About a Practical Synthesis of *Ambrox*® from Sclareol: a New Preparation of a Ketone Key Intermediate and a Close Look at its *Baeyer–Villiger* Oxidation

by **Jean Moulines***, **Jean-Paul Bats**[1]), **Anne-Marie Lamidey**, and **Nicole Da Silva**

Institut du Pin, Laboratoire de Chimie des Substances Végétales, 351, Cours de la Libération, F-33405 Talence Cédex
(e-mail : emoulines@noos.fr)

In memoriam – Jean-Paul Bats, Maître de Conférences à l'Université Bordeaux 1, emporté par un mal implacable, n'aura pas vu l'aboutissement d'un travail où il aura jeté ses dernières forces avec une détermination intacte. C'était un chimiste, passionné de recherche, dont l'intuition créatrice s'alliait à un sens pratique hors du commun. Capable de passer du laboratoire à l'atelier de fabrication sans rien perdre de son aisance et de son efficacité, il s'engageait avec d'autant plus d'enthousiasme que le problème était plus difficile, l'enjeu plus élevé.

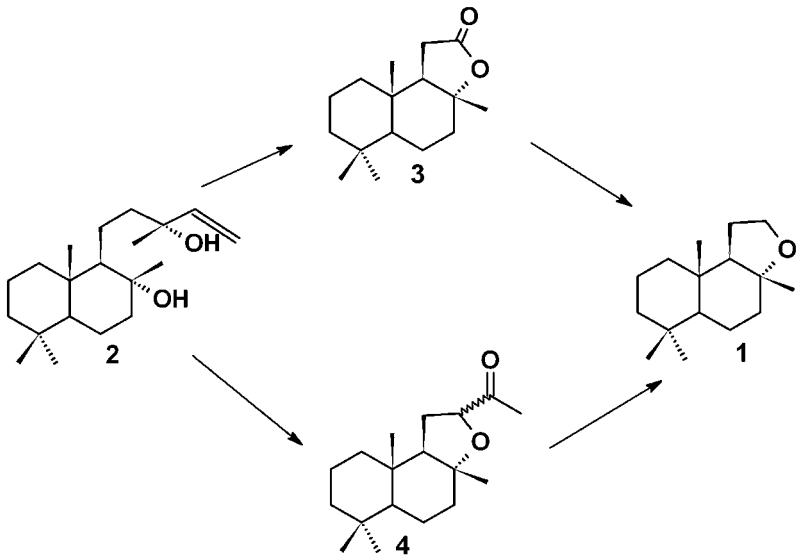
The latest route to *Ambrox*® (**1**) starting from sclareol (**2**) proceeds through an oxy ketone **4** (*Scheme 1*). A new practical synthesis of the key intermediate **4** is described; it is equivalent to a partial oxidative degradation of sclareol (**2**) with peracetic and periodic acids (*Scheme 2*). The final product of the *Baeyer–Villiger* oxidation of the oxy ketone **4** with commercial peracetic acid is decisively dependent on the reaction conditions because the expected acetate **9** reacts with any nucleophile, especially the peracid (*Scheme 3*). Furthermore, this acetate **9** is very prone to eliminative coupling (*Scheme 4*).

Introduction. – Ambergris remains the archetype of all the amber odorants [1] which play an important role in the creation of perfumes. It is a solid material excreted from the sperm whale (*Physeter catodon* L.) and is then oxidized by the action of air and sun during all the time it is floating in the sea or lying on the shore. Only a few prestige perfumes still incorporate ambergris. By the mere fact that the perfume industry needs a regular and sufficient supply with a constant quality, the synthetic ambergris-like products have been used for a long time. Among them, the (−)-8α,12-epoxy-13,14,15,16-tetranorlabdane (**1**), commonly known as *Ambrox*® (a trade name of *Firmenich SA*), is all the more valuable as it is one of the fragrant components of ambergris tincture [2]. *Ambrox*® (**1**) was obtained for the first time by *Stoll* and *Hinder* [3][4] from sclareol (**2**), a diterpenic alcohol extracted in sizeable amounts from clary sage (*Salvia sclarea* L.) (*Scheme 1*). Upon oxidative degradation with potassium permanganate, sclareol (**2**) leads to sclareolide (**3**) [5], which is then converted to *Ambrox*® (**1**) according to the usual process for reducing a lactone to a cyclic ether. Since the structural features of **1**, which control its odor properties (the profile as well as the strength) [6][7] are also found in sclareol (**2**), the latter remains the starting material of choice. Thus, **1** is still manufactured through the sclareolide route (*Scheme 1*), potassium permanganate being used as an effective and cheap oxidant [8]. The chief drawback of this route is how to discard the large amount of manganese

[1]) Deceased on October 19, 1997.

dioxide produced at the same time while preserving the environment. The waste disposal is simplified on changing potassium permanganate either for ruthenium tetraoxide, in conjunction with O-donors [9][10], or for nonmetallic oxidants [11]. A quite different solution is to replace the sclareolide route with another one. Thus, *Firmenich*'s chemists [12] have made use of the fragmentation in oxidative medium of the alkoxy radical derived from OH–C(13) of sclareol (**2**) to obtain *Ambrox*® (**1**). Unfortunately, this ingenious method is of little practical value because of the failure to generate this radical directly.

Scheme 1



About ten years ago, *Barton* and co-workers [13] pointed out a new route *via* the 8α,12-epoxy-14,15-dinorlabdan-13-one (**4**), which results from the partial oxidative degradation of the sclareol (**2**) side chain combined with the formation of the furan ring (*Scheme 1*). *Ambrox*® (**1**) follows from the reductive deacetylation of oxy ketone **4**. For an industrial application, the latter is prepared by the ozonolysis of sclareol (**2**) in alcoholic solution and in the presence of I_2 or an I-containing compound [14]. Afterwards, this preparation was modified so as to separate the two stages: first, the production of the sclareol oxide (**7**) (see below, *Scheme 2*) by ozonolysis, and second, the conversion of this cyclic enol ether to oxy ketone **4** [15]. As the ozonolysis of **2** is an unselective reaction [16], the need for controlling it presumably accounts for this modification. But the advantage of taking the oxy ketone route is brought into question, since the oxidation of the sclareol oxide (**7**) can lead to sclareolide (**3**) in good yield as well [17].

On our part, we have first attempted to work out a preparative method of oxy ketone **4** excluding ozonolysis. Second, we have re-examined the *Baeyer–Villiger*

oxidation of oxy ketone **4**, the first step of the deacetylation to *Ambrox*® (**1**), commercial peracetic acid being the most suitable oxidant on a preparative scale [15] among those previously used [13].

Results and Discussions. – We found that the epoxysclareol **5** (1 equiv.), treated with periodic acid (2 equiv.) in homogeneous hydro-organic medium, led to oxy ketone **4** in very good yield (*Scheme 2*). The reaction rate showed strong dependence on temperature; whereas it was very low at 0°, it became so high at 25° that the epoxysclareol **5** disappeared in 8 h. The proper conditions, temperature and time, were determined in THF as solvent and were unmodified in other H_2O-miscible solvents such as EtOH and *t*BuOH. Both 12-epimers of oxy ketone **4**, previously identified by *Wahlberg et al.* [18], were formed in a *ca.* 4:1 ratio, the (12*R*)-epimer being the major component. With respect to the mechanism (see *Scheme 2*), the *Malaprade* oxidation of epoxysclareol **5** is expected to yield, in accordance with its stoichiometry, hydroxy ketone **6**, well known for cyclodehydrating quickly to sclareol oxide (**7**) [19]. The oxy ketone **4** proceeds from this cyclic enol ether **7** since it does not form when the cyclodehydration is prevented from occurring. Thus, the reaction of epoxysclareol 8-acetate was restricted to the oxidative degradation of the side-chain (only the 8-*O*-acetylated derivative of hydroxy ketone **6** was obtained). As proposed by *Barton* and co-workers [14], the conversion of sclareol oxide (**7**) to oxy ketone **4** is believed to involve the iodohydrin **8**, which undergoes a semipinacol-like rearrangement with loss of HI. The formation of this iodohydrin **8** implies the addition of hypoiodous acid to the C=C bond. This kind of addition is generally achieved with I_2 in the presence of H_2O and a suitable oxidant [20]. These conditions are fulfilled in the case at hand, since the oxidation of HI by iodic acid (from the *Malaprade* reaction) continuously releases I_2; in this respect, hypoiodous acid behaves like a catalyst. The formation of I_2 was evidenced by the color of the medium and was also indicative that the reaction was in progress. Moreover, sclareol oxide (**7**) treated with I_2 and H_2O afforded oxy ketone **4** in almost quantitative yield [14]. The same result was reached when **7** was treated with aqueous periodic acid. The starting of this reaction requires a minute amount of hypoiodous acid or of its equivalent, which can only arise from periodic acid; this fact is not unprecedented but not fully explained [21][22].

For an industrial application, the *Baeyer–Villiger* reaction is usually carried out with commercial peracetic acid, *i.e.*, a *ca.* 40% peracetic acid solution in AcOH and H_2O, containing residual H_2O_2 and a little H_2SO_4. This strong acid serves as a catalyst because it protonates the carbonyl O-atom of the *Criegee* intermediate, thereby facilitating the breaking of the O–O bond. Peracetic acid is used in fairly large excess, and at temperatures somewhat below 50° for avoiding its decomposition. A first trial made under these conditions showed that oxy ketone **4** was oxidized off by commercial peracetic acid, but that the expected acetate **9** was not isolable, because it reacted with the medium as stated below. Conversely, acetate **9** (*Fig. 1*) was obtained in excellent yield by the method of *Barton* and co-workers [13], who employed the peroxyacid in small excess and in the presence of an acidic scavenger such as NaOAc or NaOOCH [15] at *ca.* room temperature. Each epimer of oxy ketone **4** led to one epimer of acetate **9**, the configuration at C(12) being retained in agreement with the known stereochemistry of the *Baeyer–Villiger* reaction.

Scheme 2

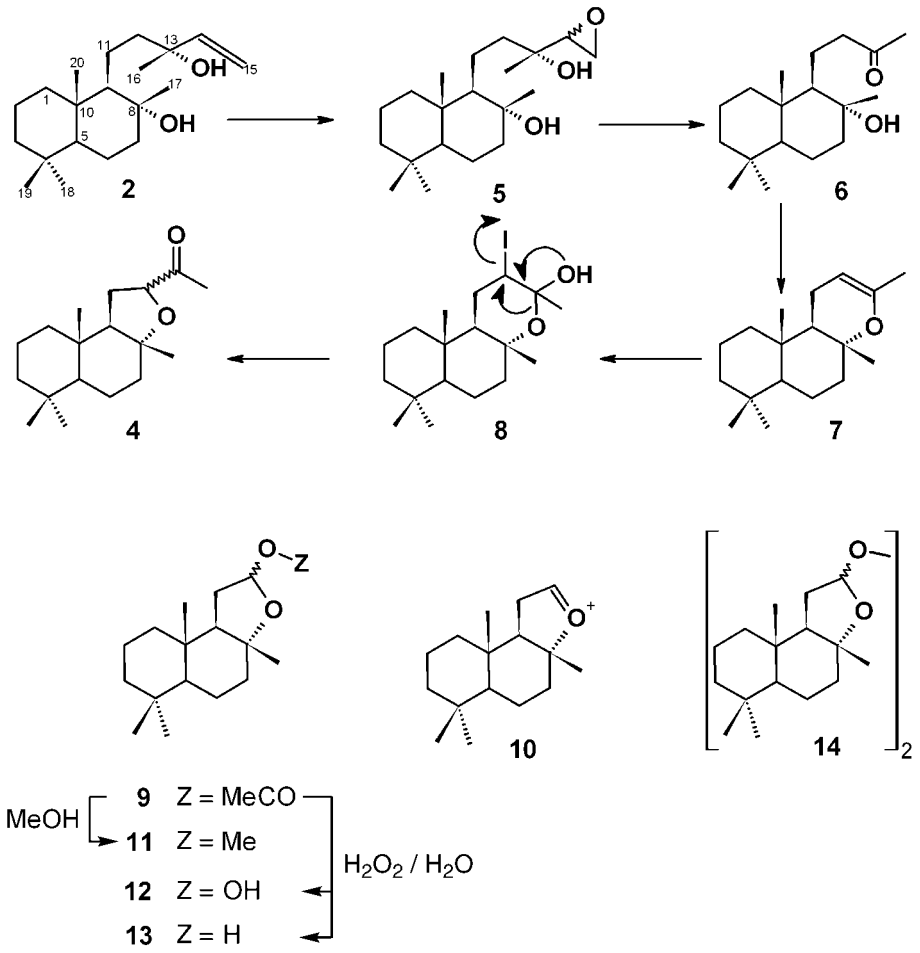


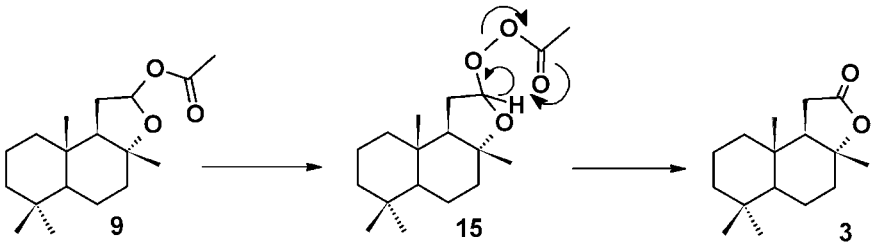
Fig. 1. *Reactivity of acetate* **9**

The great reactivity of acetate **9** towards nucleophilic substitution was exemplified by its acid-catalyzed methanolysis, which proceeded to completion in a few hours at room temperature. The formation of both C(12) epimers of methyl ether **11** (*Fig. 1*) from pure (12*S*)-acetate **9** in *ca.* 1:1 ratio established that this compound reacted by an S_N1 (or A-1 concerning an acetal) mechanism favored by the stabilization of the carbocation **10** (*Fig. 1*). Reaction of acetate **9** with 30% (*w*/*w*) hydrogen peroxide was then studied. It yielded hydroperoxide **12** and lactol **13** (*Fig. 1*) as a result of the competing nucleophilic attack of H_2O_2 and H_2O, the former being the less concentrated but the more reactive.

Finally, acetate **9** was allowed to react with commercial peracetic acid itself at two different temperatures. At 15°, peroxide **14** (*Fig. 1*) hydroperoxide **12**, and sclareolide (**3**) were the main reaction products. Hydroperoxide **12** is obviously formed from

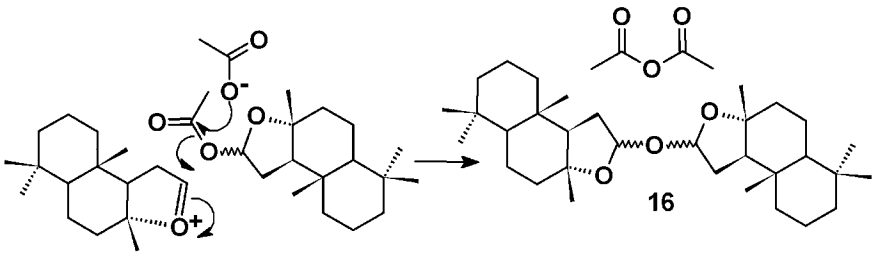
residual H_2O_2 and, in turn, acts on acetate **9** as a good nucleophile to give peroxide **14**. Sclareolide (**3**) follows from the fragmentation of peracetate **15** which arises from the exchange between acetate **9** and the peroxyacid (*Scheme 3*). At 45°, peroxide **14** was no longer detectable, and the scareolide (**3**) was the major product. The irreversible conversion from acetate **9** *via* peracetate **15** is supposed to become so fast at this temperature that the side reaction to hydroperoxide **12** is suppressed. The same was observed when oxy ketone **4** (1 equiv.) was treated with commercial peracetic acid (3 or 4 equiv., no solvent). The exothermicity of the *Baeyer–Villiger* reaction occurring first was so high that the temperature of the medium was above 45°. The acetate **9** reacted as formed with peracetic acid in excess and residual H_2O_2 to afford sclareolide (**3**) and hydroperoxide **12**, respectively. All the solvolysis products of the (12*S*)-acetate **9** were mixtures of stereoisomers. The 12-epimers of hydroperoxide **12** but not those of lactol **11** could be separated. It should be noted that the ester exchange between the peroxyacid and the acetate during a *Baeyer–Villiger* reaction has been reported [23]. A similar exchange, followed by the fragmentation of the perester so generated, is the basis of the *Grieco* method for converting a cyclic methyl acetal into a lactone [24].

Scheme 3

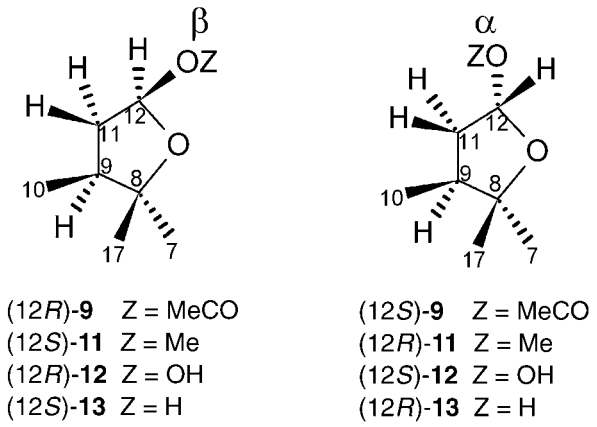


On the other hand, we repeatedly observed that (12*S*)-acetate **9** was converted to lactol anhydride **16** at room temperature in the course of time (over a period of 20 days at most); in addition, the acetate that had not yet reacted was epimerized. We also checked that the same occurred with (12*R*)-acetate **9**. Moreover, hydrolysis of acetate **9** in AcOH medium gave only lactol **13**. This whole set of facts suggests that the carbocation **10** is involved in a process as shown in *Scheme 4*, which is likely facilitated by the arrangement and the vicinity of molecules in the solid state. Thus, the nucleophilic attack of the acetate ion at the carboxy C-atom of a neighboring molecule would produce Ac_2O [25], while the leaving oxy anionic moiety would become bound to the cationic centre. The configuration (*12R*,12′*R*) was assigned to the most abundant (*ca.* 80%) stereoisomer of lactol anhydride **16**. This stereoisomer was doubtless identical with the compound that *Stoll* and *Hinder* had obtained by attempting to sublimate lactol **13**, and that they had identified by any available means some fifty years ago [26]. As pointed out by these authors, the hydrolysis of lactol anhydride **16** to lactol **13** required rather drastic conditions. To the best of our knowledge, the quantitative conversion at room temperature of 1-acetoxyisochromane to di(isochroman-1-yl)ether [27] is the only other example of this reaction type reported in the literature.

Scheme 4



In all experiments, the main problem was the determination of the configuration at C(12) (*Fig. 2*) since the oxygenated substituent could lie either on the same side of the molecule as the Me(17) and Me(20) (β-oriented) or on the opposite side (α-oriented). The solution of this problem resulted from a set of NMR data.



(12*R*)-**9** Z = MeCO
(12*S*)-**11** Z = Me
(12*R*)-**12** Z = OH
(12*S*)-**13** Z = H

(12*S*)-**9** Z = MeCO
(12*R*)-**11** Z = Me
(12*S*)-**12** Z = OH
(12*R*)-**13** Z = H

Fig. 2. *Determination of the configuration at C(12) of* **9** *and* **11**–**13**

By ^{1}H-NMR, it was easy to detect the signal of H–C(12), which formed with 2 H–C(11) and H–C(9) a four-spin system. The latter could be analyzed in the first-order approximation, provided the δ of 2 H–C(11) and H–C(9) were not too close. As H–C(12) was coupled with 2 H–C(11) but not with H–C(9) (from COSY plot), its signal was expected to be a *q*. When the oxygenated substituent was α-oriented, the *q* was reduced to a *d*, because one of the two vicinal coupling constants was too weak to bring about resolvable line splitting. When the oxygenated substituent was β-oriented, the inner lines of the *q* stood nearby or coalesced at times (*t* pattern), because the difference between the two vicinal coupling constants was very small or even below the resolution of the spectrometer. With the (12*R*)-hydroperoxide **12**, second-order effects in the intensities distribution and in the line spacing were visible within the *q*. On the other hand, the C(12) configuration of the two epimers of oxy ketone **4** has been assigned by *Wahlberg et al.* [18] on the basis of a ^{1}H,^{1}H-NOE interaction between the H–C(12) and the Me(17), which is observed only for the (12*R*)-epimer. Indeed, in this case, these protons are located on the same side of the molecule (acetyl group α-oriented). The same interactions were now most easily found in the NOESY plot of each pair of 12-epimers. By ^{13}C-NMR, the most-conclusive evidence for the configuration at C(12) arose from the γ-effect at C(9) with reference to *Ambrox*® (**1**). Thus, the introduction of an α-oriented oxygenated substituent caused a low-frequency shift on the order of 3 ppm.

Conclusions. – Another method of preparing oxy ketone **4**, easy to employ and suitable for large-scale production, is devised. Like that of *Barton* and co-workers [14] before, it is based upon the rearrangement of a iodohydrin **8** from sclareol oxide (**7**). Its typical feature is that a single reagent, periodic acid, is sufficient for generating both **7** and **8**, provided the starting material is epoxysclareol **5**. In short, the overall process amounts to a two-step semi-degradation of the sclareol (**2**) side chain with two commercial oxidants, peracetic acid and periodic acid. *Baeyer–Villiger* oxidation of oxy ketone **4** requires definite conditions to succeed in the isolation of the expected acetate **9**, which proves to be nucleophile-sensitive. Thus, under usual conditions, acetate **9** is wholly converted to sclareolide (**3**) by the nucleophilic peracetic acid. This reaction is likely to be of practical value, because the sclareolide (**3**) thus obtained is free from its open form (hydroxy or acetoxy acid), unlike the one resulting from the oxidation of sclareol (**2**) with metallic oxidants. Finally, the strong tendency of acetate **9** in the solid state to undergo coupling with concomitant elimination of Ac_2O is evidenced; the product **16** of this uncommon reaction is fully characterized.

We wish to thank *Marie-Laure Sanchez* and *Marc Pignot*, Dortmund Universität, for preparing some sclareol derivatives and *Françoise Dumas* for conducting trial experiments with periodic acid. We are indebted to *Christiane Vitry* for mass spectral data and to *Michel Petraud* for 2D-NMR analyses. The helpful comments of *Christian Gardrat* on structural determinations are appreciated. *N. Da Silva* is grateful to *Biolandes* (Le Sen-Labrit, France) for a grant during the course of her research work. We acknowledge the skillful assistance of *Eric Moulines* in preparing this manuscript.

Experimental Part

1. *General*. Sclareol (**2**) was available from *Biolandes* (Le Sen-Labrit, France; m.p. 104°). Commercial 40% peracetic acid was supplied by *SEPPIC* (Paris), having the following composition (*w*/*w*): AcOOH, 40%; AcOH, 40%; H_2O_2, 5%; H_2O, 14%; H_2SO_4, 1%. Titration of this chemical by the *Sully* and *Williams* iodometric method [28] showed 38% of AcOOH (0.50 mol/100 g). Over 99% pure periodic acid was purchased from *Acros Organics*. A 90% (*w*/*v*) aq. soln. of periodic acid (assay value 89.0% or 3.90 mol/l) used for large-scale experiments was available from *S.V.P.C.* (*Levallois-Perret*, France). HPLC: *Waters* system with a *Lichrosorb® RP 18* (10 μm; 4.6 × 250 mm) column (flow 1.2 ml/min, eluent MeOH/H_2O) or a *Partisil™* silica gel (10 μm; 4.6 × 250 mm) column (flow 2 ml/min, eluent hexane/Et_2O). Flash column chromatography (FC): silica gel (70–200 μm).

M.p.: *Reichert* hot-stage microscope; uncorrected. IR Spectra: *Perkin-Elmer 1600-FT-IR* spectrometer; in cm^{-1}. NMR Spectra: $CDCl_3$ solns.; *Bruker AC-200* (^1H at 200 MHz, ^{13}C at 50.3 MHz), *AC-250* (^1H at 250 MHz, ^{13}C at 62.9 MHz), and *DPX-400* (^1H at 400 MHz, ^{13}C at 100.3 MHz) spectrometers; chemical-shift values δ in ppm, rel. to residual $CHCl_3$ (δ 7.26 for ^1H and 77.0 for ^{13}C), coupling constants *J* in Hz. Mass spectra: *VG-AutoSpec-Q* machine; in *m*/*z* (rel. %).

2. *Reaction of Epoxysclareol* **5** *with Periodic Acid: 8α,12-Epoxy-14,15-dinorlabdan-13-one* (*=1-[(3a*R*,5a-*S*,9a*S*,9b*R*)-Dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan-2-yl]ethanone;* **4**). Epoxysclareol **5** was obtained by epoxidation of sclareol (**2**) with *m*-chloroperbenzoic acid (*m*-CPBA) [29] or commercial peracetic acid [11]. To a stirred soln. of **5** (4.0 g, 12.3 mmol) in THF (20 ml) was added dropwise a soln. of periodic acid (6.0 g, 26.3 mmol) in THF/H_2O 3:2 (40 ml) at 25°. Towards the end of the addition (after *ca.* 20 min), the mixture turned deep brown. Stirring was continued at 25° for 8 h. Then the mixture was treated with 40% aq. $Na_2S_2O_3$ soln. until the color disappeared. The bulk of the THF was evaporated, and H_2O (50 ml) was added. The mixture was extracted with Et_2O (3 ×), the combined org. layer washed with sat. aq. $NaHCO_3$ soln. 10% aq. $Na_2S_2O_3$ soln., and brine, dried (Na_2SO_4) and evaporated, and the light-yellow waxy solid purified by FC (hexane/Et_2O 95:5–80:20): (12*R*)/(12*S*)-**4** *ca.* 80:20 (2.9 g, 84%). White crystalline solid. The most abundant, (12*R*)-**4**, eluted first on FC thus allowing epimer separation. Spectral data: in close agreement with those previously reported [18].

*Data of (12*R*)*-**4**: Solid. M.p. 72° ([13]: 71–73°). IR (KBr): 1716 (C=O). ^{1}H-NMR: 4.38 (*q*, *J* = 9.9, 3.0, H–C(12)); 2.20 (*s*, Me(16)); 1.16 (*s*, Me(17)); 0.88 (3 H), 0.83 (6 H) (2*s*, Me(18), Me(19), Me(20)). ^{13}C-NMR: 210.9 (C(13)); 82.5 (C(8)); 80.8 (C(12)); 59.2 (C(9)); 57.0 (C(5)); 42.2 (C(3)); 39.7, 39.6 (C(1), C(7)); 36.1 (C(10)); 33.4 (C(18)); 32.9 (C(4)); 27.0 (C(11)); 26.6 (C(16)); 21.4 (C(17)); 20.9 (C(19)); 20.4 (C(6)); 18.1 (C(2)); 14.8 (C(20)).

*Data of (12*S*)*-**4**: Solid. IR (KBr): 1716 (C=O). ^{1}H-NMR: 4.32 (*t*, *J* = 8.3, H–C(12)); 2.24 (*s*, Me(16)); 1.07 (*s*, Me(17)); 0.88 (3 H), 0.83 (6 H) (2*s*, Me(18), Me(19), Me(20)). ^{13}C-NMR: 211.2 (C(13)); 82.5 (C(12)); 82.2 (C(8)); 60.5 (C(9)); 56.9 (C(5)); 42.2 (C(3)); 39.8, 39.7 (C(1), C(7)); 36.2 (C(10)); 33.4 (C(18)); 32.9 (C(4)); 26.7 (C(16)); 26.0 (C(11)); 22.8 (C(17)); 20.9 (C(19)); 20.6 (C(6)); 18.2 (C(2)); 15.2 (C(20)).

3. *Procedure for the Practical Preparation of Oxy Ketone* **4**. Epoxysclareol **5** (40.0 g, 123 mmol) was dissolved in EtOH (200 ml) warmed to 30°. To this stirred soln., kept at 30°, was added portionwise a commercial 90% *w*/*v* aq. periodic acid soln. (65 ml, 254 mmol) diluted with H_2O (100 ml) and EtOH (250 ml). After 8 h stirring at 30°, the mixture was worked up as described in *Exper. 2*, but after the treatment with solid $Na_2S_2O_3 \cdot 5\ H_2O$ (instead of 40% aq. soln.), the sulfur from the acidic decomposition of thiosulfate was filtered off. Oxy ketone **4** was obtained as a 93% pure (by HPLC) epimer mixture (32.4 g, 88%) suitable for use without the need of FC purification. This oxy ketone **4** could be stored under Ar in a refrigerator for several months without oxidative degradation. *Note: oxy ketone* **4** *reacted with molecular oxygen at r.t. producting AcOH and sclareolide* (**3**).

4. *Reaction of Sclareol Oxide* (**7**) *with Periodic Acid*. Sclareol oxide (**7**) was obtained by selective permanganate oxidation of sclareol (**2**) [5][19]. A soln. of **7** (3.1 g, 12 mmol) in THF (20 ml) was treated by periodic acid (2.7 g, 12 mmol) in THF/H_2O 3:2 (20 ml) as described in *Exper. 2* for **5** (including the extraction). FC afforded (12*R*)/(12*S*)-**4** *ca.* 80:20 (3.3 g, 97%).

5. *Reaction of Epoxysclareol 8-Acetate with Periodic Acid: 8α-(Acetyloxy)-14,15-dinorlabdan-13-one* (*= 4-[(1*R*,2*R*,4a*S*,8a*S*)-2-(Acetyloxy)decahydro-2,5,5,8a-tetramethylnaphthalen-1-yl]butan-2-one*. Sclareol (**2**) was selectively mono-acetylated according to *Vlad et al.* [30] to give sclareol 8-acetate (67%, m.p. 122° (hexane)). Epoxidation of this acetate with *m*-CPBA in $CHCl_3$ under the usual conditions led to epoxysclareol 8-acetate (= 8-(acetyloxy)-14,15-epoxylabdan-13-ol; 90%; m.p. 126°, (hexane); ^{1}H- and ^{13}C-NMR data in agreement with those previously reported by *Christenson* [31]). To a stirred soln. of epoxysclareol 8-acetate (5.0 g, 13.6 mmol) in THF (20 ml) was added dropwise a soln. of periodic acid (6.5 g, 28.6 mmol) in THF/H_2O 3:2 (40 ml) at 25°. This pale yellow mixture was stirred at 25° for 8 h without turning brown. The THF was evaporated, and H_2O (50 ml) was added. The mixture was extracted with Et_2O (3×), the combined org. phase washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/Et_2O 95:5 → 80:20): 8α-(acetyloxy)-14,15-dinorlabdan-13-one (3.35 g, 76%). White solid. Spectral data: in agreement with those previously reported [32]. M.p. 114° (hexane) ([32]: 118–121°). IR (KBr): 1725 (C=O, ester), 1708 (C=O, ketone). ^{1}H-NMR: 2.12 (*s*, Me(16)); 1.91 (*s*, MeCOO); 1.45 (*s*, Me(17)); 0.85 (*s*, Me(18)); 0.83 (*s*, Me(20)); 0.77 (*s*, Me(19)). ^{13}C-NMR: 208.7 (C(13)); 169.6 (*Me*COO); 87.6 (C(8)); 57.8 (C(9)); 55.3 (C(5)); 46.3 (C(12)); 41.5 (C(3)); 39.3 (C(1)); 39.2 (C(10)); 38.5 (C(7)); 33.1 (C(18)); 32.8 (C(4)); 29.6 (C(16)); 22.7 (*Me*COO); 21.2 (C(19)); 20.1 (C(17)); 19.7 (C(6)); 19.3 (C(11)); 18.0 (C(2)); 15.3 (C(20)).

6. Baeyer–Villiger *Oxidation of Oxy Ketone* **4**: *8α,12-Epoxy-13,14,15,16-tetranorlabdan-12-ol Acetate* (*= (3a*R*,5a*S*,9a*S*,9b*R*)-Dodecahydro-3a,6,6-9a-tetramethylnaphtho[2,1-*b*]furan-2-ol Acetate*; **9**). AcOOH (4.4 g, 22 mmol) was added to a stirred soln. of (12*R*)-**4** (5.6 g, 20 mmol) in AcOEt (40 ml), in which NaOAc (0.9 g, 11 mmol) was suspended. After being stirred for 18–20 h (NMR monitoring) at 20°, the mixture was diluted with AcOEt (10 ml) and then poured into H_2O (50 ml) for bringing AcOH, unreacted AcOOH, and H_2O_2 into the aq. layer. The org. layer was separated, washed with 10% aq. Na_2CO_3 soln. and brine, dried (Na_2SO_4), and evaporated: (12*S*)-**9** (5.4 g, 92%), sufficiently pure for use in the following experiments; storable without further purification in a refrigerator for several months without apparent alteration.

The (12*S*)-**4** treated under the same conditions gave (12*R*)-**9** (partly epimerized).

*Data of (12*R*)*-**9**: White solid. ^{1}H-NMR: 6.20 (*q*, *J* = 6.4, 4.9, H–C(12)); 2.05 (*s*, MeCOO); 1.25 (*s*, Me(17)); 0.88 (3 H), 0.84 (6 H) (2*s*, Me(18), Me(19), Me(20)). ^{13}C-NMR: *Table.*

*Data of (12*S*)*-**9**: Solid. M.p. 92° ([14]: 92–94°). ^{1}H-NMR: 6.22 (*d*, *J* = 5.5, H–C(12)); 2.04 (*s*, MeCOO); 1.14 (*s*, Me(17)); 0.88 (3 H), 0.84 (6 H) (2*s*, Me(18), Me(19), Me(20)). The ^{1}H-NMR data did not agree with those reported by *Aryku* and *Vlad* [33]. ^{13}C-NMR: *Table.*

7. *Reaction of Acetate* **9** *with Methanol: 8α,12-Epoxy-13,14,15,16-tetranorlabdan-12-yl Methyl Ether* (*= (3a*R*,5a*S*,9a*S*,9b*R*)-Dodecahydro-2-methoxy-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan*; **11**). A soln. of the (12*S*)-**9** (1.2 g, 4 mmol) in MeOH (20 ml) with a trace amount of H_2SO_4 was left to stand at r.t. for 24 h. MeOH was evaporated, and Et_2O was added. The mixture was washed with H_2O and brine, dried (Na_2SO_4), and

Table. *^{13}C-NMR Data of Compounds* **9**, **11**, **12**, **13**, *and* **16**

	9		**11**		**12**		**13**[a])		**16**[b])
	(12*R*)	(12*S*)	(12*R*)	(12*S*)	(12*R*)	(12*S*)	(12*R*)	(12*S*)	(12*R*,12′*R*)
C(1)	39.5	39.9	39.7	39.6	39.7	39.9	39.7/39.6		39.9
C(2)	18.1	18.1	18.3	18.3	18.2	18.2	18.2		18.3
C(3)	42.2	42.2	42.4	42.4	42.3	42.3	42.3		42.4
C(4)	32.9	32.9	33.0	33.0	33.0	33.0	33.0		33.0
C(5)	56.9	56.5	56.9	57.0	56.9	57.1	56.9		57.0
C(6)	20.4	20.7	20.7	20.4	20.4	20.7	20.7/20.4		20.4
C(7)	39.4	39.7	40.2	40.0	39.6	39.8	40.1/39.9		39.7
C(8)	82.9	84.1	82.7	81.1	82.5	84.2	83.1	81.5[c])	81.2
C(9)	59.9	56.8	57.0	60.2	59.7	57.6	57.0	60.6[c])	60.2
C(10)	36.0	35.8	36.0	36.0	36.1	36.0	36.0/35.9		36.0
C(11)	29.9	30.0	30.5	30.7	27.4	28.0	31.5/31.3		30.8
C(12)	98.4	97.2	104.0	105.7	108.6	106.2	97.0	98.8[c])	101.8
Me(17)	22.9	22.7	23.0	23.4	23.4	23.0	22.9	23.9[c])	23.5
Me(18)	32.9	33.3	33.5	33.4	33.4	33.5	33.4/33.5		33.5
Me(19)	20.9	20.8	21.0	21.0	21.0	21.0	21.0		21.0
Me(20)	15.0	15.2	15.2	15.1	15.1	15.1	15.2		15.2
Me*C*O	170.7	170.2							
*Me*CO	20.9	21.3							
MeO			54.9	55.7					

[a]) Mixture of epimers; all data are in agreement with those reported by *Urones et al.* [32]. [b]) The C-atoms of the two identical moieties are homotopic. [c]) Tentative assignments by analogy with **9**, **11**, and **12**.

evaporated and the crude *ca.* 2:1 epimer mixture **11** (white waxy solid; 1.0 g, 95%) submitted to FC: major (12*S*)-**11** (97% pure; eluted with hexane/Et_2O 80:20) and minor (12*R*)-**11** (85% pure, from last fractions). The same elution order has already been observed [34].

*Data of (12*R*)-***11***: Solid. ^{1}H-NMR: 5.03 (*d*, *J* = 5.8, H–C(12)); 3.35 (*s*, MeO); 1.11 (*s*, Me(17)); 0.86 (3 H), 0.82 (6 H) (2*s*, Me(18), Me(19), Me(20)). ^{13}C-NMR: *Table.*

*Data of (12*S*)-***11***: Solid. ^{1}H-NMR: 5.01 (*q*, *J* = 5.9, 5.0, H–C(12)); 3.38 (*s*, MeO); 1.24 (*s*, Me(17)); 0.86 (3 H), 0.82 (6 H) (2*s*, Me(18), Me(19), Me(20)). ^{13}C-NMR: *Table.*

8. *Reaction of Acetate* **9** *with 30% Hydrogen Peroxide: 8α,12-Epoxy-13,14,15,16-tetranorlabdan-12-yl Hypdroperoxide* (= *(3a*R*,5a*S*,9a*S*,9b*R*)-Dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan-2-yl Hydroperoxide*; **12**) *and 8α,12-Epoxy-13,14,15,16-tetranorlabdan-12-ol* (= *(3a*R*,5a*S*,9a*S*,9b*R*)-Dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan-2-ol*; **13**). A soln. of (12*S*)-**9** (5.5 g, 18.7 mmol) in AcOEt (10 ml) was added dropwise at 15°, to a stirred mixture of 30% (*w*/*w*) aq. H_2O_2 soln. (4.0 g, 35.3 mmol) and AcOEt (20 ml) containing a trace amount of 50% H_2SO_4 soln. After being stirred for 20 h at r.t., H_2O (10 ml) was added and then enough Na_2SO_3 to destroy the excess of H_2O_2. The aq. phase was extracted with Et_2O (10 ml), the combined org. layer washed with 10% aq. Na_2CO_3 soln., H_2O, and brine, dried (Na_2SO_4), and evaporated, and the crude white solid (4.5 g) subjected to FC (hexane/Et_2O 90:10 → 50:50): **12** (1.8 g, 36%) and **13** (2.3 g, 49 %), both as epimer mixtures. (12*R*)- and (12*S*)-**12** were separated by further FC, (12*S*)-**12** being first eluted.

*Data of (12*R*)-***12***: Solid. M.p. 178° ([35]: 167–169°). ^{1}H-NMR: 9.71 (*s*, OOH); 5.60 (disym. four-line pattern, $w_{1/2}$ = 11.9, H–C(12)); 1.27 (*s*, Me(17)); 0.86, 0.84, 0.82 (3*s*, each 3 H, Me(18), Me(19), Me(20)). ^{13}C-NMR: *Table.* EI-MS (70 eV): 268 (2, $M^{\bullet+}$), 191 (100). HR-MS: 268.20381 ($C_{16}H_{28}O_3^+$; calc. 268.20384).

*Data of (12*S*)-***12***: Solid. M.p. 128°. ^{1}H-NMR: 9.56 (*s*, OOH); 5.57 (*d*, *J* = 6.2, H–C(12)); 1.14 (*s*, Me(17)); 0.87 (3 H), 0.82 (6 H) (2*s*, Me(18), Me(19), Me(20)). ^{13}C-NMR: *Table.* EI-MS (70 eV): 268 (2, $M^{\bullet+}$), 191 (100). HR-MS: 268.20394 ($C_{16}H_{28}O_3^+$; calc. 268.20384).

*Data of (12*R*)/(12*S*)-***13***: Solid. IR (KBr): 3396, 2924, 2854, 1460, 1385, 1333, 1290, 1205, 1153, 1130, 1088, 1057, 999, 966, 939, 887; the spectrum matched the one presented by *Stoll* and *Hinder* [26]. ^{1}H-NMR: 5.50 (overlapped *t* (*J* = 5.6) and *d* (*J* = 5.6) with close centers, 1 H, H–C(12)); 4.75, 4.63 (2br. *m* moving towards low

frequencies on dilution, 1 H, OH); 1.29, 1.09 (2*s*, 3 H, Me(17)); 0.86 (3 H), 0.81 (6 H) (2*s*, Me(18), Me(19), Me(20)). ^{13}C-NMR: *Table*. EI-MS (70 eV): 252 (8, $M^{\bullet+}$), 237 (100).

8α-Hydroxy-13,14,15,16-tetranorlabdan-12-al (= [(*1*R,*2*R,*4a*S,*8a*S)-Decahydro-2-hydroxy-2,5,5,8a-tetramethylnaphthalen-1-yl]ethanal; open-chain form of lactol **13**): ^{1}H NMR: 9.72 (ill-resolved *q*, $w_{1/2}$ = 4.5, H–CO); remaining signals undistinguishable from those of the lactol. ^{13}C-NMR: 203.6 (C(12)); 72.9 (C(8)); 55.8 (C(9)); 55.5 (C(5)); 44.2 (C(7)); 41.6 (C(3)); 40.0 (C(1)); 38.0 (C(10)); 33.1 (C(18)); 33.0 (C(4)); 30.8 (C(11)); 23.6 (C(17)); 21.3 (C(19)); 20.3 (C(6)); 18.2 (C(2)); 15.5 (C(20)).

9. *Reaction of Acetate* **9** *with Peracetic Acid: Bis(8α,12-epoxy-13,14,15,16-tetranorlabdan-12-yl) Peroxide* (= *(3a*R,*3′a*R,*5a*S,*5′a*S,*9a*S,*9′a*S,*9b*R,*9′b*R*)-2,2′-Dioxybis[dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1*-b*]furan]*; **14**). To a stirred soln. of (12*S*)-**9** (2.7 g, 9.2 mmol) in AcOEt (10 ml) at 15° was added dropwise AcOOH (3.7 g, 18.4 mmol). After 2 h stirring at 15°, H_2O was added, and the resulting mixture was extracted with Et_2O. The combined org. layer was washed with 10% aq. Na_2CO_3 soln., H_2O, and brine, dried (Na_2SO_4), and evaporated and the crude white solid (2.4 g) subjected to HPLC analysis: peroxide **14** (15%), hydroperoxide **12** (50%), and sclareolide (**3**; 30%). Peroxide **14** (mixture of stereoisomers) was isolated by FC (hexane/Et_2O 95:5).

When the same experiment was run at 45°, the product (2.3 g) was (by HPLC, ^{1}H- and ^{13}C-NMR) a *ca.* 3:1 mixture of **3** and **12** (the (12*R*)-epimer being the most abundant).

Data of **14** (mixture of 12,12′-stereoisomers): Solid. ^{1}H-NMR (400 MHz): 5.76, 5.73, 5.66 (*d* (*J* = 6.4), *t* (*J* = 5.9), *t* (*J* = 5.9), H–C(12,12′)); 1.29, 1.27, 1.13 (3*s*, Me(17,17′)); 0.86, 0.82 (*s*, br. *s*, Me(18,18′), Me(19,19′), Me(20,20′)). ^{13}C-NMR: 107.5, 106.1, 105.7 (C(12,12′)); 83.8, 81.9, 81.7 (C(8,8′)); 60.0, 59.7, 57.2 (C(9,9′)); 56.9, 56.9, 56.8 (C(5,5′); 42.3 (C(3,3′)); 40.1, 39.9, 39.8 (C(7,7′)); 39.6, 39.6, 39.5 (C(1,1′)); 36.1, 36.0, 35.9 (C(10,10′)); 33.4, 33.4, 32.9 (C(4,4′)); 33.0 (C(18,18′)); 28.3, 27.7, 27.5 (C(11,11′)); 23.4, 23.2, 22.9 (C(17,17′)); 20.9 (C(19,19′)); 20.9, 20.7, 20.3 (C(6,6′)); 18.2 (C(2,2′)); 15.1, 15.0 (C(20,20′)). LSI-MS (35 keV; 3-nitrobenzyl alcohol matrix): 503 (46, $[M+H]^+$), 525 (13, $[M+Na]^+$), 1027 (10, $[M+M+Na]^+$).

10. *Reaction of Oxy Ketone* **4** *with Peracetic Acid*. Powdered (12*R*)-**4** (2.8 g, 10 mmol) was impregnated with a small part of a 8-g (40 mmol) amount of AcOOH. A reaction was not long in starting as evidenced by the rapid rise in temp. While stirring gently, the remainder of the AcOOH was then added at a rate such that the temp. was maintained at 50–55°. About 5 min after the end of the addition, the temp. fell and, because the mixture was nearly solid, stirring was stopped. The mixture was kept overnight at r.t. and then partitioned between H_2O (50 ml) and Et_2O (50 ml). The org. layer was washed with 10% aq. Na_2SO_3 soln., 10% aq. Na_2CO_3 soln., and brine, dried (Na_2SO_4), and evaporated; white solid (2.1 g) consisting (by HPLC, ^{1}H- and ^{13}C-NMR) of a *ca.* 70:30 mixture of sclareolide (**3**) and hydroperoxide **12** (the (12*R*)-epimer being the most abundant).

11. *Eliminative Coupling of Acetate* **9**: *Bis(8α,12-epoxy-13,14,15,16-tetranorlabdan-12-yl) Ether* (= *(3a*R,*3′a*R,*5a*S,*5′a*S,*9a*S,*9′a*S,*9b*R,*9′b*R*)-2,2′-oxybis[dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1*-b*]furan]*; **16**). Crude freshly prepared (12*S*)- or (12*R*)-**9** (0.9 g, 3 mmol) was set aside at r.t. in a stoppered flask. The evolution of this chemical was observed every second day by ^{1}H-NMR. As the days went by, the typical signals of **9** were vanishing; after *ca.* 20 days, they ceased to be detectable. FC (hexane/Et_2O 9:1) of the solid flask content (0.75 g) gave (12*R*,12′*R*)-**16** as a white solid (0.6 g). (12*S*,12′*S*)- and (12*R*,12′*S*)-**16** were tentatively identified by NMR in the product prior to FC.

*Data of (12*R*,12′*R*)*-**16**: Solid. M.p. 168° ([26]: m.p. 160–176° after chromatography before recrystallization). IR (KBr): 2925, 2860, 2843, 1461, 1381, 1337, 1219, 1130, 1073, 1042, 999, 965, 945, 886; the spectrum matched the one presented by *Stoll* and *Hinder* [26]. ^{1}H-NMR: 5.43 (*q*, *J* = 6.0, 5.4, 2 H, H–C(12,12′)); 1.22 (*s*, 6 H, Me(17,17′)); 0.86 (12 H), 0.92 (6 H) (2*s*, Me(18,18′), Me(19,19′), Me(20,20′)). ^{13}C-NMR: *Table*. EI-MS (70 eV): 486 (0.2, $M^{\bullet+}$), 191 (100). HR-MS: 486.40425 ($C_{32}H_{54}O_3^+$; calc. 486.40730).

*Data of (12*S*,12′*S*)*-**16**: ^{1}H-NMR (distinctive signals): 5.39 (*d*, *J* = 6.0, 2 H, H–C(12,12′)). ^{13}C-NMR (distinctive signals): 100.3 (C(12,12′)); 82.6 (C(8,8′)).

*Data of (12*R*,12′*S*)*-**16**: ^{1}H-NMR (distinctive signals): 5.34 (*d*, *J* = 5.6, 1 H, H–C(12′)); 5.25 (*q*, *J* = 6.0, 5.2, 1 H, H–C(12)). ^{13}CNMR (distinctive signals): 102.4 (C(12)); 101.9 (C(12′)); 82.5 (C(8′)); 81.5 (C(8)).

12. *Hydrolysis of Lactol Anhydride* **16**. A soln. of lactol anhydride **16** (0.5 g, 1.0 mmol) in 1,4-dioxane (20 ml) was treated with 10% H_2SO_4 soln. (7 ml) and heated at 45° for two days. The solvent was evaporated, and Et_2O was added. The mixture was washed with 10% aq. Na_2CO_3 soln., H_2O, and brine, dried (Na_2SO_4), and evaporated and the residual waxy solid (0.4 g) subjected to FC: unreacted **16** (0.2 g, 0.4 mmol; with pentane/Et_2O 9:1 → 4:1) and **13** as epimer mixture (0.15 g, 0.6 mmol; with pentane/Et_2O 1:1 from the last fractions).

13. *Hydrolysis of Acetate* **9**. To a soln. of (12*S*)-**9** (1.0 g, 3.4 mmol) in AcOEt (5 ml) were added AcOH (1.5 ml) and H_2O (0.5 ml). The reaction at r.t. was monitored by ^{1}H-NMR. After 20 h, *ca.* 90% of **9** was hydrolyzed into lactol **13**. The remaining acetate **9** was epimerized but no lactol anhydride **16** could be detected.

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