Pergamon

Tetrahedron Letters 39 (1998) 9781–9784

TETRAHEDRON LETTERS

OsO_4-Catalyzed Oxidative Cyclization of Geranyl and Neryl Acetate to *cis*-2,5-bis(hydroxymethyl)tetrahydrofurans

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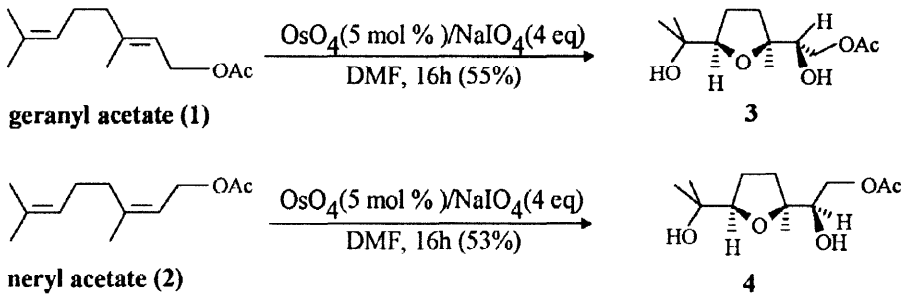
Received 10 August 1998; accepted 12 October 1998

Abstract. OsO_4 catalyzes the oxidative cyclization of the 1,5-dienes geranyl acetate (**1**) and neryl acetate (**2**) to the *cis*-2,5-bis(hydroxymethyl)tetrahydrofurans **3** and **4** respectively, in the presence of $NaIO_4$ as cooxidant in DMF. The reaction is stereospecific and proceeds with the sequential *syn* addition to both double bonds of the starting materials. The observed stereoselectivity can be explained by invoking the intermediacy of a square-based pyramidal osmium (VI) diester (**5**) that has been isolated and characterized. Evidence is reported that this substance is indeed an intermediate in the transformation of **1** to **3**.
Keywords: OsO_4, 1,5-dienes, oxidative cyclization, THF.

The development of methodologies for the stereoselective synthesis of substituted tetrahydrofurans (THF's) continues to be an area of great interest either in connection with the stereocontrolled synthesis of biologically active substances such as polyether antibiotics,[2] terpene polyethers,[3] *Annonaceous* acetogenins,[4] many of which show a range of impressive biological activities,[5] or, *inter alia*, in the synthesis of *trans*-linked oligo-tetrahydrofurans, in turn building blocks for the construction of polyether helices having ion channel activity.[6]

The conversion of acyclic 1,5-dienes into *cis*-2,5-bis(hydroxymethyl)tetrahydrofurans can be accomplished in a highly stereospecific manner with MnO_4^- (2 eq) at pH 6 (CO_2) in acetone-water (9:1) at −10°C.[7] This is an extremely appealing process that produces in a single step, and in a predictable manner, four chiral centres from an achiral reactant; the reaction, when conducted on geranyl acetate (**1**) and neryl acetate (**2**) (the Δ^2 isomer of **1**) affords the *cis*-THF diols **3** and **4**, respectively (Scheme 1). This oxidative cyclization has been successfully applied to the synthesis of the bis-tetrahydrofuran sections of monensin[8] and ionomicin[9] and more recently to the construction of a THF-containing key intemediate in the synthesis of salinomycin.[10] A similar reaction occurs with catalytic amounts of the structurally related oxide ruthenium tetroxide ($RuCl_3 \cdot 2H_2O/NaIO_4$, $CCl_4/CH_3CN/H_2O$, 2:2:3) but in this case the degree of stereoselectivity is less since a 3:1 mixture of *cis*-THF (**3** and **4**) and *trans*-THF is obtained.[11]

Scheme 1



geranyl acetate (1) **3**

neryl acetate (2) **4**

0040-4039/98/$ - see front matter
PII: S0040-4039(98)02172-8

As a continuation of our interest in oxidative processes involving transition metal oxides[12a] we report here that catalytic amounts of either OsO_4 or OsO_2,[13] when used in conjunction with sodium periodate ($NaIO_4$) as cooxidant, in DMF, are capable of inducing the oxidative cyclization of the 1,5-dienes **1** and **2** to give stereospecifically the corresponding *cis*-2,5-bis(hydroxymethyl)tetrahydrofurans **3** and **4**, respectively (Scheme 1).

In a typical experiment 5 mol % of OsO_2 was dissolved in DMF (0.5 mL) immediately giving a blue solution. To this solution, $NaIO_4$ (4 mol. eq) and the 1,5-diene (**1** or **2**, 100 mg, 0.51 mmol) were added with stirring. Alternatively, to the 1,5-diene dissolved in DMF were added in sequence OsO_4 (5 mol %) from a stock solution in DMF (100 mg/mL) and $NaIO_4$ (4 mol. eq). As the reaction proceeded the suspension turned to grey, and finally to white when the starting materials had disappeared (about 16 h, TLC analysis). The mixture was then filtered and the precipitate washed three times with $CHCl_3$. The organic phase was evaporated and chromatographed on silica gel to afford the diols **3** (from **1**) or **4** (from **2**) in 55 and 53% yields (unoptimized),[14] respectively, identified by comparison of their spectral properties with those exhibited by authentic samples prepared according to the original Klein and Rojahn' s procedure.[7a] Only 7% of the C-2 ketoderivatives of **3** and **4**, probably formed by overoxidation of these products at C-2, were isolated from the reaction mixtures. No trace of the *trans*-THF isomers of **3** and **4** could be detected amongst the reaction products by ^{1}H-NMR analysis after chromatography. In the above experiments, no care was taken to eliminate adventitious moisture.

TLC analyses of the two reaction mixtures, performed at an early stage of the oxidation process, revealed the formation of some less polar products including a brown substance along with the final *cis*-THF. This product was always present in the reaction mixture and its amount seemed unchanged as the reaction proceeded as evaluated by the intensity of its TLC carbonized spot. Our previous experience in the synthesis of osmium and ruthenium (VI) diesters[12] suggested to us that this material could be an osmium (VI) diester intermediate possibly similar to that hypothesized for the analogous reactions of other 1,5-dienes with MnO_4^-.[15,16]

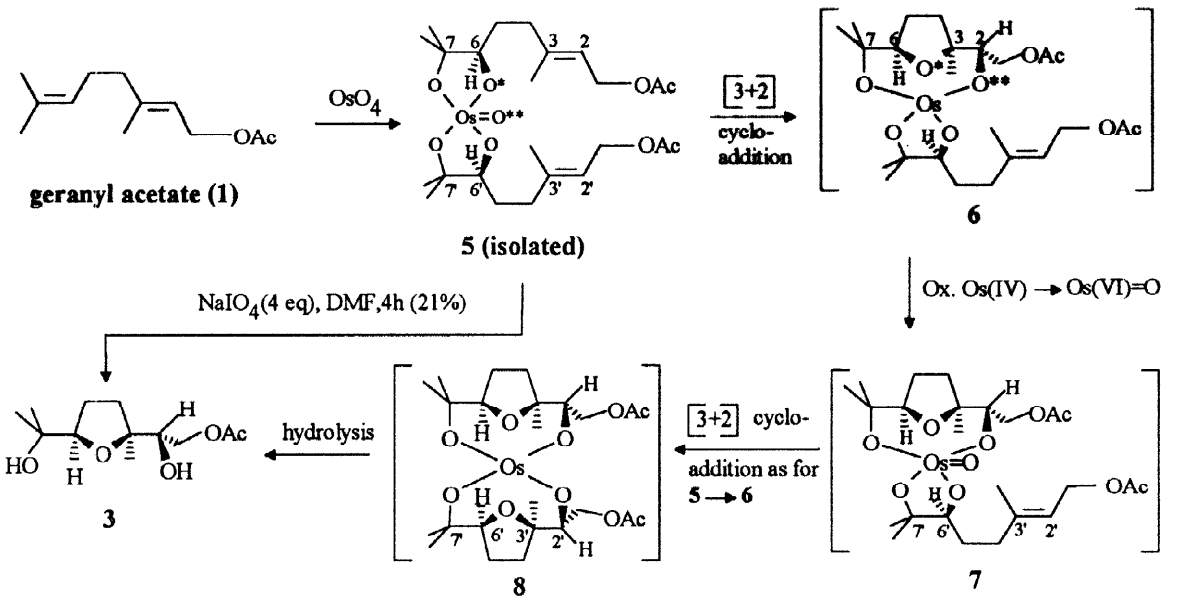
By stopping the oxidative process before its completion we could isolate enough of this material to allow its spectral characterization. The purification of this substance proved to be difficult to carry out, however and an 80% enriched sample could be obtained after two successive HPLC runs (hexane-EtOAc, 78:22). Spectral data exhibited by this material,[17] when compared with those of other osmium(VI) diesters we have on file,[12] pointed to structure **5**[19] (Scheme 2) for the osmium-containing product which is plausible based on literature precedents.[20]

In order to prove that **5** was indeed an intermediate in the conversion of **1** to **3**, we put this substance under the same conditions used for the oxidation of **1** (6.5 mg of **5** in 300 μL DMF, 4 eq $NaIO_4$) (Scheme 2). After some 4h, **5** had been completely transformed into a mixture of products from which the *cis*-THF **3** could be isolated in 21% yield by preparative TLC.

It is interesting to note that changing the cooxidant from $NaIO_4$ to N-methylmorpholine-N-oxide (NMO), a well known cooxidant used for the catalytic asymmetric dihydroxylation of olefins, radically changed the course of the reaction with **1** giving as the major reaction product the "normal" dihydroxylation product of the C-6/C-7 double bond.[21] No trace of the cyclization product **3** could be detected in this case. Interestingly, and as expected, this process also proceeds through the formation of the same above-mentioned osmium(VI) diester **5** as demonstrated by its isolation from this reaction as well.

These results seem to support the mechanism shown in Scheme 2 previously proposed in part for the related oxidative cyclization of the 6,7-dihydroxyalkenes derived from **1** and **2** promoted by a Cr(VI) oxo species[22] and for the MnO_4^--induced oxidative cyclization of 1,5-dienes.[15,16] In our case, for **1**, the first event should be the addition of OsO_4 to the C-6/C-7 double bond of the two geranyl acetate units with formation of the symmetrical[19] osmium(VI) diester **5**, which adopts a square-based pyramidal arrangement. This then evolves to the osmium(IV) diester **6** through, at least in principle, a [3+2], or a Sharpless type [2+2], cycloaddition. These processes involve, respectively, the addition of

Scheme 2



the O^{*}-Os=O^{**} grouping to the C-2/C-3 double bond to give **6** directly or, alternatively, the insertion of the olefinic π bond into the Os=O^{**} bond, to give an osmaoxetane intermediate, which then undergoes reductive elimination to give **6**. We currently favour the [3+2] mechanism for this step. In fact, examination of molecular models of **5** revealed that the approach of the C-2/C-3 double bond to the O^{*}-Os=O^{**} portion (C-3 approaching O^{*} and C-2 the Os=O^{**} oxygen) did not suffer steric congestion whilst for the alternative [2+2] process there seems not to be a plausible conformational arrangement that could assure, as required, the positioning of the double bond (C-3 approaching the metal and C-2 the apical Os=O^{*} oxygen) at a distance suitable for bond formation, without the intervention of angle distortions and/or steric interactions. To complete a plausible mechanistic route, how the second geranyl acetate unit (the lower) in **5** is released as a THF needs to be explained. One can speculate that a route analogous to that operating for the transformation **5**→**6** could be involved in the transformation of **6** to **3**. Thus, the Os(IV) compund **6** could be reoxidized to the Os(VI) derivative **7** by regenerating the Os=O bond. Then the (C-6')O-Os=O portion of **7** could be engaged in a [3+2] cycloaddition with the double bond (C-2'/C-3') of the second geranyl acetate unit to produce the Os(IV) species **8** embodying two THF units whose release could occur hydrolytically.

It is to be noted that the our results are in agreement with the mechanism proposed by Baldwin *et al.*[15] for the MnO_4^--induced oxidative cyclization of 1,5-dienes later amended by Wolfe and Ingold.[16] In particular, the former authors suggested that the oxidation of labelled hexa-1,5-dienes proceeds *via* the sequential oxidation of the two double bonds with the intermediacy of a tetracoordinated manganese (VI) ester embodying, however, only one molecule of substrate. The latter, to account for evidence from ^{18}O labelling experiments in the oxidation of 1,5-hexadiene, proposed that the manganese-containing intermediate could have a trigonal-bypiramidal geometry hypothesizing also that one of the apical oxygens of this intermediate could derive from water (the solvent) and that this atom was transferred to the second double bond of the co-ordinated diene unit along with one of the two manganese ester oxygens (the nearest to the double bond) in a manner similar to that shown in scheme 2 for the transformation **5**→**6**. How can these similarities be interpreted? Could the two processes involve the same mechanism with the intermediate of the MnO_4^--induced process adopting the same square-based pyramidal geometry as **5**? And if so, could the oxygen derived from water to which Wolfe and Ingold[16] refer be the apical oxygen of this species? This of course necessitates

further experimental work and at this stage prudence stops speculative reasoning. We are currently devising experiments *ad hoc* to throw light on the mechanism of the above described OsO_4-induced cyclization as well as exploring its scope and synthetic utility.

Acknowledgments. We are grateful to MURST, Italy, for a grant in support of this investigation, to the "Centro di Metodologie Chimico-Fisiche dell'Università Federico II di Napoli" for NMR facilities, and to the "Servizio di Spettrometria di Massa del CNR e dell'Università di Napoli" for mass spectral data.

References and Notes

1) Prof. Vincenzo Piccialli wishes to dedicate this work to his daughter Francesca.
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3) See for example (a) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *J. Org. Chem.* **1991**, *56*, 2299-2311. (b) Kodama, M.; Yoshio, S.; Tabata, T.; Deguchi, Y.; Sekiya, Y.; Fukuyama, Y. *Tetrahedron Lett.* **1997**, *38*, 4627-4630.
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13) The osmium oxide used in the reported experiments has been obtained by decomposition of a recently synthesized omium (VI) diester of cholesteryl acetate.[12a] This ester is prone to decompose slowly (5°C, one year) but its decomposition has also been induced by water, as reported by other substances of this class (Subbaraman, L. R.; Subbaraman, J.; Behrman, E. J. *Inorg. Chem.* **1972**, *11*, 2621-2627). The identity of the blue-black, osmium oxide obtained as above, although generally assumed to be OsO_2 or one of its hydrates, han never been established with certainty and some authors have given evidence that it is instead an Os(V) oxide. For calculation purposes we assumed it to be $OsO_2 \cdot 2H_2O$.
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17) **5**: IR (film) 2972, 2929, 2857,1739(C=O, acetate), 1451, 1382, 1367, 1233, 1025, 990 (Os=O^{18}), 910, 727 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 5.38 (2H, bt, J=7.1 Hz, H-2/H-2'), 4.59 (4H, bd, J=7.1 Hz, H_2-1/H_2-1'), 4.48 (2H, dd, J=8.7, 3.3 Hz, H-6/H-6'), 2.50, 2.16 (2H each, m's, H_2-4/H_2-4'), 2.05 (6H, s, acetates), 1.73 (6H, bs, 2xMe), 1.57 (12H, bs, 4xMe)); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 171.1, 141.4, 118.8, 98.4, 95.9, 61.2, 36.1, 30.0, 26.0, 22.4, 21.0, 16.6; FABMS: ion clusters at *m/z* 663-667 (MH^+), 603-607 (MH^+-AcOH), 543-547 (MH^+-2AcOH).
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