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A Short Efficient Access to a Bicyclic 1,2,4-Exoperoxide, Precursor of New Potential Antimalarial Compounds

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Summary: We describe an efficient synthesis to a 1,2,4-exoperoxide, intermediate to new simple potential antimalarial compounds. The key step of this synthesis is the ozonolysis of the double bound of an ethylenic intermediate prepared by a Wittig reaction.

Key words: bicyclic compounds, peroxides, ozonolysis, cyclization, Wittig reaction

Synthèse d'un bicyclique 1,2,4 trioxygéné, précurseur de nouveaux composés potentiellement antipaludiques

Résumé: Nous décrivons une méthode efficiente d'obtention d'un exoperoxide 1,2,4 trioxygéné, intermédiaire réactionnel dans la synthèse de molécules simples, potentiels composés antipaludiques. L'étape clé de cette synthèse est constituée d'une ozonolyse sur un composé éthylénique préparé en appliquant une réaction de Wittig.

Mots clés : bicycles, peroxydes, ozonolyse, cyclisation, réaction de Wittig

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1. Introduction

Malaria is one of the most common parasitic diseases in about a hundred countries in the world, especially in underprivileged tropical areas of Africa, Asia and Latin America. African continent is the most affected with 90% of cases in endemic areas. *Plasmodium falciparum* mainly transmitted by female *Anopheles mosquitoes* is the most virulent among the four species of the parasite that cause malaria. Eradication efforts failed, leaving endemic propagation and increasing resistance to chloroquine and sulfadoxine-pyrimethamine treatments [1-3]. Actually, artemisinin-based combination therapies, using artemisinin **1** and its derivates **2** is the usual antimalarial treatment (Figure 1) [4-5]. But very recently a chemo-resistance to this usual therapeutic agents appeared at the thai-cambodia border [6-10]. The discovery and the development of new synthetic, low cost routes to novel active anti-malarial compounds are still necessary.

Most the 1,2,4 trioxane structural fragment present in artemisinin **1** and derivatives **2** is essential for antimalarial activity [11-15]. However studies demonstrated that peracetal doesn't need to be intracyclic and that artemisin skeleton could be simplified [16-20] keeping biological activity.

As a part of our ongoing programme on the synthesis of new antimalarial compounds, we previously prepared some functionalized compounds **3** from the exoperoxide **4**, featuring various side chains (**Figure 2**). These compounds have been tested against *Plasmodium falciparum* and we have been encouraged by the first results of the biological activities. Thus, by developing simple and efficient access to exoperoxide **4** we would be able to synthesize a large scale of compounds **3** in order to determine the structural requirements for active molecules.

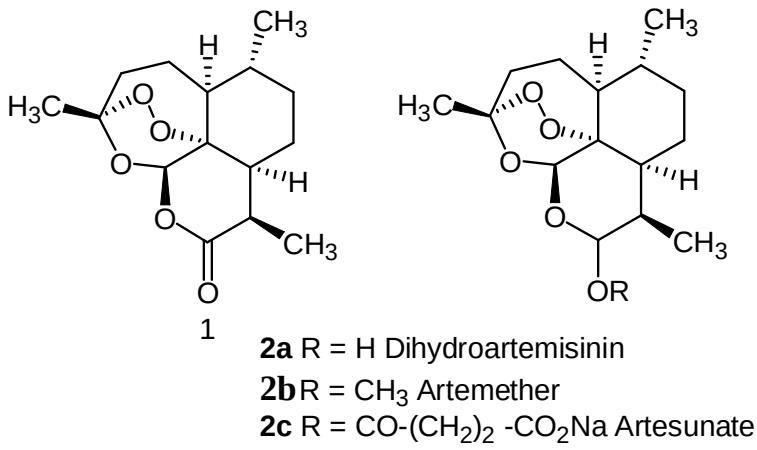

Figure 1: Artemisinin and first generation derivatives

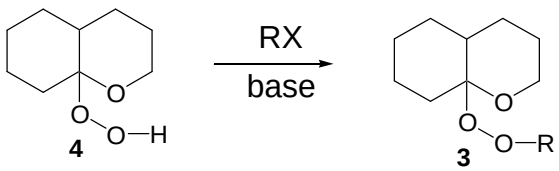

Figure 2: Usefulness of the precursor

This 1,2,4 oxygenated exoperoxide **4** was previously described by Nikishin and al. by hydroperoxidation of the 2-oxabicycloalkene **5** (84-95%). This one was prepared from the cyclohexanone **6** with a moderate yield (28%) [21] (**Figure 3**).

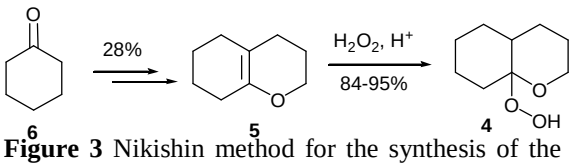

Figure 3 Nikishin method for the synthesis of the exoperoxide **4**

2. Methodology

In aim to prepare active compounds in low cost, we have developed a new efficient access to hydroperoxide **4**. We have adopted the schema in **Figure 4** for synthesis.

3. Results and discussions

In this paper, we purpose a new synthetic access to the same peroxide **4** since equally ketone **6** with higher global yield (55% in 5 steps). First, the readily available cyclohexanone **6** was condensed with the pyrrolidine **7** in refluxing cyclohexane to afford the enamine **8** in 92% yields after distillation. A Stork addition between **8** and the methyl acrylate **9** in anhydrous toluene furnished, after acid work-up of the intermediate imine (AcOH 10%, 15mn), the desired 2-alkylcyclohexanone **10** in 73% yield (**Figure 5**).

The next step is a Wittig reaction applied to ketoesters **10** according to **Figure 6**.

Preliminary, in anhydrous tetrahydrofuran (THF), reaction at 0°C to 20°C, of 2 equivalents of the methyl ylide **11a** prepared by addition of phenyllithium on the methyltriphenylphosphonium bromide appeared very sluggish. After one day, a thin-layer chromatography (tlc) revealed a lot of starting product and only 8% of **12a** was isolated (**Table I**, entry 1). Under similar conditions using 1.15 or 2 equivalents of sodium hexamethyldisilazide (NaHMDS) instead of PhLi, Wittig reactions afforded the expected ethylenic **12a** with a moderate yield of nearly 50% (Table I, entry 2-3), but also furnished a side-product **13** (**Figure 7**).

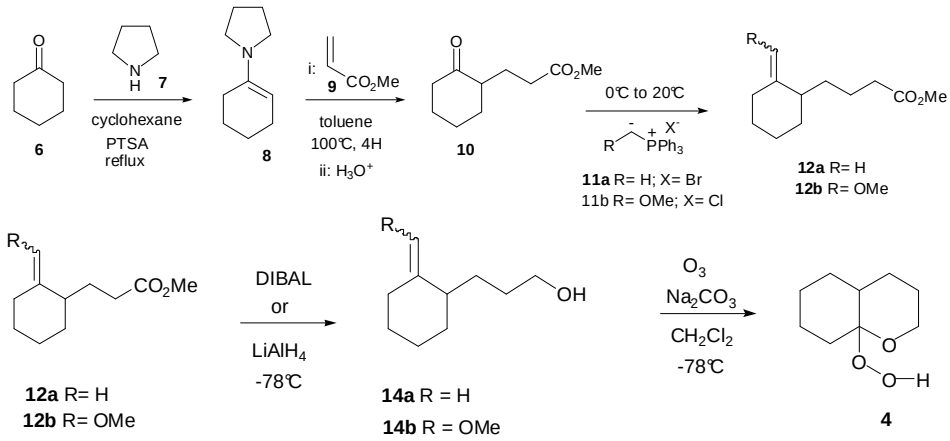

Figure 4 Synthesis schema

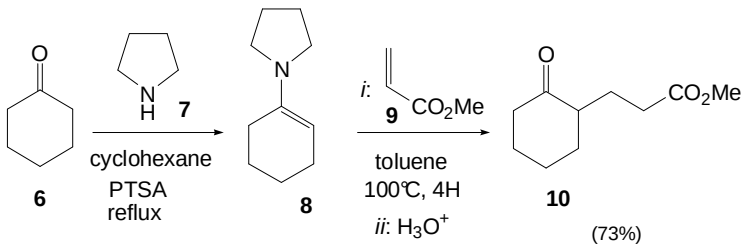

Figure 5 : Synthesis of the ketoester intermediate **10**

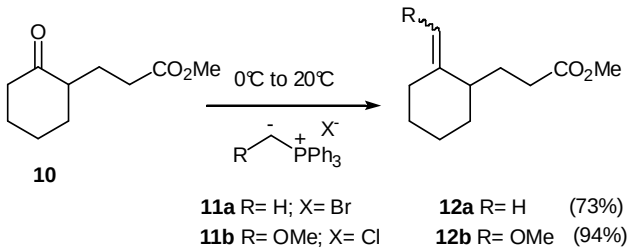

Figure 6 : Wittig reaction apply to ketoesters **10**

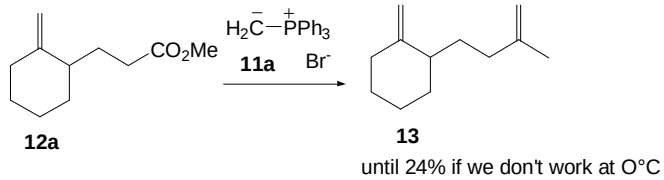

Figure 7: Formation of the side-product **13**

This compound **13** is always obtained in a very poor yield (< 5%), resulting of two additions of ylide **11a** on ester function of **12a**. Formation of the bis-ethylenic **13** could be favoured in presence of a very large excess of ylide, and could be avoid if reaction was performed at 0°C.

To improve the Wittig reaction, using of a less polar solvent like toluene, advantageously replaced THF. Carried out in anhydrous toluene, using 1.15 equivalents of NaHMDS to form ylide **11a**, reaction time decreased to 3 hours and the yield was increased to 73% (**Table I**, entry 4). The use of 2 equivalents of ylide furnished **12a** in similar yield (**Table I**, entry 5).

We also prepared the enol ether **12b** with a view to facilitate the key-step of this synthesis. The last reaction is the ozonolysis of the double bond of the ethylenic function. This kind of oxidation is enhanced with an alkene activate by an electrodonor group like an alkoxy substituent. The methoxymethyl ylide **11b** was prepared and added to the ketoester **10**, in the optimum conditions used previously. In anhydrous toluene, NaHMDS was used to deprotonate 1.15 equivalents of methoxymethyltriphenylphosphonium chloride, and the corresponding ylide was added to ketoester **10**. The enol ether **12b** was isoled with a moderate yield (45%, **Table I**, entry 6). Using 2 equivalents of ylide **11b**, yield up to 69% (**Table I**, entry 7). Optimized with 3 equivalents of **11b**, Wittig adduct was obtained with 94% yield (Table I, entry 8). Compound **12b** was formed in his isomers mixture forms in 88/12 proportion. It could be noted that yields of these Wittig reactions are excellent, but the presence of the remaining triphenylphosphinoxide which did not precipitate during work-up, disturbing purification. Indeed, compounds **12a-b** possess a good affinity to triphenylphosphine oxide**.**

The penultimate reaction, the reduction of the ester group of **12a-b** into alcohol function was easily realized using diisobutylaluminium lithium (DIBAL-H) or lithium aluminium hydride ($LiAlH_4$) at -78°C in dichloromethane (CH_2Cl_2) affording **14a-b** with yield up to 85% after purification (**Figure 8**).

Table I : Summary of the Wittig reactions results

Entry	Products	Base	Solvant	Equiv	Time	Yield
1	**12a**	PhLi	THF	2	24H	8%
2	**12a**	NaHMDS	THF	1.15	12H	51%
3	**12a**	NaHMDS	THF	2	6H	55%
4	**12a**	NaHMDS	Toluene	1,15	3H	73%
5	**12a**	NaHMDS	Toluene	2	3H	73%
6	**12b**	NaHMDS	Toluene	1.15	3H	45%
7	**12b**	NaHMDS	Toluene	2	3H	69%
8	**12b**	NaHMDS	Toluene	3	3H	94%

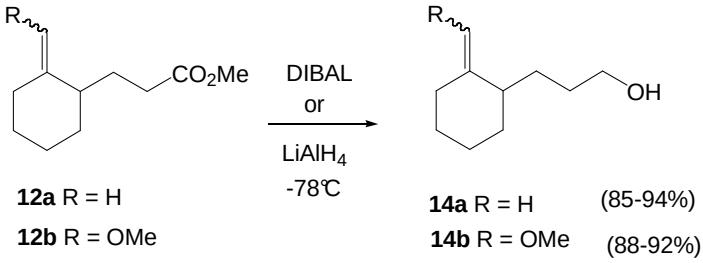

Figure 8: Reduction of the Wittig adducts into alcohols

The last step, ozonolize of the ethylenic alcohol **14a-b** was performed in anhydrous CH_2Cl_2 at –78°C in presence of sodium carbonate (Na_2CO_3). Oxidation furnished corresponding carbonyl oxide **15** which spontaneously cyclised into hemiperketal **4** with a quantitative yield (**Figure 9**). Reaction goes faster using **14b**.

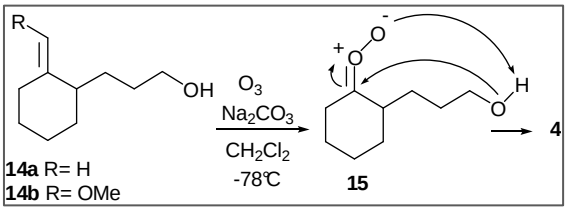

Figure 9: Mechanism of the intramolecular cyclisation, formation of the compound **4**

The oxidation of the non or actived alkenes **14a-b** afford the exoperoxide **4** in different proportions of cis/trans isomers (respectively 50/50 from **14a** and 35/65 from **14b**) (**Figure 10**). Existing forms *cis*-**4** and *trans*-**4** could be easily observable in NMR ^{1}H by the presence of the proton of the hydroperoxide function nearly 9 ppm, and in ^{13}C NMR with the tertiary carbon shift of the *cis* isomer at 38 ppm and of the *trans* one at 43 ppm.

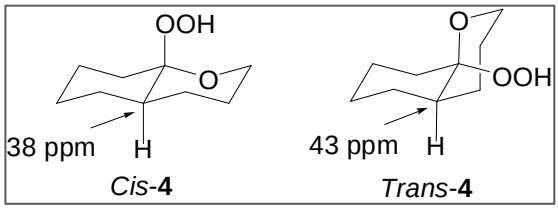

Figure 10 : The exoperoxide **4** isomers

This bicyclic compound **4** could easily preserve at 0°C and seems stable until 45°C.

4. Conclusion

In summary, an efficient access to a bicyclic oxygenated exoperoxide has thus been achieved from the commercial cylohexanone with a good global yield. Functionalization of this exoperoxide and biological activity are under investigation in our laboratory.

Experimental Section

Tetrahydrofuran (THF) and toluene were distilled from Na-benzophenone ketyl. Infrared spectra were recorded on a Brüker VECTOR 22 spectrometer.and Nuclear magnetic resonance spectra on a Brüker AC-300P (300 MHz for proton and 75 Mz

for carbon) or AC-400. $CDCL_3$ was used as internal reference. Chemical shifts were expressed in ppm. Analytical thin-layer chromatography was performed on Kieselgel $60F_{254}$ aluminium plates. Crude products were purified by column chromatography on silica gel using Merk silica gel 60 (40-63 µm). Elemental analyses were performed by the service de microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin–Elmer 2400 analyser.

1-cyclohexenylpyrrolidine (8). Cyclohexanone **6** (4 g, 40.8 mmol, 1 equiv), pyrrolidine (3.3 mL, 1 equiv) and some crystals of para-toluene sulfonic acid (PTSA) in cyclohexane (25 mL) was heated at reflux during 6 hours, water's eliminated as formed with a Dean-Stark apparatus. The solvent was then evaporated in vacuo. The crude was distilled under vacuo (Eb = 112°C) to furnish **8** was as a yellow oil (5.67 g, 92%). IR: 2926, 2855, 1714, 1639, 1449, 1393, 1346, 1310 cm-1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.24 (s, H), 2.95 (t, 2 × 2H, N–CH_2, *J* = 6.45 Hz), 2.14 (m, 2H, $NCCH_2$), 1.4-2.2 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ □= 143.03 (NC), 93.29 (CH), 47.17 (NCH_2), 27.31 (NC-$\underline{C}H_2$), 24.31 (CH_2), 23.16 (CH_2), 22.82 (CH_2).

Methyl3-(2-oxocyclohexyl)propanoate (10). Methyl acrylate (3.43 mL, 1 equiv) was added dropwise to a solution of the enamine **8** (37.55 mmol, 1 equiv) in anhydrous toluene (30 mL), with catalytic hydroquinone. The mixture was stirred at 100°C during 4 hours under argon atmosphere after which 7 mL of water were added. The mixture was stirred for an additionnal 20 mn at 20°C. The solvent was then evaporated in vacuo. Water (7 mL) was then added again and the residue was extracted with ether (three 10 mL portions). The combined organic layers were washed with 7 mL hydrochloric acid (0.01 M), dried over sodium sulphate and concentrated. The crude was distilled under vacuo (126°C) to give a yellow liquid, the product **10** with 73% yield (5.04 g). IR: 2934, 2861, 1735, 1707, 1435, 1312, 1165 cm-1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.7 (s, 3H), 1.4-2.5(m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.57 (CO), 173.03 (OCO), 51.49 (CH_3), 49.71 (CH), 42.13 (CH_2), 34.14 (CH_2), 31.60 (CH_2), 28.01 (CH_2), 25.03 (CH_2), 24.79 (CH_2). Anal. Calc for $C_{10}H_{16}O_3$: C, 65.19, H, 8.75. Found: C, 64.88, H, 8.70.

Methyl3(2(methylene)cyclohexyl)propanoate (12a). Methyl bromide triphenylphosphonium (11.26 g, 1.15 equiv) dried and grounded, was dissolved in anhydrous toluene (100 mL). Under argon atmosphere, the solution was cooled at 0°C then NaHMDS (2M in THF, 14.6 mL, 1.15 equiv) diluted in 5 mL of toluene was added drop by drop. This mixture was stirred during 1 hour then the yellow solution was added at 0°C in small portions by cannular to **10** (27.41 mmol, 1 equiv) previously dissolved in anhydrous toluene (7 mL). After stirring 3 hours at room temperature (18°C), AcOH 10% was added drip until the mixture colour change. The mixture was filtered and washed with distilled water then extracted with ether (three 15 mL portions). After drying, filtration and evaporation the crude material was purified by flash column chromatography (cyclohexane/ethyl acetate 95:5). **12a** was obtained with 73% yield (3.64 g). IR: 3071, 2928, 2855, 1738, 1644, 1436, 1374, 1324, 1166 cm-1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.45, 4.6 (2s, 2x1H); 3.55 (s, 3H), 2.6 (t, 2H, *J* = 7.37), 1-2, (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.39 (C); 151.59 (C); 106.38 (CH_2); 51.42 (CH_3); 42.61 (CH); 34.22 (CH_2); 33.64 (CH_2), 32.17 (CH_2); 28.62 (CH_2); 27.09 (CH_2); 23.78 (CH_2).

Methyl3(2(methoxymethylene)cyclohexyl) propanoate (12b). The general procedure is the same as **12a** but instead of

the solid methyltriphenylphosphonium bromide, methoxymethyltriphenylphosphonium chloride (28.19 g, **3 equiv) was used and 40.96 mL of NaHMDS (3 equiv).** The ylure is red instead of yellow. Purification of the crude material by flash column chromatography (cyclohexane/ethylacetate 95:5) afforded a mixture of the *Z*/*E* enantiomer **12b** (5.46 g, 94%) as a yellow oil. IR: 2927, 1736, 1678, 1122 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (*major isomer*) = 5.69 (s, 1H), 3.65 (s, 3H, CH_3), 3.52 (s, 3H, CO-OCH_3), 2.35-2.17 (m, 3H, $C\underline{H}_2$(C=$COCH_3$), C$\underline{H}$), 1-2 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (*major product*) = 174.42 (CO), 139.66 (=CH), 119.47 (C), 59.33 (CH-O$\underline{C}H_3$), 51.40 (CO-O$\underline{C}H_3$), 38.52 (CH), 33.33 (CH_2), 32.42 (CH_2), 27.16 (CH_2), 26.82 (CH_2), 22.95 (CH_2), 22.52 (CH_2). Anal. Calc for $C_{12}H_{20}O_3$: C, 67.89, H, 9.5. Found: C, 67.82, H, 9.06.

1(3methylbut3enyl)2methylenecyclohexane (13). IR: 2927, 2855, 1645, 1445, 884 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.59 (s, 2H, 2 x C=CH), 4,56 (s, 1H, C=CH), 4.48 (s, 1H, C=CH), 2.13 (m, 1H, CH), 1.88 (t, 4H, 2 x CH_2), 1.66-1.16 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$): 152.84 (C), 146.37 (C), 109.6 (=CH_2), 105.65(=CH_2), 42.79 (CH); 35.67, 34.75, 33.91, 30.36, 29.41, 23.46 (6 x CH_2), 22.57 (CH_3).

3-(2-(methylene)cyclohexyl)propanol (14a). A solution of Dibal-H 1M (34.06 mL, 2 equiv) in anhydrous toluene was added dropwise to a solution of the ester **12a** (20.01 mmol) in anhydrous dichloromethane (50 mL) under argon at -78°C. The mixture was stirred after back at room temperature under argon atmosphere, was hydrolysis with 25 mL of water, and was then extracted with dichloromethane (three 25 mL portions). The combined organic layers were washed with brine, dried, filtered and concentred under vacuo. Purification of the crude material by flash column chromatography (cyclohexane/ethylacetate 90:10) afforded the colorless **14a** (85%). IR: 3316, 2925, 2852, 1644, 1446, 1056, 887 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.65, 4.57 (2s, 2 × 1H); 3.65 (t, 2H, J = 6 Hz), 2.3–1.2 (m, 16 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.71 (C), 105.67 (CH_2), 63.24 (CH_2), 42.95 (CH), 34.64 (CH_2) 33.88 (CH_2); 30.77(CH_2); 28.79 (CH_2); 28.13 (CH_2); 24.14 (CH_2). Anal. Calc for $C_{10}H_{18}O$: C, 77.87, H, 11.76. Found: C, 76.84, H, 11.19.

3(2(methoxymethylene)cyclohexyl)propanol (14b). The general procedure is the same as **14a** but instead of **12a** the reactif was **12b** (25.76 mmol). Purification of the crude material by flash column chromatography (Eluant: cyclohexane/ethyl acetate 90:10) afforded **14b** with 88% yield. IR: 3359, 2925, 1679, 1125 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.78 (s, 0.33 H, =C$\underline{H}$–OCH_3), 5.72 (s, 0.67H, =C$\underline{H}$–OCH_3), 3.66-3.61 (m, 2H C$\underline{H}_2$–OH), 3.53 (s, 2.04H, OCH_3), 3.49 (s, 0.96H, OCH_3), 1-2.3 (m, 14 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (*major isomer*) = 139.14 (=CH), 120.72 (C), 63.21 (CH_2OH), 59.32 (CH_3), 38.93 (CH), 33.55 (CH_2), 31.02 (CH_2), 27.83 (CH_2), 26.33 (CH_2), 23.32 (CH_2), 22.95 (CH_2).

8a-hydroperoxy-octahydro-2H-chromene (4). **14a** or **14b** with catalytic $NaHCO_3$ in dry chloroform under argon at -78° C were bubbled by a stream of O_3 until the solution became blue. Then a current of pure O_2 was passed to remove excess of O_3.The NMR spectroscopy showed that the reaction is quantitative. IR: 3400, 2928, 1457, 1100, 1085 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63 (s, 1H), 3.74, 3.90 (2s, 2H, OCH_2), 2.3–1.1 (m, 13H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 104.14 (C), 62 (OCH_2), 35.49 (CH), 33.32 (CH_2), 28.25 (CH_2), 25.03 (CH_2), 24.13 (CH_2), 22.78 (CH_2), 20.1 (CH_2). The minor product gives respectively 103.76, 61.65, 43.64, 32.22, 29.35, 24.78, 24.13, 22.12, 20.1.

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