Abstract: Abietic acid, the main component of pine rosin, was used as starting material for the hemisynthesis of the ambergris-type ketal. The key intermediate step consisted of the synthesis of an exocyclic olefin through appropriate handling of a very sensitive aldehyde generated as an intermediate precursor.

Key words: ambergris perfume, rosin, abietic acid, ketalization

Ambergris is a metabolic product of the sperm whale and is considered one of the most valuable animal perfumes besides civet, musk, and castreum.1a–1e Like all aromatic substances of animal origin, ambergris may be considered a pheromone that acts through a proposed 3D amber olfactophore at the sensorial receptor of ambery smell.1e From ancient times ambergris tincture has been used as a fixative for rare perfumes since it has the effect of making other fragrances last much longer than they would otherwise. Ambergris is rarely used anymore because of its very high price due to enforced whale protection; thus, chemists have been looking for new, commercially viable, synthetic substitutes.2 Among the most expensive synthetic equivalents of the scarce natural ambergris source is the ambreketal 1 which possesses a strong and tenacious ambergris-type odor.1a The natural chiral pool of precursors include manool,3 sclareol,4 and the resinic acids, antico- palic,5 and podocarpic,6,7 for the synthesis of ambreketalts, but in all cases the synthesis of ambreketalts or its analogues was undertaken from (–)-abietic acid 3.

Figure 1

In this paper we report the synthesis of new ambergris-type analogue 2 from abietic acid 3, using Portuguese Pinus pinaster Ait. rosin as a readily available renewable source.

The use of abietic acid 3 as a precursor for compounds possessing an ambergris-type fragrance was reported in the early 1980s by Buchbauer et al.8 and Ohno et al.9 Later, Cambie et al.6,7 described the conversion of abietic acid into several analogues of ambergris perfumes.

The strategy described herein for the stereoselective synthesis of a new potential ambergris-type ketal 2 starting from abietic acid 3 (Scheme 1) was based on the oxidative degradation of the C-ring to the labdan-13-one side chain and subsequent regiospecific construction of a C-7 exocyclic double bond to achieve the desired final intramolecular δ,e-epoxyketone cyclization to a spiroketal.

As different structure–activity concepts have been investigated to explain the presence or absence of ambergris scent,10 its presence in ketal 2 was expected to be influenced by the slight structural difference at C-13 and C-14, where an isopropyl and a methyl ester group are present instead of the methyl substituents shown in the ambreketal skeleton.

The first step in our strategy aimed at building a labdan-13-one side chain was inspired by the route described by Ohno et al.9 for the synthesis of (–)-Ambrox®. Abietic acid 3 was readily converted to the corresponding methyl ester 4 with diazomethane in 50% yield or alternatively with dimethyl sulfate, in quantitative yield (Scheme 2). Treatment of 4 with a catalytic amount of osmium tetroxide in refluxing tert-butanol, pyridine, and water in the presence of trimethylamine N-oxide as co-oxidant, produced diol 5 (74%) as a mixture of β-diol and α-diol in a ratio of 7:3, which is comparable to that previously reported.9 Diol 5 could also be prepared in the same ratio using the NMO–acetone system at room temperature. The NMR
data recorded after regioselective attack on the C-ring of methyl abietate 4 is in accordance with that reported previously.9,11 The 13C NMR data of 5 revealed typical signals for an abietane skeleton, but also significant upfield shifts for C-13 at 76.26 ppm (β-diol) and 75.01 ppm (α-diol) and for C-14 at 73.29 ppm (β-diol) and 77.30 ppm (α-diol); these should be compared with 145.33 ppm (C-13) and 120.62 ppm (C-14) for methyl abietate 4, indicating the hydroxylation of these positions accompanied by the absence of a double bond in 5. The aldehyde 69 was subsequently produced by adopting alternative conditions for oxidative cleavage at room temperature to the not-so-environment-friendly lead(IV) acetate in benzene reported by Ohno et al.9 Thus, a mixture of diol 5 was treated with sodium periodate in water and ethanol (Scheme 2) to give aldehyde 6 (98%). The 1H and 13C NMR data confirmed the presence of the aldehyde group with chemical shifts at 9.36 and 194.82 ppm, respectively. The next, and key, step in the synthesis of ketal 2 involved the conversion of aldehyde 6 into exocyclic olefin 9. Initially we attempted the selective thiketalization of aldehyde 6 with 1,2-ethanediithiol and p-toluenesulfonic acid at room temperature, followed by Raney nickel reduction in ethanol which afforded a mixture of unsaturated compounds 6b (60%) in a 3:1 ratio (endolex) (Scheme 3).

We then attempted to adopt a strategy which had been successfully applied to the TBS derivative of our substrate, however, when we applied the photo-induced isomerization9 in order to obtain exclusively the desired exo-olefin, unreacted starting material was always recovered (Scheme 3).

Scheme 2  Reagents and conditions: a) acetone, K2CO3, Me2SO4, stirred overnight, 99%; b) OsO4 (cat.), Me3NO·2H2O, py–H2O–t-BuOH, reflux, 22 h, 74%; c) NaIO4, EtOH–H2O, 98%.

Scheme 3  a) 1,2-ethanediithiol, EtOH, p-TsOH; b) Raney Ni, EtOH–AcOH, 60% (2 steps; endolex, 3: 1); c) hv, xylene, i-PrOH; d) Raney Ni, THF, 78%; e) 1, imidazole, PPh3, CH2CN–toluene (1:2), reflux; f) i-BuOK, THF; g) p-TsCl, py, 70%; h) DBU, glyme, NaI, reflux, 54%; i) OsO4 (cat.), Me3NO·2H2O, py–H2O–t-BuOH, reflux, 34%.
A second route for the synthesis of the exo-olefin 9 was studied, consisting of the selective reduction of both the conjugated double bond and the aldehyde group in the presence of the ketone group with Raney nickel, as described by Barrero et al.\textsuperscript{12,13} Using this approach the aldehyde 6 was treated with an aqueous suspension of Raney nickel in THF, at room temperature, to afford alcohol 7 (78\%) (Scheme 3). The structure was established by \textsuperscript{1}H and \textsuperscript{13}C NMR spectroscopy with the aid of 2D experiments. The \textsuperscript{13}C NMR data of 7 showed significant upfield shifts for C-7 to 28.84 ppm and C-8 to 39.74 ppm, compared to 152.28 and 144.27 ppm, respectively, in aldehyde 6, indicating reduction of the conjugated double bond. The conversion of the aldehyde into an alcohol group was also observed by the appearance of the C-14 signal at 61.36 ppm in the \textsuperscript{13}C NMR spectrum.

In order to produce the exo-olefin 9, alcohol 7 was subjected to nucleophilic substitution with iodide followed by dehydrohalogenation with potassium tert-butoxide. The conversion of the hydroxyl on 7 into a iodide group was carried out using a reagent system reported in the literature for carbohydrates\textsuperscript{14,15} and used in the total synthesis of (+)-pumiliotoxin A.\textsuperscript{16} Triphenylphosphine, imidazole, and iodine in toluene converted all chromatographically homogeneous pure starting material into a crude mixture which was readily subjected to dehalogenation with potassium tert-butoxide in THF at room temperature. Taking into account the instability of iodide compounds, it is perhaps not surprising that this failed to produce olefin 9 as desired (Scheme 3).

Finally, we attempted a third route for the synthesis of exo-olefin 9 (Scheme 3) which proved to be successful. We converted the alcohol 7, previously obtained, into tosylate 8 (70\%) following the standard procedure with p-toluenesulfonyl chloride in pyridine at room temperature. The structure of the tosylate 8 was elucidated by \textsuperscript{1}H, \textsuperscript{13}C, DEPT, HETCOR, and COSY spectroscopy. The presence of two aromatic signals at 7.35 and 7.78 ppm in the \textsuperscript{1}H NMR spectrum showed the presence of the tosylate group, which was also confirmed by the assignment of four aromatic carbon signals at 127.79, 129.85, 133.05, and 144.79 ppm in the \textsuperscript{13}C NMR spectrum. From the COSY spectrum two methyl groups at 1.08 ppm (d, J = 6.6 Hz) both coupled with a septet (J = 6.9 Hz) centered at 2.55 ppm indicating the presence of an isopropyl group. The H-14 signal was clearly coupled with one proton resonance centered at 2.06 ppm assigned to H-8. A regioselective elimination to produce the exo-olefin 9 was achieved using a reported procedure by the reaction of the primary tosylate with DBU in the presence of sodium iodide\textsuperscript{17} in glyme under reflux. The presence of the unsaturated compound was confirmed by \textsuperscript{1}H NMR spectral analysis, where two olefinic hydrogens were assigned at 4.47 and 4.83 ppm along with the signals of the \textsuperscript{sp}\textsuperscript{2} carbons which were unequivocally located at 147.73 (C-8) and 106.89 ppm (C-14) in the \textsuperscript{13}C NMR spectrum. This result is particularly remarkable since Barrero et al.\textsuperscript{12} reported no reaction when 14,15-dinorlabdan-8,17-on-4-al was subjected to these conditions, thus we can unequivocally state that Raney nickel is indeed an efficient reagent to achieve the chemoselective 1,4-hydrogenation of \alpha,\beta-unsaturated carbonyl labdanes according to the method described by Barrero et al.\textsuperscript{13} Finally the new ambergris type analogue 2 was obtained by treatment of the exo-olefin 9 with a catalytic amount of osmium tetroxide in reflowing tert-butanol, pyridine, water, and trimethylamine N-oxide\textsuperscript{2c,2d} under reflux in moderate yield (34\%).

The formation of ketal 2 with the most desired stereochemistry is due to the intramolecular hydroxyxarbonyl rearrangement which occurs by attack of the primary hydroxyl group on the electron-deficient carbon C-13, whose carbonyl oxygen then reacts at C-8 in order to build the trans-fused spiroketal ring of 2 as shown in Scheme 4. The \(\delta,\varepsilon\)-epoxycarbonyl rearrangement has been extensively studied by the authors and will be published later. Compound 2 was fully characterized by \textsuperscript{1}H NMR spectral analysis where the chemical shift for H-14 was observed as two doublets at 3.25 (J = 7 Hz) and 4.30 ppm (J = 7 Hz), which is in good agreement with the data reported for the ambraketal\textsuperscript{3} and its C-4 methyl ester analogues previously synthesized by Barrero et al.\textsuperscript{2c,2d} The structure of ketal 2 was further elucidated by \textsuperscript{13}C NMR, COSY, HETCOR, and MS analysis. An unequivocal characteristic amber-type fragrance was empirically detected, showing that the substitution of a methyl by an isopropyl group at C-13 in the ambraketal skeleton, leaving an ester group at C-4, still retains ambergris unique olfactory scent.

The solvents used in the reactions were dried by standard procedures. FTIR spectra were recorded on a Perkin-Elmer 1725X. NMR spectra were run on a Bruker AMX 300 MHz or Bruker 400 MHz using CDCl\textsubscript{3} as solvent and TMS as internal reference; structure elucidation was performed with the aid of DEPT, HETCOR, and COSY NMR methods. The chemical shifts are reported in ppm, and coupling constants (J) in Hz. TLC was performed using silica gel (Merck silica gel GF254). Chromatographic separations were carried out by flash column on Merck silica gel 60 (230–400 mesh).
Methyl Abietadien-19-oate (4)
To a stirred solution of abietic acid 3 (2.45 g, 8.1 mmol), acetone (75 mL), and K$_2$CO$_3$ (1.2 equiv, 1.34 g, 9.7 mmol) was added Me$_2$SO$_4$ (0.8 mL) and the resulting solution was stirred overnight at r.t. After removing the solvent the mixture was diluted with CH$_2$Cl$_2$ (20 mL), washed with H$_2$O (20 mL), dried over MgSO$_4$, filtered, and concentrated. The residue was filtered through a pad of silica gel, washed with CH$_2$Cl$_2$, and the filtrate was concentrated to afford methyl abietadien-19-oate 4 (2.22 g, 99%) as an oil.

$^1$H NMR (300 MHz): δ = 0.82 (s, 3 H, H-20), 1.00 (d, J = 6.9 Hz, 3 H, H-16 or H-17), 1.01 (d, J = 6.9 Hz, 3 H, H-17 or H-16), 1.25 (s, 1 H, H-18), 2.16–2.29 (m, 1 H, H-15), 3.63 (s, 3 H, CH$_3$-21), 5.33–5.41 (m, 1 H, H-7), 5.77 (s, 1 H, H-14).

$^{13}$C NMR (75.6 MHz): δ = 14.03 (C-20), 17.01 (C-18), 18.14 (C-2), 20.85 (C-16 or C-17), 21.42 (C-17 or C-16), 22.46 (C-11), 25.68 (C-6), 27.48 (C-12), 34.53 (C-10), 34.88 (C-15), 37.12 (C-3), 38.33 (C-1), 45.10 (C-5), 46.59 (C-4), 50.94 (C-9), 51.85 (C-21), 120.62 (C-14), 122.36 (C-7), 153.55 (C-8), 145.33 (C-13), 179.01 (C-19).

APCI-MS: m/z (%) = 317.2 (100) [M+H$^+$], 315.2 (77), 313.2 (47), 257.2 (25).

Methyl 13,14-Dihydroxyabiet-7-en-19-oate (5a and 5b)
Methyl abiate 4 (500 mg, 1.58 mmol) was added to a stirred mixture of Me$_2$NO$_2$H$_2$O (1.5 equiv, 178 mg, 2.37 mmol), H$_2$O (1 mL), t-BuOH (3 mL), pyridine (0.13 mmol), and OsO$_4$ (2.5% wt in t-BuOH, 0.08 equiv, 0.13 mmol, 0.13 mL) which was then heated at reflux under argon. When the reaction was complete (TLC, 50 h), the reaction mixture was cooled, treated with an aq solution of NaHSO$_3$ (0.08 equiv, 0.13 mmol, 0.13 mL) which was then heated at reflux under argon. The reaction mixture was stirred for 4 h under nitrogen. Pyridine was removed under vacuum, the crude was distilled pyridine (3 mL), the reaction mixture was stirred for 4 h under nitrogen. To a solution of alcohol (2.45 g, 99%) as an oil.

IR (film): 3435, 1724, 1458, 1362, 1176 cm$^{-1}$.

$^1$H NMR (300 MHz): δ = 0.74 (s, 3 H, H-20), 0.94–1.02 (m, 2 H, H$_1$-ax, H$_2$-ax), 1.10 (d, J = 6.9 Hz, 3 H, H-16, H-17), 1.14 (s, 3 H, H-18), 1.24–1.33 (m, 1 H, H-9), 1.40–1.56 (m, 6 H, H-2, H-3, H$_6$-ax, H$_7$-ax, 1.59–1.77 (m, 3 H, H$_1$-eq, H$_2$-eq, H-7), 1.78–1.88 (m, 1 H, H-8), 1.89–2.01 (m, 1 H, H-17), 2.34–2.57 (m, 2 H, H-12), 2.60 (sept, J = 6.9 Hz, 1 H, H-15), 3.40 (t, J = 9.9 Hz, 10.2, 1 H, H-14), 3.65 (s, 3 H, CH$_3$-21), 3.65 (m, 1 H, H-14).

$^{13}$C NMR (75.6 MHz): δ = 15.96 (C-20), 16.39 (C-17 or C-16), 17.84 (C-2), 18.28 (C-16 or C-17), 18.38 (C-17 or C-16), 19.27 (C-11), 20.66 (C-6), 28.84 (C-7), 36.86 (C-3), 37.58 (C-10), 38.21 (C-11), 38.94 (C-12), 39.74 (C-8), 40.98 (C-15), 47.74 (C-4), 50.79 (C-5), 51.89 (C-13), 52.77 (C-9), 61.36 (C-14), 179.31 (C-19), 215.19 (C-13).

HRMS-ESI: m/z calc for C$_{21}$H$_{34}$O$_8$ [M+Na$^+$]: 375.25057; found: 375.25045.

Methyl 14-p-Toluenesulfonate-abiet-13-one-19-oate (8)
A solution of Na$_2$O$_4$ (1.5 equiv, 0.618 mmol, 132 mg) in H$_2$O (0.7 mL) was added to a solution of diol 5 (144.2 mg, 0.412 mmol) in EtOH (3 mL). The reaction mixture was stirred for 5 h at r.t. After removing the solvent under vacuum, the crude product was dissolved in EtOAc (10 mL), washed with H$_2$O (7 mL), dried over MgSO$_4$, filtered, and concentrated. The concentrate was filtered through a pad of silica gel to afford 6 (142.7 mg, 98%) as a colorless oil. This material was used directly in the next reaction.

$^1$H NMR (300 MHz): δ = 0.98 (s, 3 H, H-20, H-21), 3.64 (s, 3 H, H-21), 6.74 (qt, J = 2.1, 2.4 Hz, 1 H, H-7), 9.36 (s, 1 H, H-14).

$^{13}$C NMR (75.6 MHz): δ = 14.19 (C-20), 18.24 (C-16 or C-17), 18.36 (C-17 or C-16), 17.02 (C-18), 17.67 (C-20), 20.74 (C-11), 26.76 (C-6), 36.36 (C-10), 37.00 (C-3), 37.71 (C-1), 40.68 (C-15), 42.48 (C-12), 44.11 (C-5), 46.21 (C-4), 49.88 (C-9), 52.99 (C-21), 144.27 (C-8), 152.26 (C-7), 178.54 (C-19), 194.82 (C-14), 215.37 (C-13).

Methyl 14-Hydroxyabiet-13-one-19-oate (7)
An aqueous suspension of Raney Ni (520 mg) was added to a stirred solution of aldehyde 6 (55 mg, 0.18 mmol) in THF (10 mL) and the mixture was stirred at r.t. overnight. The mixture was diluted with Et$_2$O (10 mL), filtered through silica, and the solvent was evaporated. The residue was purified by flash column chromatography (hexane:EtOAc, 4:1:1:1:1:1) to afford alcohol 7 (43 mg, 78%) as a colorless oil.

IR (film): 3435, 1724, 1458, 1249 cm$^{-1}$.

$^{13}$C NMR (75.6 MHz): δ = 15.96 (C-20), 16.39 (C-17), 18.74 (C-2), 18.28 (C-16 or C-17), 18.38 (C-17 or C-16), 19.27 (C-11), 20.66 (C-6), 28.84 (C-7), 36.86 (C-3), 37.58 (C-10), 38.21 (C-11), 38.94 (C-12), 39.74 (C-8), 40.98 (C-15), 47.74 (C-4), 50.79 (C-5), 51.89 (C-13), 52.77 (C-9), 61.36 (C-14), 179.31 (C-19), 215.19 (C-13).

HRMS-ESI: m/z calc for C$_{21}$H$_{34}$O$_8$ [M+Na$^+$]: 375.25057; found: 375.25045.
H-28), 2.47–2.52 (m, 1 H, CH-12), 2.55 (sept, J = 6.9 Hz, 1 H, H-15), 3.64 (s, 3 H, CH3-21), 3.92–4.08 (m, 2 H, H-14), 7.36 (d, 2 H, J = 8.4 Hz, H-25, H-26), 7.78 (d, J = 8.1 Hz, 2 H, H-23, H-24).

1H NMR (300 MHz): δ = 0.72 (s, 3 H, H-20), 0.94 (d, J = 6.9 Hz, 6 H, H-16, H-17), 1.14 (s, 3 H, H-18), 1.77 (m, 1 H, H-7), 1.81–1.91 (m, 1 H, H-11), 1.84–1.91 (m, 1 H, H-5), 2.07–2.39 (m, 1 H, H-12 eq), 2.55 (sept, J = 6.9 Hz, 1 H, H-25, H-26), 7.78 (d, J = 8.1 Hz, 2 H, H-23, H-24).

13C NMR (75.6 MHz): δ = 14.99 (C-20), 16.63 (C-18), 16.88 (C-22), 17.25 (C-16, C-17), 17.37 (C-11), 22.71 (C-60), 30.72 (C-12), 34.84 (C-15), 35.45 (C-7), 36.76 (C-3, C-10), 37.93 (C-1), 47.32 (C-4), 49.85 (C-5), 51.95 (C-21), 53.95 (C-9), 73.65 (C-14), 82.33 (C-8), 109.76 (C-33), 179.06 (C-19).

HRMS-EI: m/z calcd for C19H14O3 [M+]: 334.245161; found: 334.24866.

References


