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RuO_4-promoted *syn*-oxidative polycyclization of isoprenoid polyenes: a new stereoselective cascade process

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Abstract—Isoprenoid polyenes farnesyl acetate, geranylgeranyl acetate and squalene undergo oxidative polycyclization to bis-, tris-, and penta-tetrahydrofurane products, respectively, in the presence of catalytic amounts of RuO_4 (from $RuO_2{\cdot}2H_2O$) and $NaIO_4$ as primary oxidant. The stereochemistry of the bis-cyclization product was established as *cis-threo-cis-threo* through chemical methods and 2D-NMR experiments, and a cascade mechanism was proposed that explains the reactivity exhibited by all the related polyenes. A similarity with rhenium(VII) chemistry has emerged.

2,5-Disubstituted tetrahydrofurans (THFs) are structural fragments commonly encountered in such natural substances as polyether antibiotics, squalene-derived metabolites such as eurilene, teurile and glabrescol, and *Annonaceous* acetogenins. Very often in these substances two or more such THF rings are adjacent to one another and the resulting poly-THF subunit is flanked by one or two hydroxymethyl groups. The wide range of biological activities exhibited by *Annonaceous* acetogenins,[1] including inter alia cytotoxic, antitumor, antimicrobial and immunosuppressive properties, is attributed to the binding ability of their core poly-THF with physiologically important metal cations such as Ca^{2+} and Mg^{2+}.

The synthesis of many of these substances, or their non-natural analogues, has been carried out where a central point was the stereoselective construction of the poly-THF portion. Different approaches have been used to this aim. Besides classical methods such as the epoxidation/*anti* cyclization sequence of bis-homoallylic alcohols, or the five-membered-ring-selective multiple Williamson reaction of poly-hydroxytosylates,[2] a totally different approach, involving the action of transition metal oxo species both on bis-homoallylic alcohols and 1,5-dienes,[3] has been developed mostly in the last decade. This allows the obtention of THF rings with a stereochemistry often described as 'complementary' to that accessed with the former methods. On this ground, great attention is currently being paid to the development of new methodologies involving metal oxides that could allow the stereocontrolled closure of THF rings.

As a continuation of our interest in the ruthenium tetroxide chemistry,[4] we report here the first example of a RuO_4-mediated oxidative polycyclization process that allows the assembly of up to five contiguous THF rings in a single step. Readily available farnesyl acetate, geranylgeranyl acetate and squalene[5] were chosen as starting materials for the preliminary study here presented.

In a typical experiment, farnesyl acetate (1.2 mmol) was dissolved in the biphasic mixture $EtOAc/CH_3CN/H_2O$ (3:3:1)[6a] (140 mL),[6b] then $NaIO_4$ (4 equiv.) and a catalytic amount of $RuO_2{\cdot}2H_2O$ (Table 1) were added in sequence to the vigorously stirred mixture. After consumption of the starting product (30 min, TLC monitoring), excess of a saturated $Na_2S_2O_3{\cdot}5H_2O$ solution was added (ca. 1 mL) until the mixture turned black (RuO_2 precipitation). Filtration followed by extraction with EtOAc and HPLC separation (hexane–EtOAc, 3:7) afforded the bis-THF diol **1** and the corresponding C-2 ketone **2** (Scheme 1; for yields see Table 1) as the main reaction products. A product (**3**), eluted slightly after **1** on HPLC, was tentatively identified as a bis-THF isomer of **1**. Spectral analysis of the remaining products from HPLC indicated they mainly arose from

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Keywords: isoprenoid polyenes; RuO_4; oxidative polycyclization; poly-THF; cascade process.

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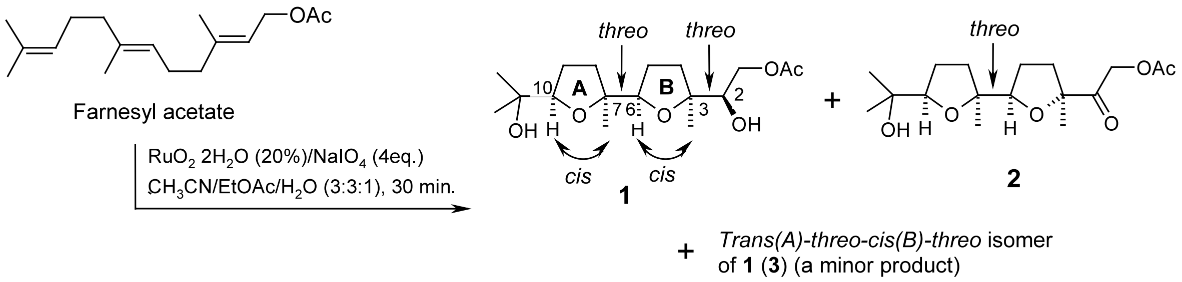


Scheme 1.

the scission of the Δ^6 and Δ^{10} double bonds, according to the known RuO_4 reactivity.

The structural relationship between **1** and **2** was proven by oxidation of **1** to **2** with $TPAP_{(cat.)}$/NMO/MS in CH_2Cl_2 (80%, 1 h).

Extensive 2D-NMR studies (COSY, ROESY, HSQC, HMBC) were carried out on **1**. As for the configuration of **1**, as observed for structurally related molecules,[7] the presence of strong ROESY effects between H-10 and Me-7, and H-6 and Me-3, but not between H-6 and H-2, unambiguously pointed to a *cis* configuration for both THF rings in **1**. However, spectral methods alone were unable to furnish unequivocal information on the stereochemical relationship between chiral centers C-2,C-3, and C-6,C-7 that was established to be *threo* in both cases through chemical methods, as detailed below.

The effect of the RuO_2 (Table 1) and $NaIO_4$ amounts on the process with farnesyl acetate was evaluated. When the RuO_2 amount is maintained constant, an increase of the amount of the co-oxidant does not affect yields of either **1** or **2** but the amount of co-oxidant needed for the process to go to completion depends on the number of double bonds composing the polyene. In particular, we observed that one more equivalent of $NaIO_4$ is required for each additional double bond. Referring to the RuO_2 amount, the best yield of bis-THF diol **1** is obtained with 20% RuO_2 (Table 1, entry 2) while 90% RuO_2 (entry 9) gives the highest amount of bis-THF ketone **2**. 10% RuO_2 (20% RuO_2 gave almost the same result) affords the best overall yield of the bis-THF products (**1**+**2**), while the yield of isomer **3** is always acceptably low (0.8–2.5%).

Table 1. Yields refer to isolated (HPLC) products

Entry	$RuO_2 \cdot 2H_2O$ (%)	1	2	3	1+2
1	10	23.4	33.2	2.2	56.4
2	20	28.8	27.4	1.6	56.2
3	30	28.5	16.9	2.1	45.4
4	40	18.5	22.9	1.3	41.4
5	50	27.0	19.5	2.5	46.5
6	60	13.8	24.2	1.7	38.0
7	70	16.9	27.5	0.8	44.4
8	80	16.4	30.0	1.1	46.4
9	90	15.5	34.1	1.1	49.6
10	100	18.5	28.5	0.8	47.0

Attempts to lessen the yield of **2** by reducing reaction times (RuO_4 can overoxidize **1** at C-2) only resulted in an incomplete process while leaving the **1**/**2** ratio almost unchanged.

A further improvement of the yield of **1** would be synthetically useful. McDonald reported[8] that reduction of the ketone function flanking a *cis*-THF ring in a molecule strictly similar to **2**, with the $NaBH_4/CeCl_3 \cdot 7H_2O$ system, afforded the alcohol with the chirality corresponding to that of **1** at C-2 with a >90% diastereoselectivity. Reduction of **2** in the above conditions gave, however, a mixture of **1** and its C-2 epimer in a ca. 2:1 ratio (^1H NMR). Nevertheless, after one recycle step (oxidation of the unwanted C-2 epimer with $TPAP_{(cat.)}$/NMO/MS in CH_2Cl_2, followed by reduction), **2** could be converted into **1** in a 79% yield (for three steps) bringing the total yield of **1** to 50.5% (Table 1, entry 2).

When the oxidation process was stopped before its completion, the two mono-THF diols **4** and **5** (Fig. 1), could be isolated from the reaction mixture. It is likely that these derive from partial oxidative cyclization of farnesyl acetate and that they eventually lead to bis-THF **1** and **3**, respectively, in a second cyclization step. 2D-ROESY experiments indicated that the THF ring was *cis* in **4** and *trans* in **5** (observed NOE effects as shown). This not only further supported that the THF ring A was *cis* in **1** as well, but also suggested that the observed polycyclization was a sequential process starting from the double bond (Δ^{11}) farthest from the acetate.[4a,9]

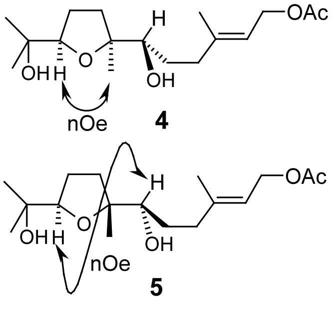


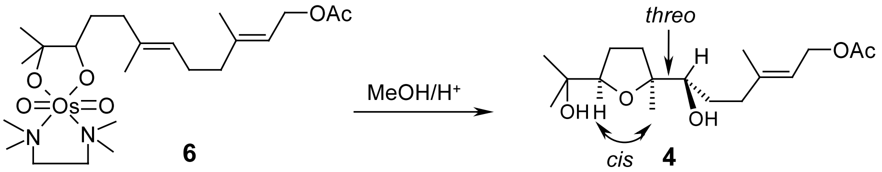
Figure 1.

The *cis* nature of the THF ring in **4** was further proven by its stereoselective synthesis through the recently reported Donohoe's methodology,[10] starting from the osmate ester **6** (Scheme 2), in turn obtained from reaction of farnesyl acetate with OsO_4 in the presence of TMEDA. This experiment also settled the *threo* relationship between the THF and C-6 oxygens in **4**. In fact it is known that in the OsO_4-mediated monocyclization of 1,5-dienes the three oxygen atoms composing the THF-diol portion are added through a double *syn* addition across both the double bonds. The *threo* relationship between C-2 and C-3 in **1** came from the following evidence. The C-2 epimer of **1**, obtained by reduction of **2** as above described, was shown to be identical to one of the two bis-THF diol products obtained from **4** by the one-pot epoxidation/acid-catalyzed epoxide opening carried out with MCPBA (2 equiv.) in CH_2Cl_2. This result also chemically correlated **4** and **1** thus fixing the C-6/C-7 *threo* relationship also in the latter, having been demonstrated in the former.

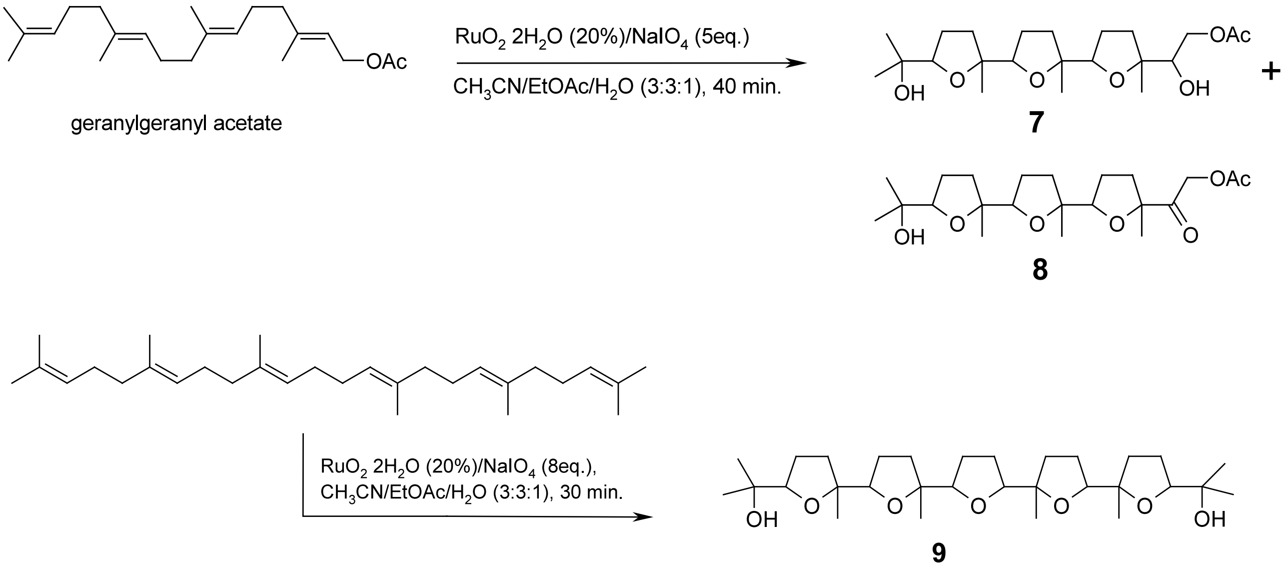
Polycyclization of geranylgeranyl acetate (20% RuO_2) required 5 equiv. of $NaIO_4$ and 40 min. to go to completion (Scheme 3). A mixture of tris-THF diol **7** and the corresponding tris-THF ketone **8** was obtained though in an overall (**7**+**8**) 28–30% yield (HPLC:hexane–EtOAc, 3:7; **7**/**8** ca. 2:1). The structural relationship between **7** and **8** was proven by conversion of the former into the latter as for the pair **1**/**2**.

Oxidation of squalene (Scheme 3) required 8 equiv. of $NaIO_4$ and was complete in 30 min, giving the penta-THF diol **9** in a 50% yield corresponding to an 87% average yield for each cyclization event (Scheme 4). The presence of 30 carbon peaks in the ^{13}C NMR of **9** and eight distinct methyl peaks in its ^1H NMR spectrum indicated that it possessed a non-*meso* structure. This compound has the same constitution of glabrescol, a *meso* naturally occurring substance isolated from the Caribbean plant *Spathelia glabrescens*.[11] Elucidation of its configuration had required synthetic efforts by Corey[12a] and Marimoto[12b] groups that culminated in the revision of the initially proposed configuration for this compound. In the light of the complexity of synthetic routes towards this type of substances and the low yields often obtained (1–4%) for those synthesized (all *meso*), the one-pot obtention of the non-*meso* product **9**, though racemic, in a 50% yield, appears to be a remarkable result.

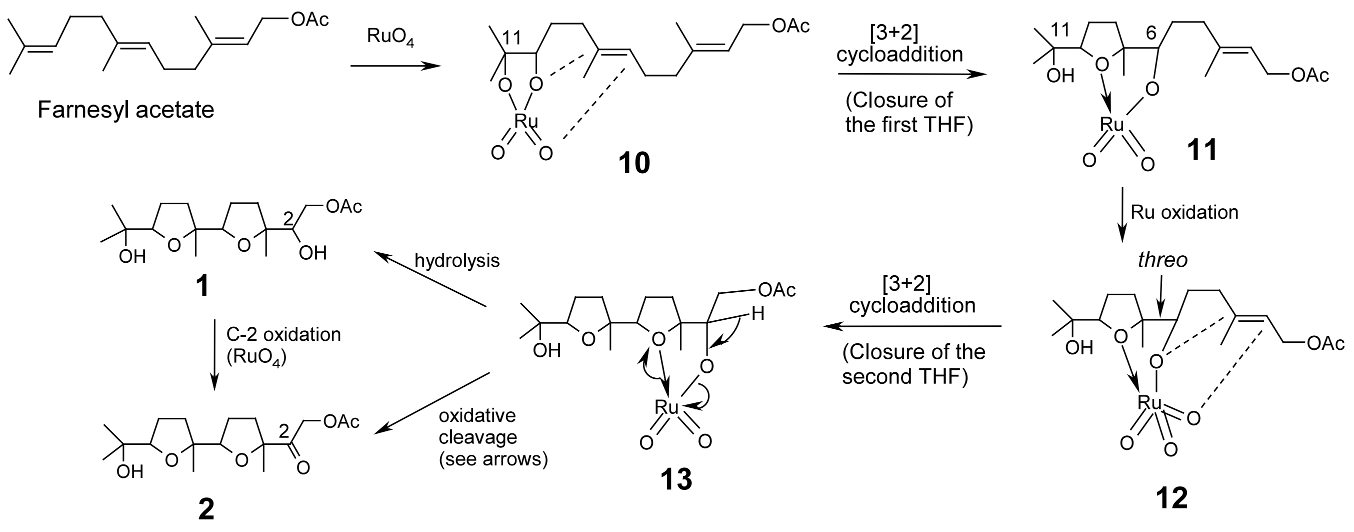
A mechanistic hypothesis for the new process is shown in Scheme 4 for farnesyl acetate, that envisages a cascade of ring-closing steps. In particular, in the first step the ruthenium(VI) diester **10** is formed by interaction of RuO_4 and the Δ^{10} double bond. Closure of the first THF ring, through a [3+2] cycloaddition of the O–Ru=O portion of **10** on the nearest (Δ^6) C–C double bond, and hydrolysis of the C(11)O–Ru bond, would then follow leaving an $ORuO_2$ appendage linked at C-6



Scheme 2.



Scheme 3.



Scheme 4.

in **11**. *cis* Stereoselectivity for this cyclization step is generally attributed to the steric constrain imparted to the cyclizing system by the intact C(10,11)–O–Ru bonds. Ruthenium oxidation would need at this stage to bring the Ru atom at the 'active' oxidation level (possibly Ru(V)→Ru(VII)), generating species **12**. This well explains the need for the observed increasing of the $NaIO_4$ amount when the number of double bonds of the polyene increases. The experimental data can be explained considering that each oxidation step at Ru requires one $NaIO_4$ equivalent. Intermediate **12** is now similar to the perrhenate ester involved into the reaction of bishomoallylic alcohols and acylperrhenates. The second THF ring would be formed through another [3+2] cycloaddition step involving O–Ru=O and the Δ^2 double bond to give **13**, a species similar to **11**, from which **1** would be released by hydrolysis and **2** by, at least in part, oxidative cleavage. Tris- (**7**/**8**) and penta-THF (**9**) products would be obtained by reiteration of the above sequence.

The *cis* stereoselectivity for the first cyclization is in accord with the known reactivity of RuO_4 with 1,5-dienes.[4a,9] The *cis* selectivity of the second ring-closing step can be explained invoking recent results from related rhenium(VII) chemistry reported by Sinha et al.[13] These authors proposed that in the single step biscyclization of polydisubstituted alkenols with $CF_3CO_2ReO_3$, the stereochemistry of the second cyclization step depends on the ability of the THF ring formed in the first cyclization to chelate the Re atom and on the relative configuration of the two vicinal oxygens formed in the first cyclization (*O*-THF and *O*-C(6) in **12**). In particular, a *threo* relationship produces a *cis*-THF, an *erythro* relationship a *trans*-THF. Our results are in agreement with the first of these rules, further enforcing the above, and previously,[4b] proposed similarity between rhenium and ruthenium behavior in oxidative cyclization processes.

Based on the all-*trans* nature of geranylgeranyl acetate and the above rules, it could be anticipated that the tris-THF **7** possesses a *cis*-*threo*-*cis*-*threo*-*cis*-*threo* configuration. In order to prove this hypothesis, and to provide further support to the above rules, determination of the relative configuration of the synthesized tris- and penta-THF products remains to be accomplished. Work is in progress toward this goal.

From the above mechanistic model, taking into account RuO_4 chemistry[4a,9] (minor amounts of a *trans*-THF product are obtained in the monocyclization of geranyl acetate), as well as isolation of intermediate **5**, it can be hypothesized that the bis-THF isomer **3** has a *trans*-*threo*-*cis*-*threo* configuration.

Re(VII)- or Cr(VI)-promoted double and triple, oxidative cyclizations have been previously observed,[14] but formation of a penta-THF product through a *quintuple* oxidative cyclization is unprecedented.

Future efforts of our group will be aimed at establishing the relationship between the configuration of the starting polyene and the poly-THF product by synthesizing suitable polyene substrates. This would allow to use this reaction in a stereochemically predictable way.

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5. Farnesol and geranylgeraniol were purchased from Aldrich and acetylated; squalene was purchased from Aldrich as well. All products were further purified by HPLC prior the use.
6. (a) We have shown[4a] that this solvent mixture improves the stereoselectivity level and yields of the oxidative cyclization of isoprenoid 1,5-dienes geranyl and neryl acetate; (b) Be sure that the amount of solvent used dissolve all the $NaIO_4$; otherwise lower yields result.
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