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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5131–5135

Ruthenium-catalyzed oxidative cyclization of 1,7-dienes. A novel diasteroselective synthesis of 2,7-disubstituted *trans*-oxepane diols

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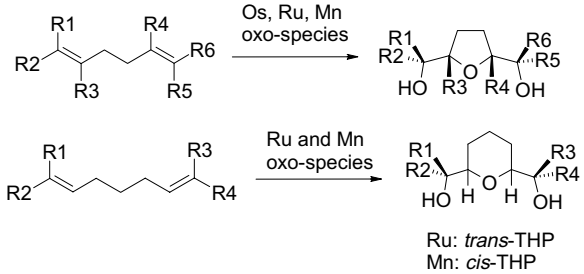
Received 5 April 2007; revised 8 May 2007; accepted 11 May 2007
Available online 18 May 2007

Abstract—The ruthenium-catalyzed oxidation of some representative 1,7-dienes has been investigated. Tetrasubstituted 1,7-dienes are transformed into the corresponding *trans*-2,7-bis-hydroxyalkyl-oxepanes through an oxidative cyclization process. The process proceeds with an excellent stereoselectivity level.

Ruthenium tetroxide is known to catalyze the stereoselective formation of 2,5-bis-(hydroxyalkyl)-substituted THF and THP rings from 1,5-[1] and 1,6-dienes,[2] respectively (Scheme 1), in the presence of sodium periodate as the reoxidant. Related oxidative cyclization processes, mediated by other transition metal-oxo species such as OsO_4, MnO_4^-, RuO_4^-, are also known;[3] on the other hand, the ruthenium-mediated oxidation of 1,7-dienes has never been investigated. Therefore, we decided to probe the possibility of obtaining 2,5-disubstituted oxepane diol products under conditions causing the oxidative cyclization of other diene types. Seven-membered oxacycles are present in many biologically active natural products such as *Laurencia* acetogenin metabolites[4] and polyether marine toxins.[5] In these compounds the oxepane ring is very often 2,7-dialkylsubtituted. While some efficient methods toward the stereoselective synthesis of 2,7-*cis*-oxepanes have been developed,[6] few methods have been so far devised to generate the 2,7-*trans*-oxepane system.[6]



Scheme 1. Formation of THF and THP diols by oxidative cyclization of 1,5- and 1,6-dienes with metal-oxo species.

We report here the first successful ruthenium-catalyzed oxidative cyclization of 1,7-dienes to *trans*-oxepane diol products and related results on the oxidation of less substituted 1,7-dienes. Starting dienes **1**–**3**[7] were synthesized as shown in Scheme 2. The parent diene 1,7-octadiene is commercially available.

Taking into account the electrophilic character of RuO_4, and precedents from the oxidation of 1,5-[1] and 1,6-dienes,[2] the substituted diene 2,9-dimethyldeca-2,8-diene (**1**) was initially selected as a good substrate to probe the effectiveness of the cyclization process. The first attempt to cyclize diene **1** was carried out under the conditions we previously employed for THF and THP formation (5 mol % $RuO_2 2H_2O$ as *pre*-catalyst, $NaIO_4$ (4 equiv), $EtOAc/CH_3CN/H_2O$ (3:3:1)) (Table 1, entry 1). Although TLC analysis revealed a clean conversion, as indicated by the presence of a single spot at $R_f = 0.25$ (hexane/EtOAc, 7:3), the reaction failed to go to completion and a 60% mass recovery resulted after work-up at ca 60% conversion. Preparative HPLC[8] afforded the cyclization product **4a**[9] (Scheme 3) in an encouraging

Keywords: Oxidative cyclization; 1,7-Dienes; *trans*-Oxepanes; Ruthenium-catalyzed process.
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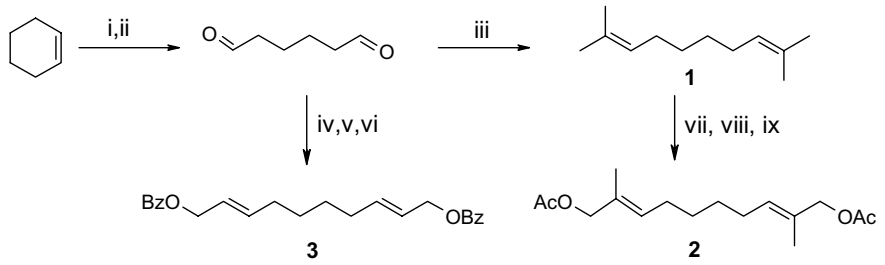
doi:10.1016/j.tetlet.2007.05.078

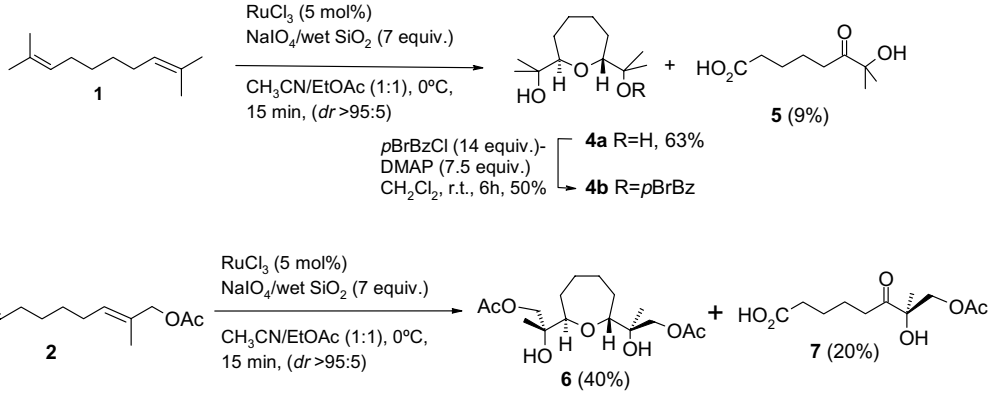


Scheme 2. Synthesis of 1,7-dienes. Reagents and conditions: (i) OsO_4 (2 mol %)/NMO (1.2 equiv), acetone/H_2O (9:1), 1 h; (ii) $NaIO_4$ (2 equiv), dioxane/H_2O (7:3), 15 min (90%, for two steps); (iii) Me_2CPPh_3 (2.2 equiv), THF, −78→0 °C, 2 h (50%); (iv) $(EtO)_2POCH_2CO_2Et$, NaH, THF, rt; (v) DIBAL–H, THF, −78°C; (vi) BzCl, py, rt, 2 h; (vii) SeO_2 (0.5 equiv), *t*-BuOOH (2 equiv), CH_2Cl_2; (viii) $NaBH_4$, EtOH, 0.5 h; (ix) Ac_2O–py, 50 °C, 2 h (58% for three steps).

Table 1. Optimization of the reaction conditions for the cyclization of diene **1**

Entry	Co-oxidant (equiv)	Solvent	Ru *pre*-catalyst (mol %)	Temperature (°C)	Yield (%)	Time
1	$NaIO_4$ (4)	EtOAc/CH_3CN/H_2O (3:3:1)	$RuO_2{\cdot}2H_2O$ (5)	0	26[a]	1.5 h
2	$NaIO_4$ (7)	EtOAc/CH_3CN/H_2O (3:3:1)	$RuO_2{\cdot}2H_2O$ (20)	−10	38[b]	2 h
3	$NaIO_4$ (7)/wet silica	THF/CH_2Cl_2 (9:1)	$RuCl_3$ (10)	0	24	24 h
4	$NaIO_4$ (7)/wet silica	EtOAc/CH_3CN (1:1)	$RuCl_3$ (5)	0	63	15 min

[a] Based on reacted **1** at 60% conversion.
[b] Based on reacted **1** at 90% conversion.



Scheme 3. RuO_4-catalyzed oxidative cyclization of 1,7-dienes.

26% yield (based on reacted **1**) and, most importantly, as a single diastereoisomer.

Derivatization of **4a**, carried out with *p*-bromobenzoyl chloride/DMAP in CH_2Cl_2, afforded mono *p*-bromobenzoate **4b**[10] (Scheme 3) suitable for NMR studies. The proton spectrum of this material showed a good proton dispersion allowing to collect unambiguous stereostructural evidence from a set of 2D NMR experiments. Aided by the strong tendency of **4a** to crystallize, we could confirm the stereostructure of this compound by X-ray diffraction analysis (Fig. 1)[11] carried out on a single crystal of **4a** obtained from $CHCl_3$ by slow evaporation of the solvent. The collected data confirmed the *trans*-configuration of **4a** and showed that the oxepane ring adopts the twisted-chair conformation, as usually found in the X-ray structures of other oxepane derivatives.[12] This conformation also appears to be the one adopted by **4b** in solution as indicated by NOE data and *J* values.

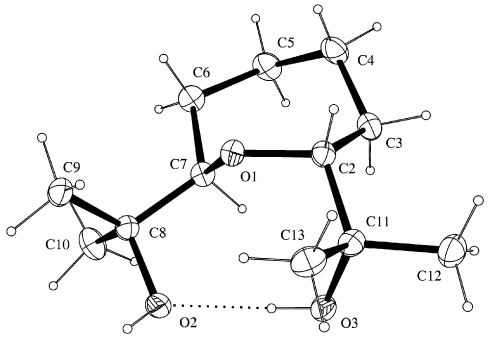


Figure 1. ORTEP drawing of oxepane **4a**.

Further attempts to improve the yields of the process were carried out as shown in Table 1. In an attempt to force the process to completion the oxidation was conducted by raising the RuO_2 amount to 20% and initially using 4 equiv $NaIO_4$. However, two further amounts of

co-oxidant (20%+10%; overall $NaIO_4$ 7 equiv; consecutive additions within 16 h) and an additional 20 mol % of *pre*-catalyst were required to cause a complete consumption of the substrate; nevertheless, still a modest yield (24%, HPLC) of oxepane diol **4a** was obtained. When the 7 equiv amount co-oxidant was added all at once at −10 °C (Table 1, entry 2) the yield was improved to 38% with a <10% recovered starting diene. Successive reactions were carried out employing this amount of co-oxidant. The need for such a quantity of $NaIO_4$ is difficult to explain in view of our own experience,[1b,2a,3] and results reported by others,[1a–d,2b] which show the amount of co-oxidant required to force to completion the cyclizations of 1,5- and 1,6-dienes to be 2.5–4 equiv.

Exclusion of water from the reaction mixture has recently been demonstrated to increase yields of the THF diols obtained from the Ru-catalyzed oxidation of 1,5-dienes.[1d] However, running the process in THF/CH_2Cl_2 (9:1), with $RuCl_3$ as *pre*-catalyst and $NaIO_4$ (7 equiv) supported on wet silica (entry 3), as reported,[1d] **4a** was obtained in a diminished 24% yield along with ketol **5** (50%) and scission products, among which adipic acid was the most abundant one (ca. 20%). Gratifyingly, an improved 63% yield of **4a** was eventually obtained when the oxidation of **1** was carried out in EtOAc/CH_3CN (1:1) by using the same $NaIO_4$ (7 equiv)/wet SiO_2 pair (entry 4);[2b] the yield of ketol side product **5** was also reduced to 9%.

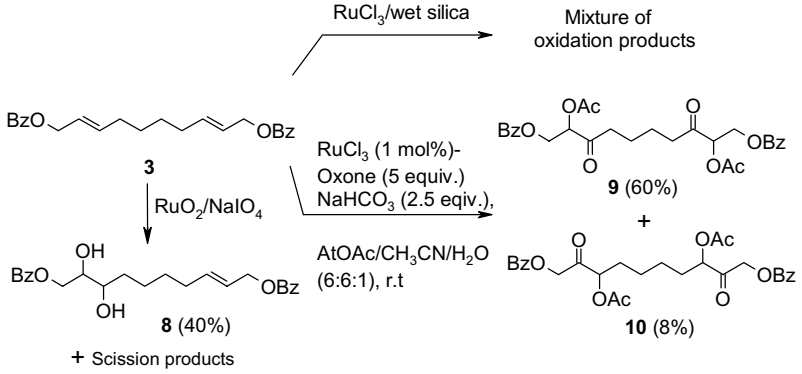
Next, the process was tested on other 1,7-dienes under the optimized conditions. 1,8-Diacetoxy-diene **2** gave *trans*-oxepane **6** (Scheme 3)[13] in a 40% yield along with the scission product **7** (20%). Commercially available 1,7-octadiene only gave adipic acid in >90% yields through the scission pathway. All-*trans* diene **3** could not be persuaded to cyclize under a variety of conditions (Scheme 4). In particular, oxidation of **3** under optimized conditions gave a mixture of oxidation products including scission products and di- and tetra-hydroxyderivatives. Oxidation with $RuO_2/NaIO_4$ gave alkene diol **8** in a 40% yield along with small amounts of scission products. A further attempt was carried out using Oxone® as the co-oxidant, according to the procedure recently reported by Plietker[14] for the oxidation of alkenes. In this case regioisomeric bis-ketols **9** and **10**, isolated as acetylderivatives (HPLC, hexane/EtOAc, 6:4), were obtained as the main reaction products (ca. 70% overall yield, **9**/**10**, 8:1). This result is in good agreement with the results reported by this author for the oxidation of simple alkenes and indicates a preference for ketone group formation at the internal carbons of each double bond. As far as we know this is the first report of the ketohydroxylation of a diene and, due to the good regiocontrol, this process, when suitably tuned, may have synthetic value.

From a mechanistic point of view, we presume a pathway similar to that proposed by Baldwin et al.[15] for the analogous MnO_4^--mediated oxidative cyclization of 1,5-dienes (Scheme 5). Thus, the initial [3+2] cycloaddition[16] between RuO_4 and one of the double bonds of the diene lead to the formation of a ruthenium(VI) diester. Next, this one intercepts the distal double bond through a second, intramolecular, [3+2] cycloaddition involving an O–Ru=O portion. This is a diasteroselective step that sets the trans junction of the oxepane ring. Release of the products by hydrolysis then follows with concomitant production of a low-valent Ru-species whose reoxidation by $NaIO_4$ regenerates RuO_4.

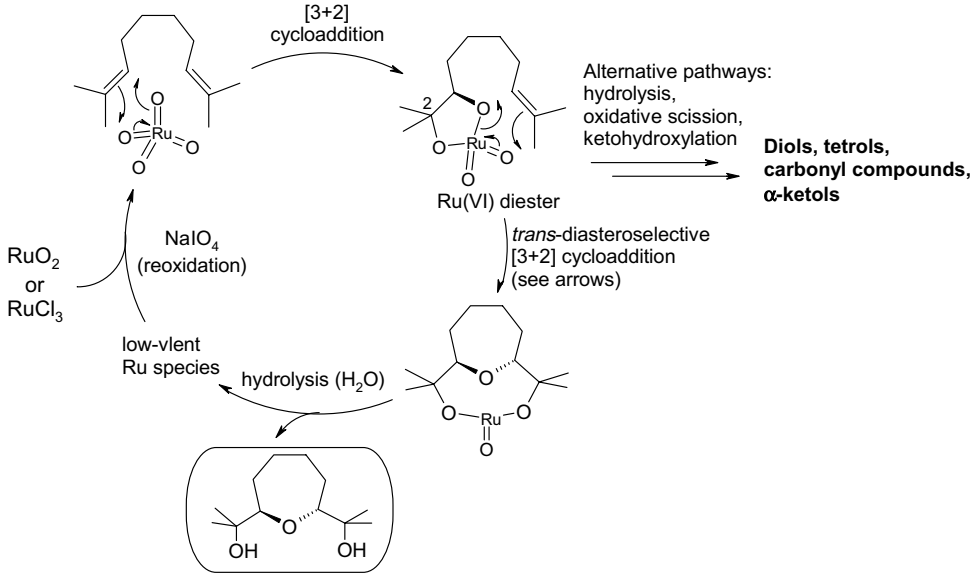
It is probable that both the increased conformational freedom and the stability of the first-formed ruthenium(VI) diester play a role in determining the success of the cyclization step. We presume that for less substituted dienes, the Ru(VI) diester intermediate is more susceptible to decompose (Scheme 5) hydrolytically, generating a diol that can undergo successive oxidative scission to carbonyl compounds. Alternatively, the direct fragmentation of the intermediate may occur giving rise to carbonyl compounds that are further oxidized to carboxylic acids. α-Hydroxy ketones **9** and **10** may form from the same intermediate according to Plietker's mechanistic proposal (ketohydroxylation pathway).[14]

It is also to be noted that the above results are in line with those reported for the oxidative cyclization of 1,5- and 1,6-dienes with RuO_4 for which the best yields of cyclized products are usually obtained with more substituted substrates.[1c,d,2]

In conclusion we have shown for the first time that the closure of oxepane rings through the RuO_4-catalyzed oxidative cyclization of an 1,7-diene is a possible



Scheme 4. Ru-catalyzed oxidation of a disubstituted 1,7-diene.



Scheme 5. Proposed catalytic cycle for the ruthenium-catalyzed oxidative cyclization of 1,7-diene.

process. This represents a novel approach to the formation of seven-membered oxacycles[17] that further amplify the knowledge of Ru-catalyzed oxidative cyclization of dienes.

Acknowledgement

We are grateful to the 'Centro di Metodologie Chimico-Fisiche dell'Università Federico II di Napoli' for NMR facilities.

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8. HPLC was carried out on a Varian 2510 apparatus equipped with a Waters R403 dual cell differential refractometer using a phenomenex® Luna, 250×4.6 mm column (5 μ). Solvent hexane/EtOAc, (7:3); flow: 1.0 mL/min, $t_R = 34$ min.
9. Compound **4a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.63 (1H, dd, $J = 10.6$, 2.2, H-3/H-8), 1.94, 1.87 (2H each, H_2-4/H_2-7), 1.52, 1.37 (2H each, H_2-5/H_2-6), 1.22, 1.16 (6H each, $4 \times$ Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.6, 73.9, 29.6, 27.8, 27.7, 24.2.
10. Compound **4b**: ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.83 (2H, dd, $J = 8.4$, 1.6, H-2′/H-6′), 7.36 (2H, dd, $J = 8.4$, 1.8, H-3′/H-5′), 4.32 (1H, d, $J = 10.8$, H-8), 3.60 (1H, d, $J = 9.8$, H-3), 1.97 (2H, overlapped d's, $J = 15.0$ both, H_α-4 and H_β-5), 1.90 (1H, dd, $J = 14.6$, 5.9, H_β-7), 1.76 (1H, br d, $J = 14.6$, H_a-6), 1.59 (1H, m, H_α-7), 1.62, 1.69 (3H, each, s's, Me-10 and Me-12), 1.42 (1H, m, H_β-4 and H_b-6), 1.33 (1H, m, H_α-5), 1.14, 1.06 (3H, each, s's, Me-1 and Me-11); ^{13}C NMR (175 MHz) δ 164.9, 132.0, 131.2, 130.7, 127.9, 86.3, 84.1, 81.3, 73.2, 29.8, 29.1, 28.5, 28.4, 26.1, 24.2, 23.2, 23.0.
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13. Compound **6**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.09 (4H, apparent s, $2 \times CH_2OAc$), 3.81 (2H, dd, $J = 10.9$, 2.3, H-3/H-8), 2.10 (6H, s, $2 \times Me$). ^{13}C NMR (125 MHz) δ 171.2, 78.5, 74.8, 69.2, 29.3, 27.5, 21.0.
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