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Synthesis of cardamom peroxide analogues by radical cyclization of hydroperoxyalkenes

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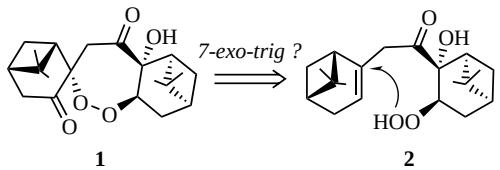
Abstract—Three pinenic hydroperoxides were synthesized according to the Dussault method. Two of them could cyclize under radical conditions to give the *exo-trig* isomer as a single regioisomer. Only five- and six-member ring peroxides were obtained, whereas none of the possible seven-member ones was observed. This strategy could be employed in the total synthesis of cardamom peroxide.

The terpenic peroxide **1** was isolated from the spice cardamom, the fruit of *Amomum krervanh* Pierre.[1] As many other natural peroxides[2] like artemisinin, cardamom peroxide exhibited an antimalarial activity as was shown in vitro against *Plasmodium falciparum* ($IC_{50}=170$ nM).[1] First its relative configuration was elucidated with the help of X-ray diffractometry. Its absolute configuration could then be deduced from those of known monoterpenes isolated conjointly in cardamom. In connection with our program on antimalarial peroxides,[3] we envisaged the synthesis of this natural product not only for establishing the absolute configuration but also for searching derivatives with better antimalarial activity. The strategy adopted here was to introduce later the chemosensitive peroxide function for stability reasons. Thus, an attractive strategy to obtain cardamom peroxide could use a sequence developed by Porter,[4] cyclization of a peroxy radical on double bond in the presence of oxygen, and oxidation of the resulting α-peroxy hydroperoxide into the corresponding α-peroxy ketone,[4a] using the functionalized hydroperoxide **2** (Scheme 1). This crucial step required a *7-exo-trig* cyclization of a peroxy radical on a double bond. Results from the literature showed that *5-exo-trig* was favored compared to *6-endo-trig* and *6-exo-trig* is favored compared to *7-endo-trig*.[4,5] However, to our best knowledge, this has never been reported for seven-member cyclic peroxides. Furthermore, the corresponding *7-exo-trig* ring closure center appeared to be the most hindered carbon of the double bond, therefore possibly being responsible for an *8-endo-trig* cyclization enhancement.[5b]



1 **2**

Scheme 1.

In order to check the behavior of such a reaction before starting the synthesis of precursor **2**, we decided to prepare the pinene hydroperoxides **8a–c** (Scheme 3) as models to study the regioselectivity of the cyclization as a function of the size of the ring (five-, six- or seven-membered rings).

We report herein the synthesis of these pinene hydroperoxides **8a–c** and the result of our study on their radical cyclization.

In order to prepare the pinene hydroperoxide **8a–c** we first synthesized the corresponding bromides **4a–c** (Scheme 2). Thus, nopyl bromide **4a** was prepared from nopol **3a** according to a known procedure: the corresponding tosylate was substituted with sodium bromide in DMSO at 70°C.[6] The same sequence was used to prepare the bromides **4b** and **4c**. However, the tosylate derived from homonopol **3b** was less stable so it could not be obtained in good yields. Moreover, its substitution with sodium bromide had to be conducted in DMSO at room temperature. Homonopol **3b** was prepared as previously reported as a condensation product from formaldehyde with the Grignard reagent

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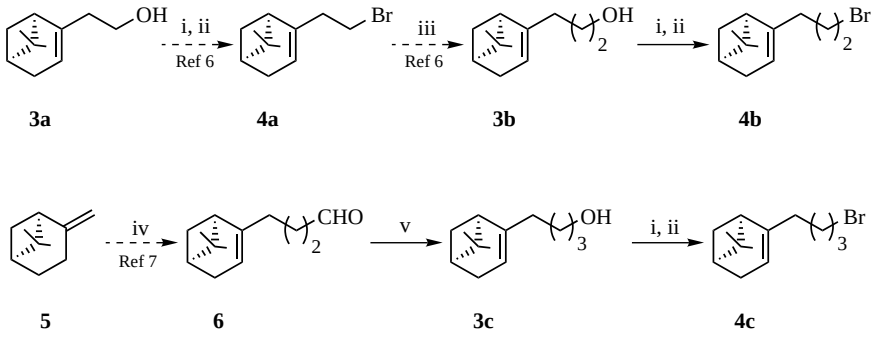


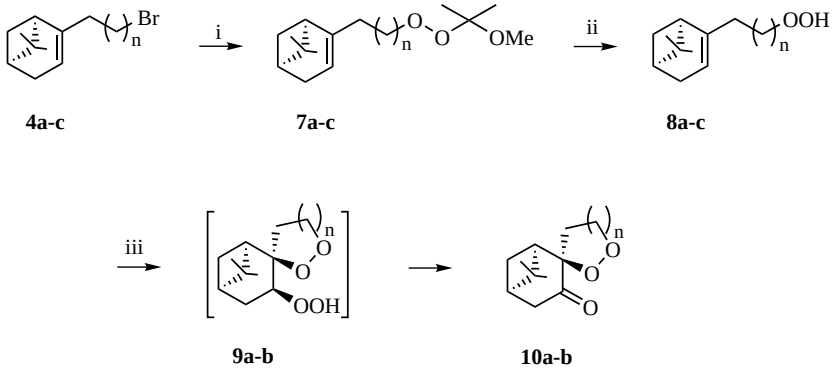
Scheme 2. *Reagents and conditions:* (i) TsCl, pyridine, 0°C then rt 3 h, 89% from **3a**, 46% from **3b**, 77% from **3c**; (ii) NaBr, DMSO, rt 20 min then 70°C 2 h for **4a** and **4c**, rt 18 h for **4b**, 78% for **4a**, 98% for **4b**, 66% for **4c**; (iii) Mg°, THF rfx, 3 h then CH_2O gas, 66%; (iv) acrolein, $ZnBr_2$, Et_2O, rt 96 h, 29%; (v) $NaBH_4$, EtOH, rt 2 h, 79%.

derived from nopyl bromide **4a**.[6] As we experienced some difficulties to obtain this alcohol in its pure form, the higher homologue **3c** was prepared in a quite different manner: by $NaBH_4$ reduction of the corresponding aldehyde **6** previously obtained by a $ZnBr_2$-catalyzed ene reaction between β-pinene and acrolein.[7] With the three bromides **4a–c** in hand, we prepared the corresponding hydroperoxides **8a–c** using Dussault's procedure (Scheme 3).[8]

Substitution with 2-methoxyprop-2-yl hydroperoxide **11**[8a] led to perketals **7a–c** in moderate to good yields for **7c**. The reaction times were extremely long (1–3 weeks) compared to those of straight-chain primary alkyl bromides (1–2 h).[8a] This could be attributed to steric hindrance of proximal pinene bulky moiety, as yields and reaction time improved by increasing the length of the alkyl chain between the pinene and the bromide function. Deprotection of perketals **7a–c** with aqueous acetic acid[8] gave the corresponding hydroperoxides **8a–c**. The difficulty to prepare the perketals **7a–c** and the rather poor stability of hydroperoxides **8a–c** can explain that no other method tried so far could give the desired hydroperoxides **8a–c** from either the bromides **4a–c** (KO_2, DMSO or DMF;[9] Mg then O_2[10]) or their corresponding tosylates (H_2O_2, MeOH, KOH;[4] NH_2NH_2[11] or NH_2NHTs[11,12] then H_2O_2). In our case, the Dussault procedure appeared far superior to the others.

Concerning the peroxy radical cyclization, nopyl hydroperoxide **8a** was subjected to the Porter conditions,[4b] e.g. O_2, benzene and di-*t*-butyl peroxyoxalate (DBPO, CAUTION)[13] as a radical initiator. The cyclized hydroperoxide **9a** was formed together with the ketone **10a**[14] in a 7:3 ratio and in a 36% global yield. The transformation of a hydroperoxide into its corresponding ketone was previously reported in these conditions.[15]

A complete two-step transformation into ketone **10a** could be performed using Ac_2O/pyridine[16] in a 24% global yield and none of the *6-endo-trig* cyclized product or any other stereoisomer could be detected, pointing out the selectivity of this strategy. As was reported for other radical additions to pinene,[17] we observed a *cis* addition *anti* to the bulky *gem* dimethyl group. The configuration of the molecules was confirmed by NMR analysis. Other radical initiators proved disappointing. Under the same conditions, AIBN[18] led to the same result but in lower yield (17%) and SmI_2/O_2[19] caused a fast degradation of the hydroperoxide **8a** without any cyclization. In the case of the higher homologue homonopyl hydroperoxide **8b**, DBPO radical cyclization gave directly the ketone **10b**[14] as a sole regio- and stereoisomer in 14% yield. The spontaneous transformation, in the same reaction conditions, of hydroperoxide **9b** into ketone **10b** was easier than for



Scheme 3. $n=1$ (a), $n=2$ (b) or $n=3$ (c). *Reagents and conditions:* (i) $HOOC(CH_3)_2OMe$ (**11**), CsOH, DMF, rt 7 days (**7b** and **7c**) to 20 days (**7a**), 44% for **7a**, 69% for **7b**, 87% for **7c**; (ii) AcOH, H_2O, BHT, 97% for **8a**, 98% for **8b**, 97% for **8c**; (iii) DBPO, O_2, benzene, rt, then Ac_2O, pyridine, 36% for **10a**, 14% for **10b**.

the five-member cyclic hydroperoxide **9a**. Similar results were obtained with AIBN as radical initiator.

For the cyclization of the seven-member ring precursor hydroperoxide **8c**, we were not able to detect any trace of *7-exo-trig* or *8-endo-trig* products using either DBPO or AIBN. The increase of the degree of freedom with the length of the alkyl chain was presumably too unfavorable for the cyclization of the peroxy radical that decomposed. However, we thought that the entropic factor could be limited in retrosynthetic precursor **2**, as a second ring could significantly reduce the degree of freedom of the chain with the peroxy radical.

As *exo-trig* cyclic isomers were the sole isolated products following our strategy with five- and six-membered cyclic peroxides as starting materials, this encouraged us to pursue this route for the later synthesis of cardamom peroxide **1**.

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14. All new compounds reported here were characterized on the basis of spectroscopic data (IR, ^{1}H and ^{13}C NMR), $[\alpha]_D$ and elemental analyses. Selected spectral data: Compound **7c**: $[\alpha]_D$ −17 (*c* 0.97, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): 5.21–5.10 (m, 1H), 4.00 (t, $J=6.5$ Hz, 3H), 3.31 (s, 3H), 2.34 (dt, $J=8.3$, 5.6 Hz, 1H), 2.25–2.13 (m, 2H), 2.13–1.87 (m, 4H), 1.60 (q, $J=6.6$ Hz, 2H), 1.50–1.31 (m, 2H), 1.38 (s, 6H), 1.26 (s, 3H), 1.13 (d, $J=8.3$ Hz, 1H), 0.82 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 147.9, 116.0, 104.4, 74.8, 49.0, 45.7, 40.9, 37.8, 36.6, 31.6, 31.2, 27.6, 26.3, 23.7, 22.7, 21.1. Compound **8c**: ^{1}H NMR (200 MHz, C_6D_6): δ 6.61 (bs, 1H), 5.33–5.06 (m, 1H), 3.81 (t, $J=6.3$ Hz, 2H), 2.33 (dt, $J=8.3$, 5.6 Hz, 1H), 2.23–2.14 (m, 2H), 2.13–1.80 (m, 4H), 1.43–1.32 (m, 5H), 1.37 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 148.5, 116.4, 76.9, 46.2, 41.3, 38.2, 37.1, 32.1, 31.7, 27.9, 26.6, 24.0, 21.4. Compound **10a**: $[\alpha]_D$ +17 (*c* 0.17, EtOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.37 (dt, $J=7.9$, 4.5 Hz, 1H), 4.11 (q, $J=7.9$ Hz, 1H), 2.96 (dt, $J=11.3$, 7.5 Hz, 1H), 2.70–2.64 (m, 2H), 2.33–2.05 (m, 4H), 1.55 (d, $J=11.3$ Hz, 1H), 1.37 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 209.3, 88.8, 71.4, 48.1, 44.4, 43.3, 39.8, 38.1, 29.4, 26.5, 22.2. Compound **10b**: $[\alpha]_D$ −7 (*c* 1.62, EtOH); ^{1}H NMR (400 MHz, C_6D_6): δ 4.05 (dt, $J=12.2$, 6.1 Hz, 1H), 3.70 (dt, $J=12.2$, 4.5 Hz, 1H), 2.46–2.35 (m, 2H), 2.35–2.29 (m, 2H), 2.23–2.11 (m, 1H), 1.84 (d, $J=10.9$ Hz, 1H), 1.60–1.49 (m, 1H), 1.49–1.37 (m, 2H), 1.19 (dt, $J=13.8$, 5.0 Hz, 1H), 1.03 (s, 3H), 0.52 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ 207.5, 86.9, 72.0, 45.6, 43.7, 38.9, 38.5, 27.7, 27.3, 27.2, 22.2, 19.8.
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