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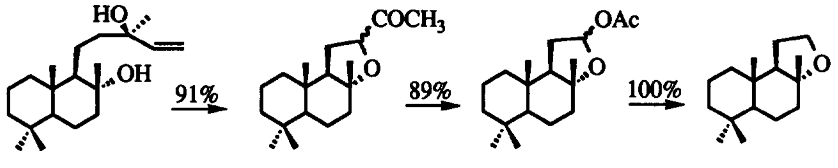
An Improved Synthesis of (-)-Dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan via Ozonolysis of (-)-Sclareol.

Derek H.R.Barton,* Dennis K.Taylor and Chi-lam Tse

Department of Chemistry, Texas A&M University, College Station,
TX 77843-3255, USA.

Abstract: *Ozonolysis of (-)-sclareol **1** under a wide range of experimental conditions has been investigated. The addition of one of the following; sodium periodate, sodium iodate, iodine or potassium iodide affords after workup the methyl-ketone **2** in excellent yield. Further elaboration of **2** afforded the title compound **4** in high yield.*

In a recent communication[1] we reported an efficient three step synthesis of Ambrox[2] **4**, a commercially important synthetic constituent of fine fragrances,[3] from naturally occurring (-)-sclareol **1** (Scheme 1). The key step involved osmium tetroxide / sodium periodate oxidative cleavage of **1** followed by an osmium catalyzed rearrangement, affording the methyl-ketone **2** in excellent yield. Baeyer Villigar oxidation of **2** followed by reduction of **3** with a variety of reducing agents in the presence of a Lewis acid completed an efficient synthesis of Ambrox **4**.



Scheme 1

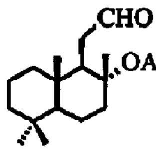
Although this route represents a simple and high yielding method for the preparation of **4**, the use of the expensive and toxic osmium tetroxide makes this synthetic sequence less attractive to industry. With this thought in mind we decided to develop a practical, inexpensive alternative for the conversion of (-)-sclareol **1** to the methyl-ketone **2**. Herein we report that ozonolysis of **1** under a variety of conditions affords **2** in excellent yield which can be further elaborated to Ambrox **4**.[1]

It was first conceived that ozonolysis of (-)-sclareol **1** in the presence of $NaIO_4$[4] might afford **2**. The results from a variety of experimental conditions are summarized in Table 1. Entries 1-3 indicate that a methanol / water cosolvent favors the formation of **2**, while *t*-butanol and *t*-amyl alcohol / water mixtures favor over oxidized products. Approximately 50% of the desired **2** is isolated when the reaction is run

Table 1: Ozonolysis of (-)-Sclareol **1** in the presence of $NaIO_4$ under a variety of conditions.[a]

Entry	Conditions	Products[b] (%)						
		2	5	6	7	8	9	10
1	MeOH / H_2O (4: 1) at 0°C	46	14	—	17	—	—	—
2	ᵗBuOH / H_2O (4: 1) at 25°C	—	26	19	—	—	—	—
3	ᵗAmOH / H_2O (4: 1) at 0°C	7	—	42	—	—	—	—
4	Temp. = 25°C or (40°C)	51	23 (16)	—	7	—	—	—
5	Temp. = -78°C	—	14	—	23	23	—	—
6	$NaIO_4$ (0.7 equiv)	63	5	—	—	—	6	5
7	$NaIO_4$ (0.2 equiv)	38	4	—	—	—	4	26
8	reaction time = 15 min.	25	8	—	—	25	11	22
9	reaction time = 30 min.	63	5	—	—	—	6	5
10	no $NaIO_4$ added	—	16	—	—	23	—	—
11	pH = 1.0[c]	5	40	—	24	—	—	—
12	pH = 2.95[c]	62	7	—	—	—	9	11
13	$NaIO_4$ ozonolysed first	77	13	—	5	—	—	4
14	$NaIO_3$[d]	51	—	—	—	6	7	—

[a] Unless otherwise stated all reactions were performed as follows: To a mixture of sclareol **1** (0.2g, 0.64mmol) in methanol / water solution (25 mL, 4:1) was added $NaIO_4$ (3.0 equiv. for entries 1-5, entries 6-7 as stated, entries 8-13, 0.7 equiv.) at 25°C. Ozone was passed through the mixture until all **1** consumed (~15 minutes, TLC). After 15 hours of additional stirring the solvent was removed in vacuo and the residue dissolved in CH_2Cl_2 (80 mL), washed with 0.4M aqueous sodium thiosulphate (2 x 50 mL), and brine (2 x 50 mL). Desiccation ($MgSO_4$) and removal of the solvent in vacuo afforded the crude mixtures. The product distributions were determined from ^1H and ^{13}C NMR analysis or by isolation by flash chromatography; [b] All new products had satisfactory micro analysis. Compounds **5**,**6** and **8** had spectral properties and physical properties in agreement with those reported (Reference 7); [c] pH adjusted with phosphoric acid or sodium acetate; [d] 1.0 equiv. employed and the reaction carried out as described above.



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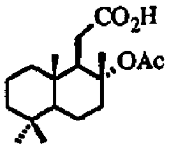

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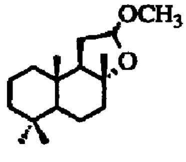

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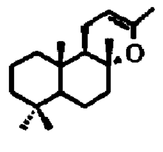

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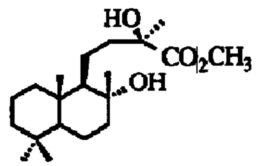

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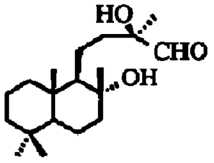

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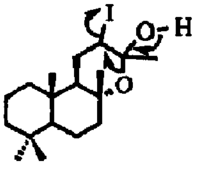

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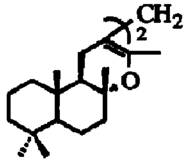

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between 0°C and 40°C (Entries 1, and 4) however at -78°C formation of **2** is not observed, (Entry 5). The methyl-ketone **2** is formed in greatest yield when 0.7 equivalents of $NaIO_4$ were employed (Entries 6-7). Further addition of $NaIO_4$ (up to 3 equiv.) had no effect on the outcome of the reaction. Under short reaction times (Entries 8-9) intermediates **8-10** were identified. The vinyl-ether **8** was confirmed as the key intermediate in these reactions by simple subjecting **1** to ozonolysis without addition of $NaIO_4$ (Entry 10). Interestingly, only traces of the desired methyl-ketone **2** were obtained below pH = 2.95 in favor of substantial quantities of products **5** and **7** (Entries 11-12). However, between pH = 3 and 7.5 good yields of **2** are found.

Mechanistically, from Table 1 it is clear that the vinyl-ether **8** is the intermediate precursor to methyl-ketone **2** formation. At this stage it is unclear as to the exact composition and structure of the species responsible for the oxidative ring-contraction of **8** into **2** but several points are worth mentioning. Treatment of **8** with $NaIO_4$ does not yield **2**. However, ozonolysis of an aqueous methanolic solution of $NaIO_4$ yielded a white precipitate. Treatment of **8** with either this white solid or the remaining filtrate quantitatively converted **8** into the methyl-ketone **2**. This lead to the conclusion that the $NaIO_4$ solution should be subjected to ozonolysis prior to the addition of (-)-sclareol **1**. Indeed, this discovery lead to a substantial increase in the yield of **2**, (Entry 13). Interestingly, $NaIO_3$ can also be successfully employed and gave moderate yields of **2**, (Entry 14). It is believed that **8** is formed via the "anomalous ozonolysis"[5] of (-)-sclareol **1** in a similar manner to that observed for other allylic alcohols.[6]

Table 2: Ozonolysis of (-)-Sclareol **1** in the presence of iodine under a variety of conditions.[a]

Entry	Conditions	Yield 2 (%)	Entry	Conditions	Yield 2 (%)
1	MeOH	62	5	I_2 (0.5 equiv.)[b]	71
2	^tBuOH	23	6	0.25 mL H_2O added	53
3	isopropanol	65	7	0.5 mL H_2O added	69
4	I_2 (1.0 equiv.)[b]	72	8	0.25 mL H_2O added[b]	85

[a] Unless otherwise stated all reactions were performed in isopropanol according to the following general procedure: To a mixture of sclareol **1** (0.2g, 0.64 mmol) in isopropanol (20 mL, water added as indicated) at 25°C was added iodine (0.1g, 0.38 mmol). Ozone was then passed through the mixture for 10-12 minutes, after which time the mixture was stirred for an additional 15 hours at ambient temperature. Workup is as indicated in Table 1; [b] These reactions were carried as follows: The isopropanol / iodine mixture was ozonolysed for 10 mins. prior to sclareol and water addition. Ozonolysis was then continued for a further 5 minutes, after which time the mixture was stirred for an additional 15 hours at ambient temperature and worked-up in the usual manner.

A possibility is that the electrophilic iodine species HOI was generated in the reaction medium and is responsible for the conversion of the vinyl-ether **8** to the methyl-ketone **2** via intermediate **11**. This seemed to be substantiated by the fact that iodine was liberated during the reaction. Moreover, treatment of **8** with a aqueous methanolic solution containing iodine afforded the methyl-ketone **2** quantitatively. Hence it was conceived that iodine or potassium iodide would be ideal substitutes for iodate and periodate and a number of reactions were performed, the results of which are summarized in Table 2.

Both methanol and isopropanol afforded moderate yields of desired **2** on ozonolysis of **1** in the presence of iodine, (Entries 1-3). The yield of **2** could be increased further by ozonolysing the isopropanol / iodine solution (10 mins.) prior to the addition of the (-)-sclareol **1**. Entries 4-5 indicate that only an half a equivalent of iodine is necessary under these conditions. Employing even less iodine substantially decreased the yield of **2**. Furthermore, if HOI was a necessary intermediate then the addition of H_2O should enhance the yield further. Indeed, a small amount of water is desirable for the formation of **2**, (Entries 6-7) while addition of 10 mL H_2O was detrimental for formation of **2**. The greatest yield of the desired methyl-ketone

2 could be obtained if the isopropanol / iodine solution was ozonolysed (10 mins.) prior to the addition of the (-)-sclareol **1** and a small but significant amount of water, (Entry 8). Finally it is worth mentioning that potassium iodide can also replace the iodine and afforded **2** in yields of 80-83%. In an attempt to isolate an intermediate (-)-sclareol **1** was subjected to ozonolysis in isopropanol. After 10 minutes the solvent was removed and the residue recrystalized from pentane affording the dimer **12**. The formation of **12** comes from the reaction of the vinyl-ether **8** and formaldehyde, a by-product of the ozonolysis reaction. Dimer **12** has been identified previously.[8]

In summary we describe several simple, inexpensive and high yielding syntheses of the methylketone **2**, an important intermediate in the synthesis of Ambrox **4**,[1] starting from naturally occuring (-)-sclareol **2**. Although the exact species responsible for the oxidative ring-contraction of **8** to **2** in the various ozonolytic reactions described herein is yet to be fully identified, these sequences should make the synthesis of Ambrox **4** from sclareol economically attractive.

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