated that the process stops at the first cyclization and suggested that only the *E* configuration of the Δ^6 double bond, and the *O*–C_6–C_7–*O threo* relationship that originates from it in the first cyclization, is compatible with the closure of the second THF ring. It is to be noted that the main difference between **13** and **16** resides in the configuration of their THF ring (*trans* versus *cis*) whose (different?) coordinating ability could in some way affect the overall process.

The above process may have synthetic value for the preparation of natural substances such as lysocell[12] or when the closure of only one THF is required, allowing to accomplish further synthetic manipulations on the rest of the molecule.

From the above evidence it appears that, at least for Ru-mediated processes, isoprenoid polyenes of the type FA and GGA give a *cis*-THF during the second cyclization provided that the *vicinal* oxygens formed in the first cyclization have a *threo* relationship. Further studies are in progress to sustain this conclusion.

Acknowledgements

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References

1. (a) Zeng, L.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. *Nat. Prod. Rep.* **1996**, *13*, 275–306; (b) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. *Nat. Prod. Rep.* **1999**, *62*, 504–540.
2. Bifulco, G.; Caserta, T.; Gomez-Paloma, L.; Piccialli, V. *Tetrahedron Lett.* **2002**, *43*, 9265–9269; corrigendum *Tetrahedron Lett.* **2003**, *44*, 3429. Oxidation of (*E*,*E*)-FA and

GGA also gave variable amounts of the C-2 ketones of **1** and **2**.
3. All products shown were pure by HPLC and fully characterized.
4. McDonald, F. E.; Schultz, c. C. *Tetrahedron* **1997**, *53*, 16435–16448 and references cited therein.
5. Donohoe, T. J.; Winter, J. J. G.; Helliwell, M.; Stemp, G. *Tetrahedron Lett*. **2001**, *42*, 971–974.
6. Cr(VI)-containing reagents PDC or PCC can also induce the assembly of up to two adjacent THF rings but overall the process has received little attention due to low (<10%) yields. See Ref. 4 and McDonald, F. E.; Towne, T. B. *J. Am. Chem. Soc*. **1994**, *116*, 7921–7922.
7. Keinan, E.; Sinha, S. C. *Pure Appl. Chem*. **2002**, *74*, 93–105.
8. Sinha, S. C.; Keinan, E.; Sinha, S. C. *J. Am. Chem. Soc*. **1998**, *120*, 9076–9077.
9. (a) Morimoto, Y.; Iwai, T. *J. Am. Chem. Soc*. **1998**, *120*, 1633–1634; (b) Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc*. **1999**, *121*, 6792–6797.
10. McDonald, F. E.; Towne, T. B. *J. Org. Chem*. **1995**, *60*, 5750–5751.
11. (a) Brown, R. C. D.; Hughes, R. M.; Keily, A.; Kenney, A. *Chem. Commun*. **2000**, 1735–1736; (b) Xie, H.; Shao, Y.; Becher, J. M.; Naider, F.; Gibbs, R. A. *J. Org. Chem*. **2000**, *65*, 8552–8563; (c) Sum, F. W.; Weiler, L. *Can. J. Chem*. **1979**, *57*, 1431–1441.
12. Horita, K.; Tanaka, K.; Inoue, T.; Yonemitsu, O. *Tetrahedron* **1996**, *52*, 551–564.
13. The process proceeds also with other cooxidants giving, in some cases, higher yields of **19**/**20**. Further details will be reported elsewhere.