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RuO_4-catalyzed oxidative polycyclization of the C_s-symmetric isoprenoid polyene digeranyl. An unexpected stereochemical outcome

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ABSTRACT

The RuO_4-catalyzed oxidative polycyclization of digeranyl, a C_s-symmetric tetraene possessing a repetitive 1,5-diene structural motif, has been studied. The required substrate has been synthesized by Ti(III)-mediated tail-to-tail homocoupling of geranyl bromide. The process afforded two hitherto unknown isomeric tris-tetrahydrofuran products possessing unexpected all-*threo cis–trans–cis* and *cis–trans–trans* relative configuration. The new stereochemical outcome is explained based on previously formulated chelation or steric control models on the basis of structural differences between digeranyl and previously studied isoprenoid polyenes farnesyl acetate, geranylgeranyl acetate and squalene.

1. Introduction

The ruthenium tetroxide mediated oxidative polycyclization (OP) of polyenes characterized by a repetitive 1,5-diene structural motif is a stereoselective process discovered a few years ago in our laboratories (Scheme 1).[1] It allows access to adjacently linked polytetrahydrofuran products in a single step employing catalytic amounts of ruthenium tetroxide in the presence of $NaIO_4$ as co-oxidant. Among the cases studied so far, the polycyclization of squalene appears to be a remarkable process since a penta-THF product (**1**) comprised of 10 chiral centres is obtained with a 50% yield as a single diastereoisomer (Scheme 1), through what appears to be a complex multistep cascade sequence.

Previous studies from our group allow a number of conclusions to be drawn. (a) Poly-THF products derived from the oxidation of all-*trans*-polyenes, all display a *threo* inter-THF stereorelationship indicating a *syn* addition of oxygen pairs to all the involved double bonds; (b) the first-formed THF along the poly-THF chain always possesses a cis configuration, in agreement with the stereochemical control operating in the strictly related oxidative mono-cyclization of 1,5-dienes catalyzed by the same oxide;[2] (c) the second and the third THF rings possess cis and trans configurations, respectively, in all the cases studied; (d) when the third double bond along the polyene chain possesses a cis configuration, such as in (*E*,*Z*)-farnesyl acetate,[1b] the process stops at the mono-THF level.

Due to the still limited number of cases examined, many of which concern the oxidation of all-*trans*, or predominantly trans, isoprenoid polyenes, the factors governing the stereochemistry of the process are not completely known and general stereochemical rules, if any, cannot yet be formulated. In order to further amplify our knowledge about this transformation we have now studied the oxidative polycyclization of digeranyl (Scheme 2, **2**), a C_s-symmetric isoprenoid tetraene, synthesized by titanocene chloride-catalyzed allylic homocoupling of geranyl bromide, according to a reported procedure.[3] In particular, we wanted to test the effect of the head-to-tail fusion of the two central isoprene units in **2**, never explored in previous instances. As will be detailed below, we have found that this structural feature profoundly affects the stereochemistry of the process.

2. Results and discussion

Isolation of pure samples of **2**[3,4] required careful chromatography on silica gel impregnated with silver nitrate to separate the required tetraene from the isomeric α–γ′ tetraene (isogeranyl,[5] **3**) obtained as the main side-product (20%) of the process (Scheme 2). The γ–γ′ coupling product **4** was also isolated in minute amount (2%), and fully characterized for the first time. Compounds **2** and **3** are naturally occurring terpenes found in the commercially available bergamot oil.[6]

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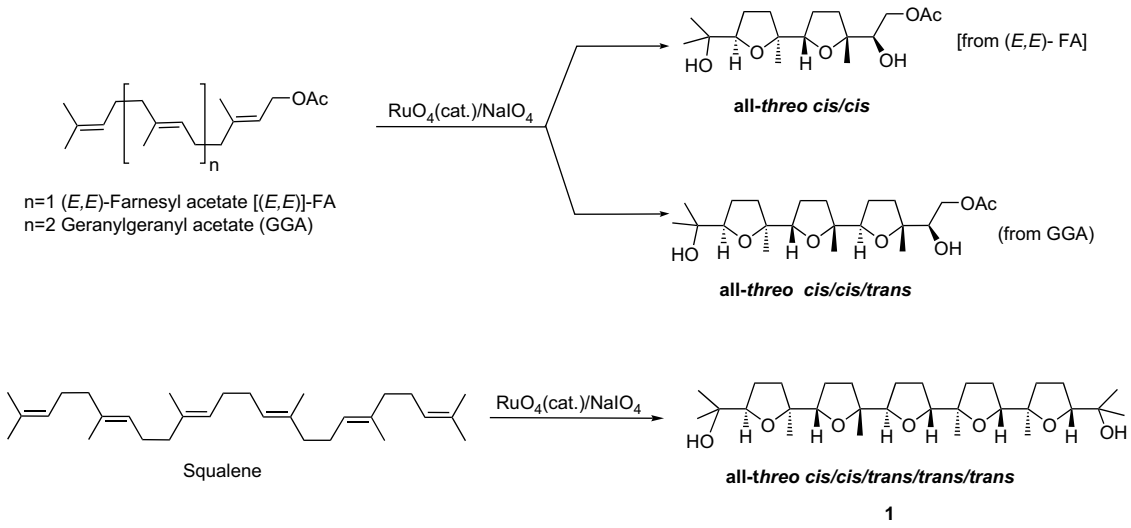
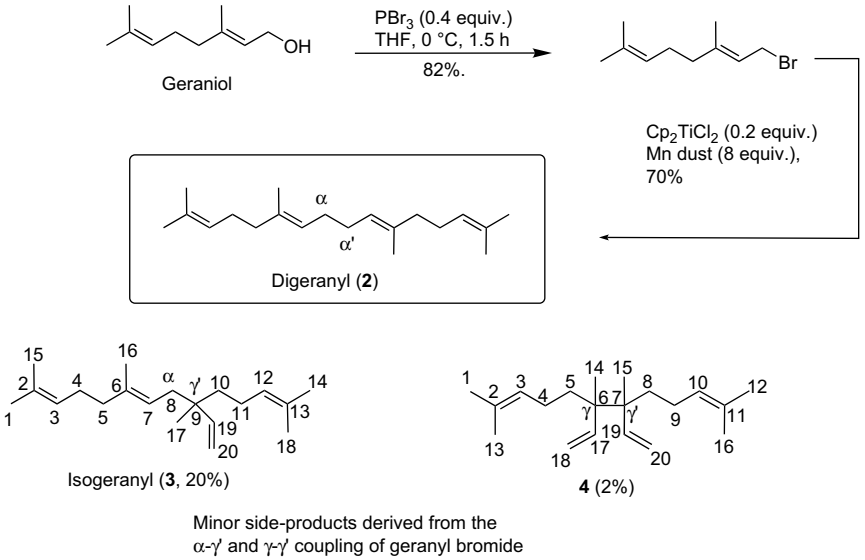


Scheme 1. Representative examples of the oxidative polycyclization of isoprenoid polyenes catalyzed by ruthenium tetroxide.

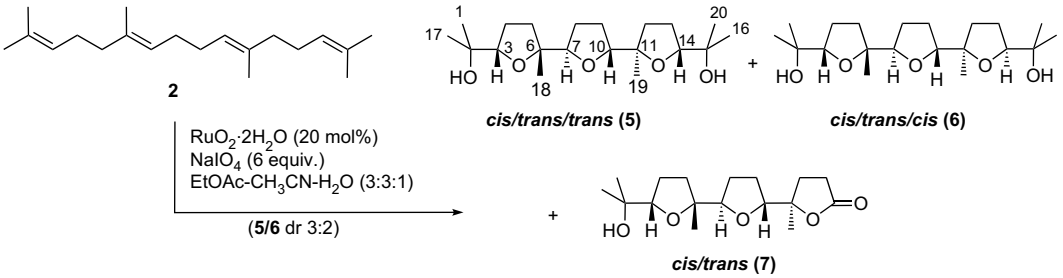
Our standard polycyclization conditions [$RuO_2 \cdot 2H_2O$ (20 mol %) as pre-catalyst, $NaIO_4$ (6 equiv), EtOAc–CH_3CN–H_2O (3:3:1)][1a] were initially employed for the oxidation of **2**. In particular, according to our previous results,[1a] the presence of four olefinic bonds in **2** called for six molar equivalents of periodate (assuming a 4 equiv amount for a 1,5-diene subunit plus one more equiv.[1a] for every additional double bond). While mass recovery was in line with that observed in previous instances,[1] the HPLC profile of the crude reaction mixture exhibited a more complex pattern. Among the major peaks, tris-THF compounds **5** and **6** (Scheme 3) were isolated in a 14% overall yield (**5**/**6** dr 3:2) along with bis-THF lactone **7** (15%) whose presence suggested that the process stops in part to the second ring-closing step.

Determination of the stereostructure of these compounds proved not trivial and required both extensive 2D NMR experiments and chemical work. A full set of 2D NMR experiments was initially carried out in $CDCl_3$ for all three compounds **5**–**7**. However, due to the high degree of superimposition of some ^1H and ^{13}C resonances pertaining to the THF rings, that occurred even in the two-dimensional experiments, the collected data did not provide unequivocal evidence on the relative configuration of either tris-THF **5** or **6**. A new set of NMR data was, therefore, collected for these compounds in pyridine-d_5 where a good proton dispersion was observed for all methyl and angular THF proton resonances in their ^1H NMR spectra, allowing to definitively clarify all the doubtful 2D NMR correlations.

In particular, the cis configuration of ring A in all three compounds **5**–**7** was suggested by the presence of a strong NOESY correlation between the angularly positioned H-3 and Me-18, as usually observed in *cis*-THF rings belonging to poly-THF compounds of the same type[1,7] (Fig. 1 shows significant NOESY correlations for **5**). Ring B in **5** and **7** was characterized by a trans-arrangement as primarily suggested by the lack of a NOE correlation between the H-7 and H-10 protons[1,7] in their NOESY spectra. Further support came from the key NOESY correlation between Me-1(or Me-17) and H-10. The latter correlation, together with the stronger one between Me-18 and H-7 indicated that A and B rings are almost orthogonally oriented one another possibly due to a hydrogen bond between the C_2-OH and the ring-A THF oxygen, as models show.



Scheme 2. Synthesis of digeranyl and two of its isomers by titanocene chloride-mediated homocoupling of geranyl bromide.



Scheme 3. Oxidative polycyclization of tetraene **2** with RuO_2(cat.)/$NaIO_4$.

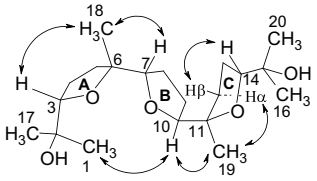


Figure 1. Spatial arrangement of **5** as derived from NOESY data (arrows).

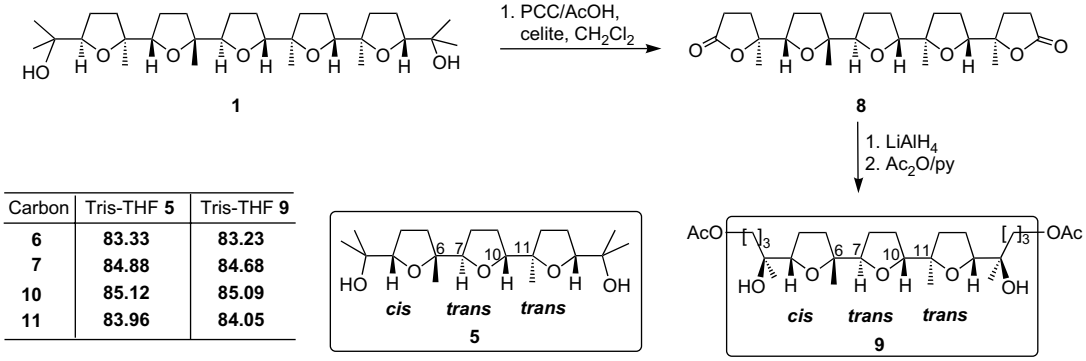
Finally ring C in **5** was shown to possess a trans configuration as well on the basis of the lack of NOE contact between angular Me-19 and H-14 and by the NOESY correlations observed between the proton pairs H-14/H-12$_\beta$ and Me-19/H-12$_\alpha$. A NOESY correlation between Me-19 and H-10 was also observed that settled the relative arrangement of rings B and C, as depicted in Figure 1. This spatial arrangement also agrees with that obtained for **5** through molecular mechanics.

The *trans* nature of the central THF ring in **5** was also corroborated by the good agreement of the chemical shift values of the oxygen-carrying carbons (C-6, C-7, C-10, C-11) belonging to the central region of this compound with those displayed by the corresponding carbons in the structurally related *cis-threo–trans-threo–trans-threo* tris-THF **9** (Scheme 4), previously obtained by bidirectional PCC-mediated oxidative degradation of penta-THF **1**,[1c] followed by LAH reduction of the resulting bis-lactone **8** and acetylation.

However, NMR studies could not provide information on the configuration of the central THF ring in **6** due to its C_2-symmetry, though the presence of a single bis-THF lactone (**7**) in the reaction mixture suggested that also in **6** the first two THF rings possess a cis–trans configuration since the former can be formed along the polycyclization route eventually leading to tris-THF **5** and **6** (see later for an explanation of the mechanistic relationship among compounds **5**–**7**). To confirm this inference compound **6** was subjected to PCC oxidation in the same conditions previously employed for penta-THF **1**[1c] (Scheme 5) to cleanly give a mixture of bis-THF lactone **7**, the C_2-symmetric bis-lactone **10**, previously obtained by penta-THF **1**,[1c] and unreacted **6** in a 2:1:3 ratio, as judged by ^{1}H NMR spectroscopic analysis and confirmed by HPLC separation. This experiment definitively inter-related bis-THF lactone **7** and tris-THF **6** confirming the trans configuration of the central THF ring in the latter compound as well. The all-*threo* arrangement in compounds **5**–**7** was assumed on the basis of all stereochemical results previously obtained in this type of process[1] and the closely related Re(VII)-mediated bis- and tris-oxidative cyclization of bis-homoallylic alcohols.[8]

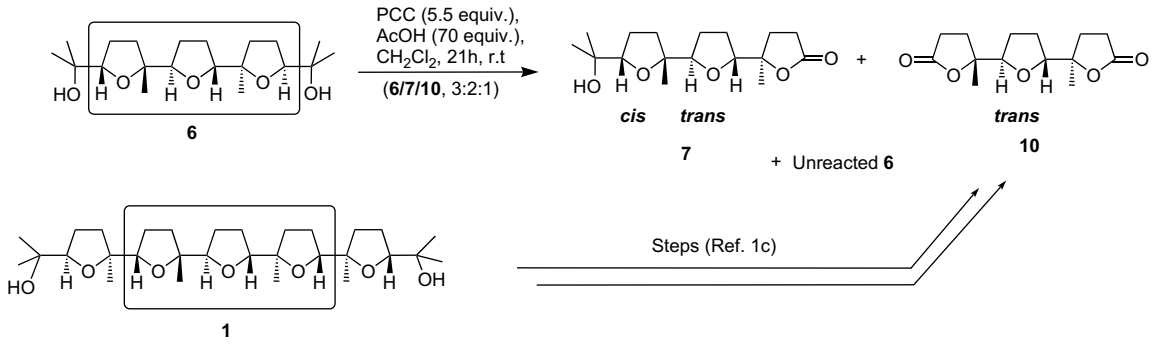
The stereochemical outcome of the above process was unexpected in view of the previously observed stereochemistry of the OP of other isoprenoid polyenes (Scheme 1), all giving poly-THF compounds as single stereoisomers (dr>95%), as well as considering the configuration of poly-THF products **5**–**7**. In fact, contrary to what happened in all the previously studied cases, where the first two THF rings both displayed a cis configuration, all three compounds **5**–**7** possess the second THF with an unprecedented trans configuration. On the other hand, the third THF ring in **5** and **6** is either trans or cis in contrast to poly-THF products obtained from the OP of geranylgeranyl acetate and squalene (Scheme 1) where the third THF was constantly trans.

The above results can be accounted for by the mechanistic path shown in Scheme 6 for tetraene **2**, that also takes into account our previously formulated hypothesis[1d,1e] and the closely related oxidative polycyclization of polyenic bis-homoallylic alcohols carried out with rhenium (VII)-oxo species.[7,8] In particular, a cascade of consecutive ring-closing steps begins with the attack of RuO_4 at the terminal double bond to give ruthenium (VI) diester **11**. Closure of the first THF ring proceeds with cis stereocontrol, as usually observed in the oxidative mono-cyclizations of 1,5-dienes mediated by all three related oxo species RuO_4,[2] OsO_4[9] and MnO_4^-.[10] Thus, a *cis-threo* mono-THF intermediate species (**13**) is obtained through a [3+2] cycloaddition of an O–Ru=O portion of the intact ruthenium bis-glycolate **11** across the second C–C double bond, with the molecule adopting the chair-like conformation **12** in the transition state. Then, the metal, is oxidized at an

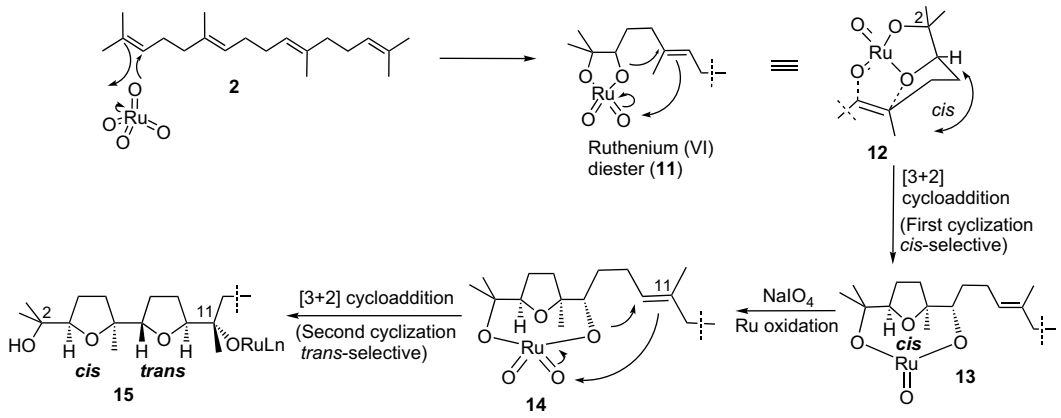


Carbon	Tris-THF **5**	Tris-THF **9**
6	83.33	83.23
7	84.88	84.68
10	85.12	85.09
11	83.96	84.05

Scheme 4. Comparison of structure and selected ^{13}C NMR data for tris-THF **5** and the closely related tris-THF diol **9**.



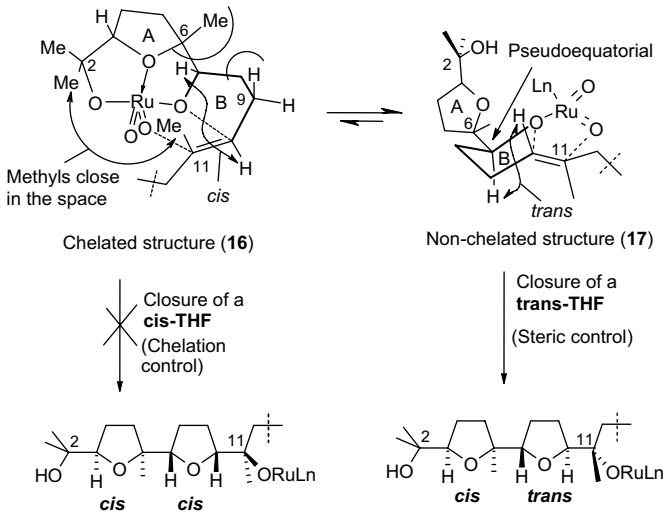
Scheme 5. Bidirectional PCC oxidative degradation of tris-THF **6** and penta-THF diol **1**, derived from the OP of squalene.



Scheme 6. Proposed mechanism for the first two cyclization steps of the Ru-catalyzed oxidative polycyclization of tetraene **2**.

'active' oxidation state (intermediate **14**) by $NaIO_4$, thereby allowing for the second cyclization step to take place via another [3+2] cycloaddition reaction once more involving a O–Ru=O and the successive double bond in the carbon chain, to give the bis cyclized intermediate **15**.

From a stereochemical point of view, we have previously hypothesized[1d,1e] that the observed cis selectivity of the second cyclization step of polyenes such as FA, GGA or squalene (Scheme 1) can be due to an arrangement of the molecule where the first-formed THF ring (A) is coordinated to the metal, so that a *chelation control* is operative (Scheme 7, **16**). However, this appears not to be the case for **2**. We note that polyene **2**, from a structural point of view, possesses a methyl group bonded to the C-11 vinyl carbon and a hydrogen at C-10, while in the previously studied polyenes, shown in Scheme 1, the head-to-tail fusion of the third isoprene



Scheme 7. Chelation control versus steric control in the second cyclization step of the Ru-catalyzed OP of **2**.

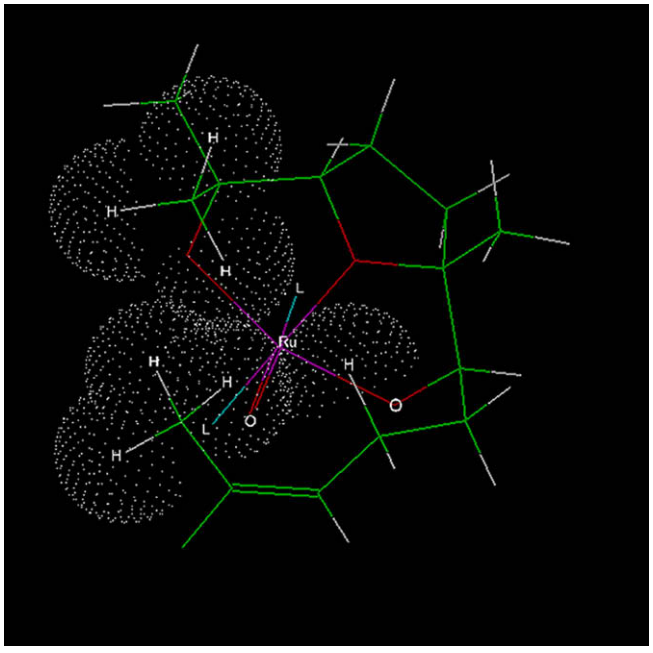


Figure 2. Computer-generated 3D structure showing the TS (**16**) for the second cyclization step of **2**. An octahedral arrangement of ruthenium is assumed. The Van der Waals radii of H-9 and protons of Me-1, Me-11 are evidenced by white dots clouds.

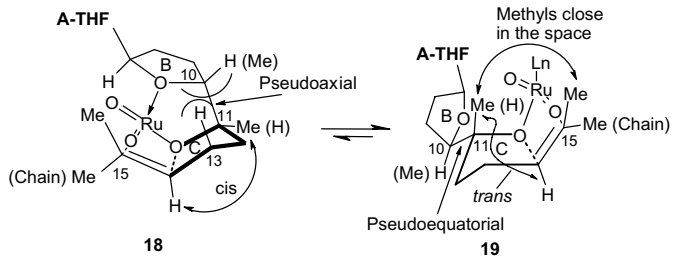


Figure 3. Arrangements that help to explain a cis-selective (**18**) third ring-closing step for tetraene **2** and a trans-selective (**19**) third ring-closing step for **2** and GGA/squalene. For **2**: C_{10}-H/C_{11}-Me/C_{15}-Me; for squalene and GGA: C_{10}-Me/C_{11}-H/C_{15}-chain.

unit places a methyl at C-10 and a hydrogen at C-11 in these compounds. This different substitution pattern in **2** appears to be responsible for the different stereochemical outcome of the second cyclization step in this polyene that is now trans-selective. In particular, when referring to the transition state for the second cyclization step, the C-11 Me group is in close proximity to Me-1 (Scheme 7, **16**). This, in addition to the 1,3-diaxyal interaction between the C-6 grouping and the H_{ax}-9, hampers the approach of the vinyl unit to the O–Ru═O portion. Figure 2 shows a computer-generated 3D structure of TS **16** where the vicinity in the space of M-11 and Me-1 can be best appreciated. Therefore, the alternative arrangement **17** (Scheme 7), where the C(2)O–Ru bond is broken and the A-THF ring is not coordinated to the metal, and pseudoequatorially disposed, appears to be now the favoured arrangement, that leads to a *trans*-THF through *steric control*. According to this model, we presume that the second cyclization step for the OP of **2** is under steric control.

Finally, we have to explain the stereochemistry of the third ring-closing step. This cyclization step, different from the OP of GGA and squalene, that typically give a *trans*-THF, is less stereoselective because either a *cis*-THF or a *trans*-THF is formed, though the compound embodying the *trans* C-THF (**5**) is still slightly predominant. The trans configuration of the second THF ring pushes the A-ring away from the metal preventing its coordination (Fig. 3). However, just as seen for the second cyclization step, B-THF ring can, in principle, coordinate to ruthenium, in which case the cyclization step would be cis-selective through a chelation control, or not coordinate to it, leading to a *trans*-THF through steric control. Once again, we believe that the exchange of the Me/H pair between C-10 and C-11, when passing from GGA and squalene to **2**, plays a crucial role in determining the balance of trans/cis configuration of the newly formed THF ring. In particular, referring to a cis-selective step, arrangement **18** would be involved where the C-10 grouping is pseudoaxially disposed. The situation for the OP of GGA and squalene, where a methyl at C-10 is present, is analogous to that seen for the second cyclization of **2** (Scheme 7) though, in this case, the Me-15 (analogous to Me-11 in **16**) does not pose steric problems due to the trans configuration of the B-THF. Overall the approach of the C–C double bond to the O–Ru═O portion appears to be unfavourable in the TS for steric reasons and the alternative arrangement **19**, where the B-ring is not coordinated to the metal and the C-10 grouping is pseudoequatorial, is favoured for these products, leading to a *trans*-THF through steric control. As far as **2** is concerned, the presence of a hydrogen at C-10, in place of a methyl group, renders arrangement **18**, and the resulting closure of the *cis*-THF, less unfavourable (Fig. 4 compares the computer-generated 3D structures of the TS for the cis- and trans-selective third cyclization steps for **2** and GGA/squalene). On the other hand, conformation **19** appears now to be less favourable than for the OP of GGA and squalene due to the presence of Me-11 that is in close proximity with the terminal Me at C-15 as well as with ruthenium (in Fig. 5 the vicinity in the space of Me-11 and Me-15 is shown).

The above reasoning can also explain the unprecedented formation of bis-THF lactone **7**. Overall, the third cyclization is problematic and the alternative hydrolysis of the ruthenium ester intermediates (**18**/**19**) can favourably compete with the third cyclization step to give the bis-THF species **20** (Scheme 8). Then, the independent oxidation of the remaining double bond, according to the known reactivity of RuO_4 (Scheme 8),[11] would follow. In particular, the following steps can be envisaged to occur involving the terminal olefin: (i) dihydroxylation; (ii) oxidative scission of the so-formed diol system; (iii) hemiacetal formation involving the C_{11}-OH and (iv) the successive oxidation of the latter to a lactone. On the other hand, formation of **7** from tris-THFs **5**/**6**, successive to their formation, appears less probable since no trace of the isomeric *trans–trans* bis-THF lactone, in principle derivable from **5** or **6** through oxidative degradation of the *trans*- or *cis*-THF terminus, respectively, has been noticed by an accurate HPLC separation of the reaction mixture.

Attempts to improve the yields of the tris-THF products were carried out varying both the co-oxidant (6 to 8 equiv) and the

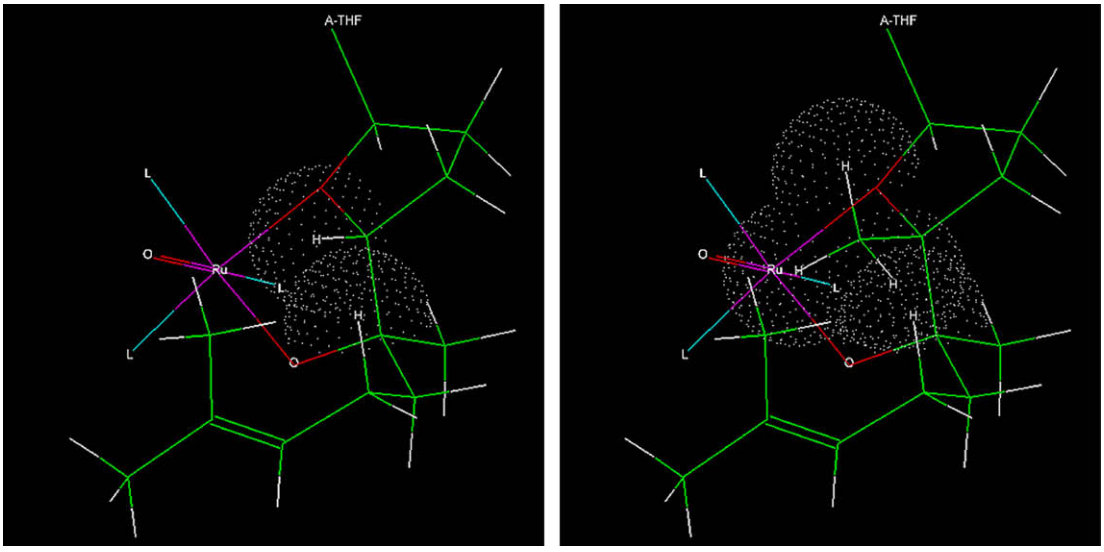


Figure 4. Computer-generated 3D structure showing the TS (**18**) for the cis-selective third cyclization step of **2** (left). On the right is shown the effect of a methyl at C-10 as in GGA and squalene. An octahedral arrangement of ruthenium is assumed. Van der Waals radii of relevant protons are evidenced by white dots clouds.

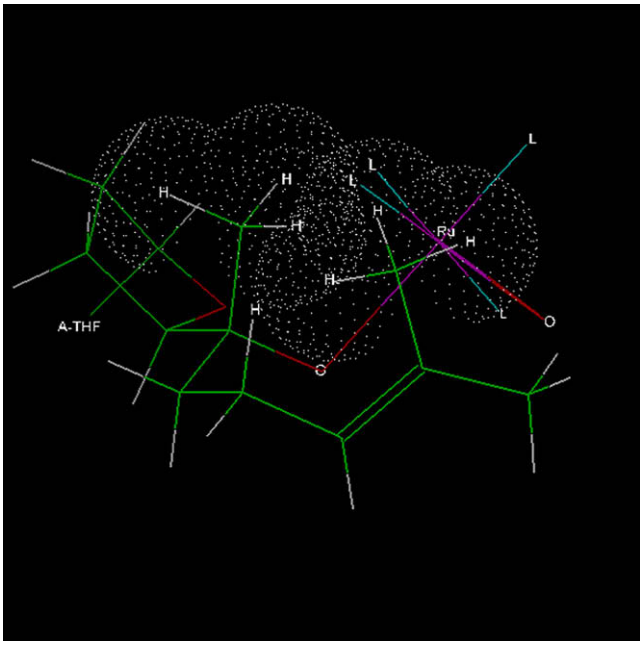


Figure 5. Computer-generated 3D structure showing the TS for the third *trans*-selective cyclization step of **2**. An octahedral arrangement of ruthenium is assumed. Van der Waals radii of relevant protons are evidenced by white dots clouds.

pre-catalyst (RuO_2 10% to 30%) amounts, but no substantial increase of the overall yield (lactone **7**+tris-THFs **5**/**6**) was observed. Carrying out the process under dilute conditions was also ineffective. On the other hand, when the process was conducted at room temperature the two tris-THFs were isolated in a ca. 1:1 ratio.

All-*erythro* tris-THF diol compounds possessing the same constitution as compounds **5** and **6** have previously been synthesized via epoxide chemistry[12] and have been shown to possess transport ability for physiologically important cations such as Na^+ and K^+. Poly-THF compounds possessing a terminal γ-lactone moiety such as compound **7** have synthetic value since this functionality can be further elaborated. Recently, these substances have been elected as key intermediates in the synthesis of the poly-THF core of Annonaceous acetogenins, a group of plant-derived active metabolites. For example, a mono-THF-γ-lactone, synthesized through related permanganate chemistry, has been used by Brown et al.[13] as an intermediate in the synthesis of membranacin, an adjacent bis-THF acetogenin. In a similar way, Gŏksel and Stark recently used a related mono-THF-γ-lactone to synthesize *cis*-solamin, a mono-THF acetogenin,[14] while Sinha et al. employed bis-THF lactones strictly similar to **7** to assemble the bis-THF diol core of a complete library of bis-THF Annonaceous acetogenins.[8j]

3. Conclusion

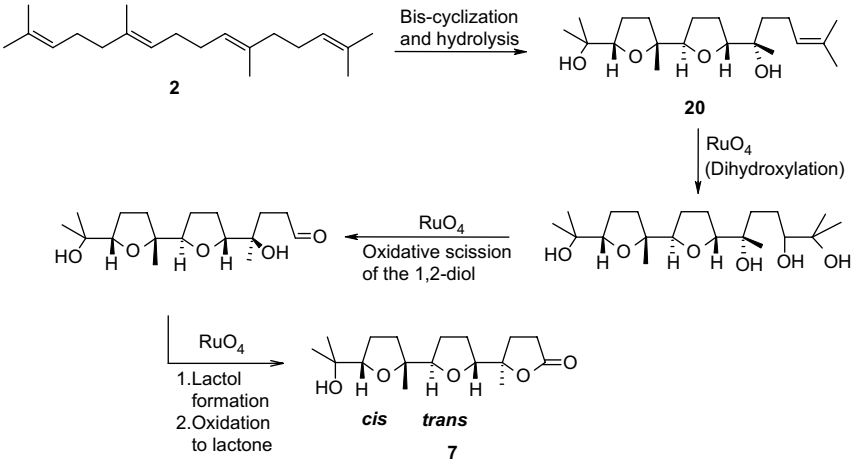
In conclusion, the oxidative polycyclization of tetraene **2** allowed access to poly-THF products with unprecedented configuration. The new stereochemical outcome here reported has shown for the first time that the type of alkyl substitution of the polyene can strongly affect, and even reverse, the stereochemistry of the RuO_4-mediated OP process of isoprenoid polyenes thus opening new opportunities for the use of this transformation in the synthesis of stereochemically defined poly-THF compounds by suitably tuning the structure of the starting polyene. The explanation given for the observed stereocontrol of each ring-closing step in terms of chelation or steric control is consistent with, and further supports, the previously formulated hypotheses for this type of process. The hitherto unknown all-*threo* tris-THF materials obtained are potentially able of cation transport. Experiments to verify this will be carried out.

4. Experimental

4.1. General methods

All reagents and anhydrous solvents were purchased (Aldrich) at the highest commercial quality and used without further purification. Where necessary, flame-dried and argon-charged glassware was used. Oxygen free THF was obtained by bubbling Argon into the solvent for 30 min. Reactions were monitored by thin-layer chromatography carried out on precoated silica gel plates (Merck 60, F_{254}, 0.25 mm thick). Merck silica gel (Kieselgel 40, particle size 0.063–0.200 mm) was used for column chromatography. Na_2SO_4 was used as drying agent in all extractive work-ups. HPLC separations were carried out on a Varian 2510 apparatus equipped with a Waters R403 dual cell differential refractometer using phenomenex 250×10 mm and 250×4.6 mm (both 5 μ) columns.

All NMR experiments were performed on a Varian Unity INOVA-500 spectrometer equipped with a 5 mm inverse detection *z*-gradient probe and Varian 300 spectrometer. The ^1H, ^{13}C and 2D NMR spectra were measured at 25 °C using $CDCl_3$ and pyridine-d_5 as solvents. Proton chemical shifts were referenced to the residual



Scheme 8. Mechanistic route to bis-THF lactone **7**.

$CHCl_3$ (7.26 ppm) or pyridine signals (8.71, 7.56, 7.19 ppm); ^{13}C NMR chemical shifts were referenced to the solvent ($CDCl_3$, 77.0 ppm; pyridine-d_5, 149.9, 135.5, 123.5 ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, br, broad. *J* values are given in hertz. One-dimensional ^1H and ^{13}C NMR spectra were acquired under standard conditions. The pulse programs of the gCOSY, gHSQC, TOCSY, gHMBC, NOESY and HSQC-TOCSY experiments were taken from the Varian software library. The gHSQC experiments were optimized for a one-bond heteronuclear coupling constant of 145 Hz. The gHMBC experiments were optimized for long-range coupling constants of 8 Hz. Two-dimensional TOCSY experiments were acquired with a mixing time of 80 ms while NOESY spectra were acquired with mixing times of 80, 200 and 350 ms.

IR spectra were collected on a Jasco FTIR-430 spectrometer. ESI mass spectrometric analyses were recorded on a Waters Micromass ZQ mass spectrometer equipped with an Electrospray source used in the positive mode. HRESIMS spectra were recorded on a Bruker APEX II FT-ICR mass spectrometer using electron spray ionization (ESI) technique in positive mode. HREIMS spectra were recorded on a Fisons VG Prospect mass spectrometer.

4.2. Synthesis of tetraene 2

To geraniol (2.15 g, 13.95 mmol) dissolved in anhydrous THF (10 mL), phosphorous tribromide (0.4 equiv, 5.6 mmol, 530 μL) was added dropwise under stirring, at room temperature. When the starting product disappeared (30 min, TLC monitoring, hexane–EtOAc, 7:3), ice was added and stirring continued for further a 10 min. The mixture was extracted with hexane (3×10 mL), dried and taken to dryness in vacuo to give geranyl bromide (2.472 g, 82%) that was used in the next step without further purification. Crude geranyl bromide (1.884 g, 8.65 mmol) was dissolved in anhydrous and strictly deoxygenated THF (20 mL), then Cp_2TiCl (431 mg, 0.2 equiv, 1.73 mmol) was added followed by portionwise addition of Mn dust (3.80 g, 8 equiv, 69.2 mmol), under an argon atmosphere. The red-wine solution turned to green within 2–3 min. After 5 min, TLC analysis (hexane/EtOAc, 95:5) revealed the disappearance of the starting allyl halide (R_f=0.6) and formation of a product at R_f=0.8. The mixture was diluted with ether and 1 N HCl was cautiously added (gas evolution) until effervescence ceased. The mixture was extracted with *t*-BuOMe (3×10 mL), dried and concentrated under reduced pressure to give an oily product (1.215 g) that was filtered on a short pad of silica gel eluting with hexane/*t*-BuOMe (4:1). ^1H NMR analysis showed the crude reaction product to be composed by a mixture of α,α′- and α,γ′ coupling products in a 3.5:1 approximate ratio. The crude mixture (906 mg) was further chromatographed on $AgNO_3$ (20%)-impregnated silica gel. Slow elution with hexane/EtOAc (98:2) gave pure **2** (581 mg, 70%), the α,γ′ coupling isomer **3** (166 mg, 20%) as well as a minute amount of the γ,γ′ coupling isomer **4** (16.5 mg, 2%).

4.2.1. Compound **2**[3,4]

Oil. ^1H NMR (300 MHz, $CDCl_3$): δ 5.19–5.05 (4H, m, olefinic protons), 2.13–1.92 (12H, m), 1.68 (6H, s), 1.60 (12H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.9, 17.6, 25.6, 26.7, 28.1, 39.7, 124.2, 124.3, 131.1, 134.9. HREIMS calcd for $C_{20}H_{34}$ 274.2661, found 274.2650 (M^+).

4.2.2. Compound **3**[5]

Oil. ^1H NMR (300 MHz, $CDCl_3$): δ 5.74 (1H, dd, *J*=17.7, 11.0, H-19), 5.08 (3H two apparent br t, overlapping, both *J*=6.0, H-3, H-7, H-12), 4.98 (1H, dd, *J*=11.0, 1.7, H_a-20), 4.90 (1H, dd, *J*=17.7, 1.7, H_b-20), 2.12–1.92 (8H, m), 1.67 (6H, br s, 2×vinyl methyls), 1.60 (6H, br s, 2×vinyl methyls), 1.58 (3H, s, vinyl methyl), 1.35–1.25 (2H, m), 0.95 (3H, s, CH_3-17). HREIMS calcd for $C_{20}H_{34}$ 274.2661, found 274.2681 (M^+).

4.2.3. Compound **4**

Oil. ^1H NMR (300 MHz, $CDCl_3$): δ 5.76 (2H, dd, *J*=17.6, 11.0, H-17 and H-19), 5.10 (2H, dd, *J*=11.0, 1.6, H_a-18 and H_a-20), 5.08 (2H, br t, overlapped with the H_a-18/H_a-20 protons, *J*=7.5, H-3 and H-10), 4.88 (2H, dd, *J*=17.6, 1.6, H_b-18 and H_b-20), 1.67, 1.56 (6H each, s, vinyl methyls), 0.93 (6H, s, CH_3-14 and CH_3-15). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.3, 17.6, 23.37, 25.7, 34.7, 45.3, 113.8, 125.4, 130.9, 144.1. HREIMS calcd for $C_{20}H_{34}$ 274.2661, found 274.2675 (M^+).

4.3. Oxidative cyclization of 2

To a solution of digeranyl (**2**, 156 mg, 0.569 mmol) in the biphasic mixture EtOAc/CH_3CN/H_2O (3:3:1) (50 mL) were added in sequence $NaIO_4$ (6 equiv, 732 mg, 3.41 mmol) and $RuO_2\cdot 2H_2O$ (20 mol %, 15.2 mg, 0.11 mmol) under vigorous stirring at 0 °C. After 20 min a saturated $Na_2S_2O_3\cdot 5H_2O$ solution (1 mL) was added and, after a further 10 min stirring, the mixture was extracted with EtOAc (3×10 mL). The combined organic phase was dried and evaporated to give 152 mg of an oily product. HPLC separation (250×10 mm column, hexane–EtOAc, 55:45, flow 2.5 mL/min, 30 mg/injection) afforded tris-THF diol **6** (10.1 mg, 5%, t_R=19.5 min), tris-THF diol **5** (18.2 mg, 9%, t_R=22.0 min) and bis-THF lactone **7** (26.6 mg, 15%, t_R=32.5 min) as oils.

4.3.1. Compound **5**

Oil. IR (neat) ν_{max} 3420 (br) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, attributions by 2D NMR): δ 3.95–3.90 (1H, m, H-10), 3.90–3.86 (1H, dd, *J*=8.2, 4.0, H-3), 3.84–3.79 (1H, m, H-7), 3.73 (1H, dd, *J*=9.2, 5.9, H-14), 2.28 (1H, m, H_a-5), 1.60 (H_b-5), 2.18, 1.65 (H_2-12), 2.10, 1.98 (H_2-4), 1.97 (H_2-9), 1.96 (H_2-8), 1.85, 1.75 (H_2-13), 1.24 (3H, s, Me-1), 1.18 (3H, s, Me-20), 1.12 (3H, s, Me-18), 1.11 (3H, s, Me-16), 1.10 (3H, s, Me-19), 1.08 (3H, s, Me-17). ^1H NMR (500 MHz, pyridine-d_5, attributions by 2D NMR): δ 4.04 (1H, dd, *J*=8.4, 6.8, H-14), 4.02–3.98 (1H, m, H-10), 3.95 (1H, dd, *J*=7.2, 6.2, H-3), 3.94–3.90 (1H, m, H-7), 2.25, 1.52 (H_2-5), 2.23, 1.61 (H_2-12), 2.10, 1.90 (H_2-4), 2.00, 1.98 (H_2-13), 1.93, 1.86 (H_2-9), 1.90, 1.88 (H_2-8), 1.39 (3H, s, Me-1), 1.37 (3H, s, Me-16), 1.33 (3H, s, Me-20), 1.25 (3H, s, Me-17), 1.13 (6H, s, Me-18, Me-19). ^{13}C NMR (125 MHz, $CDCl_3$): δ 87.1 (CH-14), 86.1 (CH-3), 85.1 (CH-10), 84.9 (CH-7), 84.0 (C-11), 83.3 (C-6), 72.2 (C-2), 70.7 (C-15), 35.1 (CH_2-5), 35.0 (CH_2-12), 27.9 (CH_3-1), 27.4 (CH_3-20), 27.1 (CH_2-9), 26.8 (CH_2-13), 25.8 (CH_2-4), 25.2 (CH_3-17), 24.6 (CH_3-18), 23.9 (CH_3-19), 23.7 (CH_3-16). HRESIMS calcd for $C_{20}H_{36}NaO_5$ 379.2460, found 379.2481 $(M+Na)^+$.

4.3.2. Compound **6**

Oil. IR (neat) ν_{max} 3420 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, attributions by 2D NMR): δ 3.93 (2H, m, H-7 and H-10), 3.84 (2H, dd, *J*=7.3, 5.8, H-3 and H-14), 2.20–2.13 (1H, m, H_a-5 and H_a-12), 1.62 (H_b-5 and H_b-12), 2.04, 1.92 (H_2-4 and H_2-13), 2.00, 1.91 (H_2-8 and H_2-9), 1.24 (6H, s, Me-1 and Me-16), 1.13 (6H, s, Me-18 and Me-19), 1.07 (6H, s, Me-17 and Me-20). ^1H NMR (500 MHz, pyridine-d_5, attributions by 2D NMR): δ 3.97 (2H, br t, *J*=5.9, H-7 and H-10), 3.88 (2H, t, *J*=7.0, H-3 and H-14), 2.19, 1.50 (H_2-5 and H_2-12), 2.06, 1.84 (H_2-4 and H_2-13), 1.83 (H_2-8 and H_2-9), 1.40 (6H, s, Me-1 and Me-16), 1.12 (6H, s, Me-18 and Me-19), 1.21 (6H, s, Me-17 and Me-20). ^{13}C NMR (125 MHz, $CDCl_3$): δ 86.1 (CH-3, CH-14), 85.5 (CH-7, CH-10), 83.8 (C-6, C-11), 71.8 (C-2, C-15), 35.4 (CH_2-5, CH_2-12), 28.3 (CH_2-8, CH_2-9), 28.1 (CH_3-1, CH_3-16), 26.3 (CH_2-4, CH_2-13), 25.3 (CH_3-17, CH_3-20), 23.6 (CH_3-18, CH_3-19). HRESIMS calcd for $C_{20}H_{36}NaO_5$ 379.2460, found 379.2475 $(M+Na)^+$.

4.3.3. Compound **7**

Oil. IR (neat) ν_{max} 3422 (br), 1766 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, attributions by 2D NMR): δ 3.96 (1H, t, *J*=7.7, H-10), 3.87 (1H, dd, *J*=8.0, 4.9, H-3), 3.84 (1H, dd, *J*=9.7, 5.2, H-7), 2.82–2.68 (1H, m, H_2-13), 2.50 (1H, dd, *J*=10.8, 3.3, H_2-13), 2.44, 1.96 (2H, H_2-12), 2.15,

1.63 (H_2-5), 2.06, 1.96 (H_2-4), 2.04 (H_2-9), 1.97 (H_2-8), 1.33 (3H, s, Me-17), 1.24 (3H, s, Me-1), 1.10 (3H, s, Me-16), 1.09 (3H, s, Me-15). ^{1}H NMR (500 MHz, pyridine-d_5, attributions by 2D NMR): δ 3.92 (1H, overlapping m, H-10), 3.91 (1H, overlapping m, H-3), 3.83–3.78 (1H, m, H-7), 2.81 (1H, dt, J=17.3, 9.4, H_2-13), 2.47 (1H, ddd, J=17.3, 10.6, 3.6, H_2-13), 2.32 (1H, ddd, J=12.4, 10.6, 3.6, H_2-12), 2.06, 1.47 (H_2-5), 2.03, 1.85 (H_2-4), 1.83, 1.80 (H_2-9), 1.81, 1.77 (H_2-8), 1.78 (H_2-12), 1.16 (3H, s, Me-17), 1.36 (3H, s, Me-1), 1.06 (3H, s, Me-16), 1.26 (3H, s, Me-15). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.0 (C-14), 86.2 (C-11), 85.9 (CH-7), 85.8 (CH-3), 85.3 (CH-10), 83.1 (C-6), 72.2 (C-2), 35.3 (CH_2-5), 32.7 (CH_2-12), 29.8 (CH_2-13), 28.0 (CH_3-1), 27.6 (CH_2-8), 26.8 (CH_2-9), 25.9 (CH_2-4), 24.9 (CH_3-15), 24.4 (CH_3-16), 23.4 (CH_3-17). HRESIMS calcd for $C_{17}H_{28}NaO_5$ 335.1835, found 335.1839 $(M+Na)^+$.

4.4. Bis-lactone 5 and monolactones 3 and 4

To a solution of **6** (1.5 mg, 0.00421 mmol) in CH_2Cl_2 (0.5 mL) were added Celite (25 mg), PCC (5.0 mg, 0.0231 mmol,) and AcOH (70 mmol, 20 μL) and the resulting heterogeneous mixture was stirred at room temperature for 21 h and then diluted with CH_2Cl_2 and filtered through a short silica gel pad. Elution with $CHCl_3$/MeOH 9:1 (10 mL) afforded a colourless oil. The crude was partitioned between $CHCl_3$ (5 mL) and a saturated aqueous $NaHCO_3$ solution (5 mL). The organic layer was washed with water, dried and concentrated in vacuo to give 1.2 mg of an oily material that was separated by HPLC (250×4.6 mm column, hexane–EtOAc, 1:1) to give pure unreacted **6** (0.5 mg, t_R=7.0 min), monolactone **7** (0.4 mg, 30% respect to reacted **6**, t_R=11.0 min) and bis-lactone **10** (0.2 mg, 18% respect to reacted **6**, t_R=12.4 min).

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