Conversion of a Cyclic α,β-Unsaturated Ketone into a Tertiary Dienyl Hydroperoxide: Application to the First Hemisynthesis of 15-Hydroperoxyabietic Acid

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Abstract: The first hemisynthesis of 15-hydroperoxyabietic acid, a major contact allergen among the oxidation products of colophony, is reported. The key step includes a new approach to easily obtain a dienyl tertiary hydroperoxide from a cyclic α,β-unsaturated ketone. The procedure is based on the formation of a bromodiene using a Vilsmeier's reagent, followed by a halogen/metal exchange and alkylation with acetone, to afford the dienyl alcohol precursor of the hydroperoxide.

Key words: colophony, 15-hydroperoxyabietic acid, dienyl hydroperoxide, α,β-unsaturated ketone, halo-diene alkylation

Colophony (rosin) is a widespread natural product obtained from different species of coniferous trees either from oleoresins, tapped from living trees, or by distillation of tall oil, a by-product of the paper pulp industry. Due to its tackifying, emulsifying, and insulating properties, it is widely used in the production of many products (i. e. adhesives, paints, cosmetics).[1,2] Today, allergic contact dermatitis (ACD) to colophony is one of the 10 most commonly encountered allergic reactions.[3] Colophony has a complex chemical composition consisting mainly of resin acids of which abietic acid **1** and dehydroabietic acid **2** (Figure 1) are the major components. It has been demonstrated that **1** and **2** are not allergenic[4,5] and that the allergenic activity of colophony is caused by air oxidation products of the resin acids.[6] The dienyl hydroperoxide 15-hydroperoxyabietic acid **3** (15-HPA; Figure 1) has been identified as a major contact allergen.[7]

Contact allergens are low molecular weight compounds (haptens) that bind covalently to endogenous proteins in the skin before they can be recognized as antigens and thereby elicit the immune reaction characteristic of ACD.[8] It is accepted that the main hapten-protein interaction mechanism is the formation of a covalent bond between the hapten and nucleophilic residues of proteins through a nucleophile/electrophile reaction.[9] However, the interaction mechanism of allergenic allylic hydroperoxides derived from the autoxidation of terpenes with skin proteins does not fit this model and is still unknown. Mechanisms involving radicals have been suggested in the discussion of hapten-protein binding, and our previous studies indicate that radical reactions could be important in the case of haptens containing hydroperoxide groups.[10]

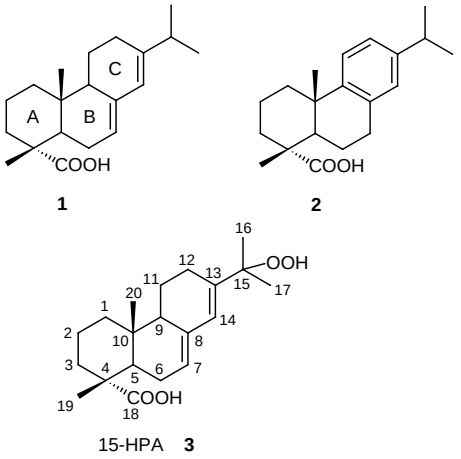

Figure 1 Structures of abietic acid **1**, dehydroabietic acid **2** and 15-hydroperoxyabietic acid **3**

In order to study the mechanisms leading to the formation of radicals from 15-HPA, and their subsequent reaction with skin proteins, relatively large quantities of the hydroperoxide are needed. The isolation of 15-HPA from samples of air oxidized colophony has been reported in a process that is very time consuming and expensive.[7] We therefore decided to pursue a stepwise synthetic route to access workable amounts of 15-HPA **3**. This letter reports a new synthetic method for the conversion of an α,β-unsaturated ketone into a tertiary dienyl hydroperoxide that has been successfully applied to the first hemisynthesis of 15-HPA from abietic acid.

A major problem for the synthesis of 15-HPA is the easy aromatization of cycle C leading to the formation of dehydroabietic derivatives. For many years, and despite several attempts, this has been a major pitfall to the access to 15-HPA.[11] We have successfully synthesized 15-HPA **3** from the known α,β-unsaturated ketone **4**, a versatile starting material for the synthesis of diterpenes, avoiding isomerization of the conjugated system as well as aromatization. Our synthetic approach is outlined in Scheme 1.

In order to build the tertiary dienyl alcohol **6**, precursor of the hydroperoxide **3**, the α,β-unsaturated ketone **4** was converted into bromodiene **5** using a Vilsmeier's reagent.

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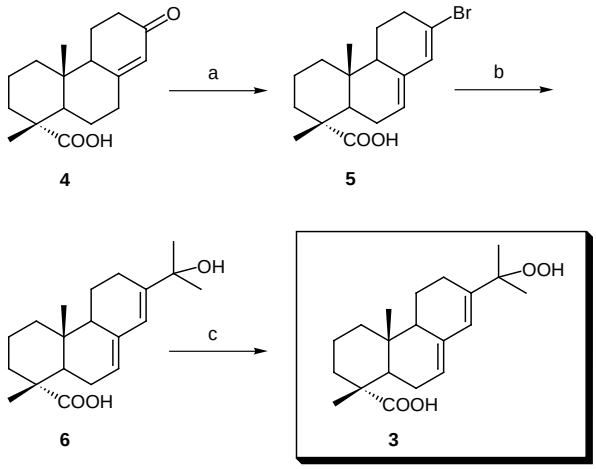
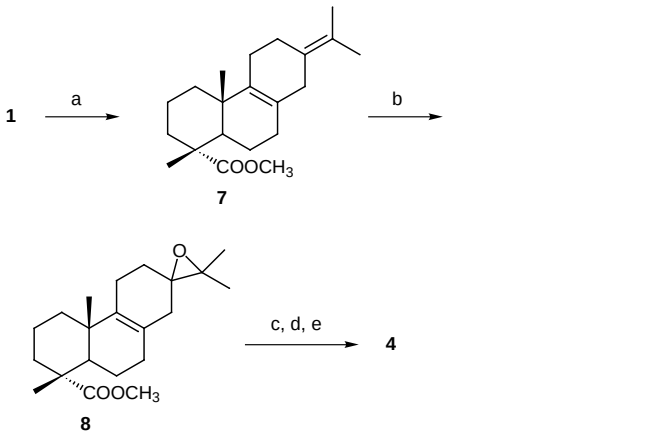


a) $(COBr)_2$, DMF, CH_2Cl_2, –78 °C to r.t., 5 h, 74%; b) *t*-BuLi, Et_2O, anhyd acetone, –78 °C to r.t., 2 h, 70%; c) H_2O_2/H_2O (35%), H_2SO_4, 0 °C, 10 h, 63%.

Scheme 1 Synthesis of 15-hydroperoxyabietic acid **3** from ketone **4**



a) see reference (20); b) MCPBA, CH_2Cl_2, 0 °C, 2 h, 90%; c) H_5IO_6, THF, –30 °C to –10 °C, 1 h, 87%; d) HCl, MeOH, 0 °C, 4 h, 96%; e) *t*-BuOK, DMSO, r.t., 45 min, 80%.

Scheme 2 Synthesis of ketone **4** from commercial abietic acid

It has been reported in the literature that treatment of 3-oxo-4-ene steroids with a Vilsmeier's reagent, typically produced by reaction between *N*,*N*-dimethylformamide and phosphorous oxychloride (DMF–$POCl_3$), affords a mixture of products of which 3-chloro-3,5-dienes are the major components.[12] Recently, Yu and Baine reported the use of a Vilsmeier's reagent, formed from oxalyl bromide and DMF, for the production of a bromodiene in rings A and B of a ketosteroidal acid.[13] Based on these results, the same experimental conditions were applied for the conversion of ketone **4** to bromodiene **5**. Treatment of **4** with 4 equivalents of DMF–$(COBr)_2$ in dichloromethane gave, after 5 hours stirring at room temperature, the diene **5** in 74% yield.[14] Alcohol **6** was then synthesized (70% yield) by alkylation, with an excess of anhydrous acetone, of the alkenyllithium derivative obtained from **5** by a halogen/metal exchange with *tert*-butyllithium in diethyl ether.[15] Finally, one of the most classical methods for the preparation of tertiary allylic hydroperoxides is the quenching with hydrogen peroxide of a carbocation generated from a hydroxyl function under acidic conditions.[16] Alcohol **6** was thus treated with a solution of H_2O_2 (35% in water) under acidic conditions (H_2SO_4) at 0 °C to give **3** in 63% yield.[17,18]

α,β-Unsaturated ketone **4** was obtained (Scheme 2) from commercially available abietic acid **1** (technical grade 70–80%) which was initially purified by way of its ethanolamine salt followed by treatment with glacial acetic acid and recrystallization.[19]

Pure abietic acid was converted into the diene compound **7** following the procedure described by Arno and coworkers.[20] In their developed methodology to synthesize diterpene derivatives from abietic acid, the exocyclic carbon-carbon double bond of **7** was cleaved by partial ozonolyzis to give a β,γ-unsaturated ketone. It was then necessary to carefully monitor the ozone flow in order to avoid the cleavage of both tetrasubstituted double bonds in compound **7**. We did find a useful alternative for the obtention of a β,γ-unsaturated ketone from **7**, based in a selective epoxidation of the exocyclic double bond, followed by an oxidative cleavage of the epoxide. Indeed, treatment of compound **7** with a stoechiometric amount of MCPBA in anhydrous dichloromethane at 0 °C led to the formation of epoxide **8** with a good yield (90%). Further cleavage of the epoxide with periodic acid in tetrahydrofuran at low temperature gave the desired β,γ-unsaturated ketone (87% yield), which was easily isomerized with HCl in methanol, and converted into an α,β-unsaturated ketone (96% yield).

We considered convenient, at this stage of the synthesis, to cleave the methyl ester in order to obtain the free carboxylic acid function of compound **4**. A number of mild, neutral methods of ester cleavage, such as LiOH, NaCN/HMPA, NaCN/DMF, LiI/pyridine, LiI/lutidine LiI/DMF, $Ba(OH)_2$/MeOH, KOH/MeOH–H_2O, were devised and used without success.[21] However, the use of potassium *tert*-butoxide (4 equivalents) in dimethyl sulfoxide allowed the ketone **4** to be obtained in 80% yield. These reaction conditions have been used considerably with di- and tri-terpenes, in particular, with methyl esters of diterpenoids with the dehydroabietic skeleton.[22]

This first reported synthesis of 15-HPA **3** will enable further fundamental studies, necessary for the understanding of its allergenic activity. Studies concerning the formation and the identification of reactive radicals derived from 15-HPA, as well as their reactivity, will now be undertaken, using a combination of chemical-trapping experiments and electron paramagnetic resonance studies (EPR), that have been already developed in the course of our investigations on allylic hydroperoxides as potential sources for radical intermediates.[10c,d] Understanding of mechanisms leading to the formation of these radicals and their subsequent reaction with proteins will open new insights in our understanding of antigen formation.

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(14) **7-Bromo-1,4a-dimethyl-1,2,3,4,4a,4b,5,6,10,10a-decahydro-phenantrene-1-carboxylic Acid**(**5**): To a solution of **4** (200 mg, 0.72 mmol) in anhyd CH_2Cl_2 (60 mL) was slowly added DMF (221.6 μL, 2.9 mmol) and oxalyl bromide (270.2 μL, 2.9 mmol) at –78 °C. After 15 min stirring at –78 °C the mixture was gradually warmed to r.t. and stirred for 5 h. H_2O (50 mL) was then added and the stirring followed for 20 min. The organic layer was separated and the aq phase extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with water (2 × 45 mL) and brine (3 × 45 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure, to give a crude residue, which was purified by column chromatography on silica gel (hexane–EtOAc, 8:2). The purification afforded 181.6 mg (0.53 mmol, 74% yield) of **5** as a white solid: mp 168–170 °C; $[\alpha]_D$ –123 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 Mhz): δ 0.81 (s, 3 H, CC*H*$_3$), 1.24 (s, 3 H, C(C*H*$_3$)(CO_2H)), 1.55–2.04 (m, 12 H, 5 × C*H*$_2$, 2 × C*H*), 2.52–2.55 (m, 2 H, C*H*$_2$), 5.44 (m, 1 H, =C*H*CH_2), 6.32 (s, 1 H, =C*H*C); ^{13}C NMR ($CDCl_3$, 50 Mhz): δ 14.1, 16.7, 18.0, 23.6, 25.6, 34.5, 36.1, 37.1, 38.2, 44.6, 46.2, 49.0, 122.5, 123.9, 132.1, 134.8, 184.9; IR ($CHCl_3$)1693 (C=O), 2935 cm^{-1} (C-H). Anal. Calcd for $C_{17}H_{23}BrO_2$: C, 60.18; H, 6.83. Found: C, 60.43; H, 6.80.
(15) **7-(1-Hydroxy-1-methyl-ethyl)-1,4a-dimethyl-1,2,3,4,4a,4b,5,6,10,10a-decahydro-phenantrene-1-carboxylic Acid**(**6**): To a solution of **5** (100 mg, 0.29 mmol) in anhyd Et_2O (15 mL) was added a solution of *tert*-butyllithium (1.74 mL, 1.74 mmol, 1 M solution in pentane) at –78 °C. The reaction was stirred at this temperature for 1.5 h and monitored by TLC (hexane–EtOAc 7:3). When the bromide-lithium exchange was completed, an excess of anhyd acetone (1 mL, 13.6 mmol) was added dropwise. To obtain anhyd acetone, this was first distilled over potassium permanganate, dried over K_2CO_3 for 48 h, filtered and distilled a second time. The reaction mixture was allowed to warm to r.t. and stirred for 2 h. The mixture was quenched with an aq sat. soln NH_4Cl (10 mL). The organic layer was separated and the aq phase extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane–EtOAc 5.5:4.5) to give 64.6 mg (0.2 mmol, 70% yield) of **6** as a white solid: mp 147–149 °C; $[\alpha]_D$ –86 (*c* 1.1, acetone); ^{1}H NMR ($CDCl_3$, 200 Mhz): δ 0.83 (s, 3 H, CC*H*$_3$), 1.26 (s, 3 H, C(C*H*$_3$)(CO_2H), 1.33 (s, 3 H, C(OH)(C*H*$_3$)$_2$), 1.35 (s, 3 H, C(OH)(C*H*$_3$)$_2$), 1.18–2.36 (m, 14 H, 6 × C*H*$_2$, 2 × C*H*), 5.48 (m, 1 H, =C*H*CH_2), 6.07 (s, 1 H, =C*H*C); ^{13}C NMR ($CDCl_3$, 50 Mhz): δ 14.0, 16.7, 18.1, 22.6, 25.7, 25.8, 28.6, 28.7, 34.4, 37.2, 38.3, 44.8, 46.3, 50.7, 72.9, 122.5, 122.9, 135.0, 144.5, 184.3; IR (DMSO) 1705 (C=O), 2878 (C–H), 3230–3620 cm^{-1} (broad, O–H). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.61; H, 9.48.
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(17) **7-(1-Hydroperoxy-1-methyl-ethyl)-1,4a-dimethyl-1,2,3,4,4a,4b,5,6,10,10a-decahydro-phenantrene-1-carboxylic acid, 15-HPA**(**3**): To an aq solution of H_2O_2 (16 mL, 35%) was added a drop of concentrated H_2SO_4 (97%). The solution was cooled to 0 °C and stirred for 10 min. A solution of **6** (40 mg, 0.12 mmol) in CH_2Cl_2 (10 mL) was then added. The reaction mixture was vigorously stirred at 0 °C and monitored by TLC (hexane–EtOAc 5:5). When no more significant evolution of the reaction (10–20 h) was observed, the solution was treated with water (15 mL). The organic layer was separated and the aq layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with a 50/50 aq sat. soln of NaCl and $NaHCO_3$ (pH = 8; 2 × 15 mL) and concentrated under reduced pressure to give the crude hydroperoxide, which was recrystallized from CH_2Cl_2/pentane. Recrystallization afforded 25.6 mg (0.076 mmol, 63% yield) of **3** as a white crystalline solid: CAS registry number [*113903-96-1*]; mp 68–70 °C; $[\alpha]_D$ –34 (*c* 1.1, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 200 Mhz): δ 0.75 (s, 3 H, CC*H*$_3$), 1.11 (s, 3 H, C(C*H*$_3$)(CO_2H)), 1.19 (s, 3 H, C(OOH)(C*H*$_3$)$_2$), 1.23 (s, 3 H, C(OOH)(C*H*$_3$)$_2$), 1.06–2.34 (m, 14 H, 6 × C*H*$_2$, 2 × C*H*), 5.42 (m, 1 H, =C*H*CH_2), 5.89 (s, 1 H, =C*H*C), 10.73 (s, 1 H, OO*H*), 12.13 (s, 1 H, COO*H*); ^{13}C NMR (DMSO-d_6, 50 Mhz): δ 13.6, 16.7, 17.6, 21.8, 23.4, 24.0, 24.4, 25.1, 33.8, 36.7, 37.8, 44.4, 45.2, 50.3, 81.9, 122.2, 124.4, 134.7, 141.9, 179.2; IR ($CHCl_3$) 887 (O–O), 1694 (C=O), 2853 (C–H), 3100–3550 cm^{-1} (broad, O–H).
(18) Structures of the synthesized compounds were established by a combination of ^{1}H and ^{13}C NMR data. The stereochemical determination was based on observations of nuclear Overhauser effects (NOE). In the case of compound **6**, a NOE between H-7 (5.48 ppm)and H-14 (6.07 ppm)

confirmed the conformation of the double bond conjugated system.
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